TREATMENT OF TUBERCULOSIS

Guidelines for treatment of drug-susceptible tuberculosis and patient care

2017 UPDATE

Annex 4
EVIDENCE-TO-DECISION TABLES

World Health Organization

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Abbreviations & acronyms

AIDS	acquired immunodeficiency syndrome
ART	antiretroviral treatment
ATS	American Thoracic Society
BMI	body mass index
CDC	United States Centers for Disease Control and Prevention
DOT	directly observed treatment
E	Ethambutol
FDC	fixed-dose combination
GDG	Guideline Development Group
Gfx	Gatifloxacin
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GTB	Global TB Programme
HIV	human immunodeficiency virus
IDSA	Infectious Diseases Society of America
IRIS	Immune Reconstitution Inflammatory Syndrome
KNCV	Royal Dutch Tuberculosis Foundation
MDR-TB	multidrug-resistant tuberculosis
Mfx	Moxifloxacin
NGO	non-government organization
PICO	Patients, Intervention, Comparator and Outcomes
RIF or R	Rifampicin
RFP	Rifapentine
SAT	self-administered treatment or unsupervised treatment
SMS	Short Message Service or text message
TB	tuberculosis
The Union	International Union Against Tuberculosis and Lung Disease
USAID	United States Agency for International Development
VOT	video-observed treatment
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

PICO 1

Question

Should a less than 6-month fluoroquinolone (FQ)-containing regimen versus. the standard 6-month treatment regimen (2HRZE-4HR) be used for patients with drug-susceptible TB?

Population:	Patients with drug-susceptible TB	Background:
Intervention:	A less than 6-month FQ-containing regimen	
Comparison:	Standard 6-month treatment regimen (2HRZE/4HR)	
Main outcomes:	Mortality all-cause; Mortality TB-related; Favourable outcome (end of treatment); Favourable outcome (end of follow-up); HIV-favourable - positive; HIV-favourable - negative; Relapse rate; Adverse effects - tx and fu - INH; Adverse effects - tx and fu - EMB; 2-month culture conversion; Unfavourable outcome (18 months); Unfavourable outcome (end of tx);	
Setting:		
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Shortening the duration of TB treatment is a global research priority. However, the risk of developing resistance to fluoroquinolones (an essential element of the MDR-TB regimens) if used in an ineffective shortened regimen is a serious concern.	
Desirable Effects	How substantial are the desirable anticipated effects? ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Desirable anticipated effects:** The less than 6-month FQ-containing regimen did trend towards better culture conversion at 2 months. However, this did not result in better treatment outcomes overall compared to standard treatment. **Undesirable anticipated effects** There are statistically significant higher rates of TB relapse and higher rates of unfavourable outcomes at 18 months in the patients treated with the less than 6-month FQ-containing regimen. Additionally, there are statistically significant worse outcomes in HIV-negative patients treated with the less than 6-month FQ-containing regimen. The higher rates of unfavourable outcomes were driven by the higher rates of relapse. **Summary of findings:**	The Guideline Development Group (GDG) felt that the shorter regimens were not at a "disadvantage" with regard to the discovery of relapse, as most relapses occur soon after stopping treatment, so most cases of relapse would be equally likely to be detected in the standard regimen and shorter regimen. The GDG also acknowledged that the comparator shorter FQ regimens varied with respect to the FQ used, the drug that the FQ replaced and the other drugs in the regimen. However, the EG believes that the FQ-based regimens at the doses tested still had similar outcomes, and those outcomes were inferior to the standard rifampicin-containing regimen. HIV-negative people did worse with the shortened FQ regimen, although this does not change the recommendations. There was no difference in mortality between the two regimens. The GDG expressed concern that a difference in mortality may not be seen between the two groups because the rates of mortality were low and a difference in mortality is not likely to be seen between a 4-month and a 6-month regimen and with the duration of follow-up seen in these studies. Mortality would be most likely to be influenced by treating patients with effective drugs early in the disease, which could have occurred in both the short FQ regimen and the standard regimen. Nevertheless, mortality after relapse is a concern, but this was not measured by the studies.

Outcome	With the standard 6-month treatment regimen (2HRZE/4HR)	With a less than 6-month FQ-containing regimen	Difference (95% CI)	Relative effect (RR) (95% CI)
Mortality all-cause	29 per 1000	**29 per 1000** (19 to 44)	**0 fewer per 1000** (from 10 fewer to 15 more)	**RR 1.00** (0.65 to 1.53)
Mortality TB-related	14 per 1000	**12 per 1000** (6 to 23)	**3 fewer per 1000** (from 9 fewer to 9 more)	**RR 0.82** (0.40 to 1.65)
Favourable outcome-(end of treatment)	912 per 1000	**922 per 1000** (912 to 940)	**9 more per 1000** (from 0 fewer to 27 more)	**RR 1.01** (1.00 to 1.03)
Favourable outcome (end of follow-up)	838 per 1000	**787 per 1000** (746 to 838)	**50 fewer per 1000** (from 0 fewer to 92 fewer)	**RR 0.94** (0.89 to 1.00)

<table>
<tr><th></th><th>Judgement</th><th>Research evidence</th><th>Additional considerations</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><th>Outcome</th><th>With the standard 6-month treatment regimen (2HRZE/4HR)</th><th>With a less than 6-month FQ-containing regimen</th><th>Difference (95% CI)</th><th>Relative effect (RR) (95% CI)</th></tr>
<tr><td>HIV-favourable - positive</td><td>763 per 1000</td><td>725 per 1000 (630 to 802)</td><td>38 fewer per 1000 (from 39 more to 133 fewer)</td><td>OR 0.82 (0.53 to 1.26)</td></tr>
<tr><td>HIV-favourable - negative</td><td>884 per 1000</td><td>802 per 1000 (763 to 835)</td><td>82 fewer per 1000 (from 50 fewer to 122 fewer)</td><td>OR 0.53 (0.42 to 0.66)</td></tr>
<tr><td>Relapse rate</td><td>49 per 1000</td><td>135 per 1000 (88 to 209)</td><td>87 more per 1000 (from 39 more to 160 more)</td><td>RR 2.78 (1.81 to 4.29)</td></tr>
<tr><td>Adverse effects - tx and fu - INH</td><td>192 per 1000</td><td>194 per 1000 (156 to 243)</td><td>2 more per 1000 (from 37 fewer to 50 more)</td><td>RR 1.01 (0.81 to 1.26)</td></tr>
<tr><td>Adverse effects - tx and fu - EMB</td><td>98 per 1000</td><td>118 per 1000 (63 to 221)</td><td>20 more per 1000 (from 35 fewer to 123 more)</td><td>RR 1.20 (0.64 to 2.25)</td></tr>
<tr><td>Unfavourable outcome (18 months)</td><td>162 per 1000</td><td>234 per 1000 (190 to 289)</td><td>71 more per 1000 (from 28 more to 127 more)</td><td>RR 1.44 (1.17 to 1.78)</td></tr>
<tr><td>Unfavourable outcome (end of treatment)</td><td>88 per 1000</td><td>74 per 1000 (60 to 92)</td><td>13 fewer per 1000 (from 4 more to 28 fewer)</td><td>RR 0.85 (0.68 to 1.05)</td></tr>
</table>
</td><td></td></tr>
<tr><td>Undesirable Effects</td><td>How substantial are the undesirable anticipated effects?
○ Large
● Moderate
○ Small
○ Trivial

○ Varies
○ Don't know</td><td></td><td>Studies in this analysis excluded FQ-resistant patients</td></tr>
<tr><td>Certainty of evidence</td><td>What is the overall certainty of the evidence of effects?
○ Very low
○ Low
● Moderate
○ High

○ No included studies</td><td>The quality of the evidence for mortality ranks as moderate, most other recommendations rank as high as the studies analysed were randomized control trials.</td><td>The certainty of evidence grade was influenced by the grade for the mortality evidence, as mortality is a critical outcome. Adverse events did not affect overall rating of evidence and did not influence the direction of the recommendation, due to high levels of inconsistency and imprecision in the adverse event data.</td></tr>
<tr><td>Values</td><td>Is there important uncertainty about, or variability in, the extent to which people value the main outcomes?
○ Important uncertainty or variability
○ Possibly important uncertainty or variability
● Probably no important uncertainty or variability
○ No important uncertainty or variability

○ No known undesirable outcomes</td><td>Main outcomes are mortality, favourable (and unfavourable) outcomes, relapse and adverse events.</td><td>This is a complex question. Patient preferences probably depend on limiting the length of treatment versus reducing the risk of relapse combined with degree of adverse events during treatment. In this case, the relatively minor reduction of treatment duration (2 months) with no difference in reducition of adverse events, combined with the increased risk of relapse, would probably lead most patients to favour remaining with the standard 2HRZE/4HR regimen. The panel feels that a major concern for patients would be relapse of TB disease.</td></tr>
</table>

	Judgement	Research evidence	Additional considerations
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? ● Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know		Decision based mostly on increased rates of relapse among the shorter FQ-containing regimen.
Resources required	How large are the resource requirements (costs)? ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence was identified.	
Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)? ○ Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Cost effectiveness	Does the cost-effectiveness of the intervention favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ No included studies	No research evidence was identified.	
Equity	What would be the impact on health equity? ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	If the 4-month FQ regimen is recommended, what is the impact on health equity?	The belief that the shortened FQ regimen may lead to a reduction in health equity is based on concerns that certain groups may not respond as well to a shorter FQ-containing regimen and that relapse may be higher in certain populations (e.g. men, people with severe disease, people with low BMI). Concerns were also raised about the increased cost of an FQ-containing regimen. However, WHO believes that the cost of a regimen should not be the driver of best treatment recommendations.
Acceptability	Is the intervention acceptable to key stakeholders? ● No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	A concern with using FQs in drug-susceptible TB treatment is that this may lead to a rise in FQ resistance and therefore to its loss as part of the drug-resistant TB regimen. This would be a very serious loss to the MDR-TB treatment armamentarium. Another concern would be that stakeholders may be reluctant to purchase a more expensive medication (FQ) that may not be as effective as the standard regimen. However, WHO believes that the cost of a regimen should not be the driver of best treatment recommendations.

	Judgement	Research evidence	Additional considerations
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	The feasibility of using a shorter FQ-containing regimen may be reduced by the fact that many locations cannot test for FQ resistance.

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know	
Desirable Effects	**Trivial**	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	**Moderate**	Small	Trivial		Varies	Don't know	
Certainty of evidence	Very low	Low	**Moderate**	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			No known undesirable outcomes	
Balance of effects	**Favours the comparison**	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies	
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies	
Equity	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	**No**	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	**Probably yes**	Yes		Varies	Don't know	

Conclusions

Should a less than 6-month fluoroquinolone (FQ)-containing regimen versus the standard 6-month treatment regimen (2HRZE-4HR) be used for patients with drug-susceptible TB?

Type of recommendation	Strong recommendation against the intervention ●	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
Recommendation	The GDG recommends that the 6-month rifampicin-based regimen should be used rather than shorter 4-month FQ-containing regimens in drug-susceptible TB (strong recommendation, moderate certainty in the evidence).				
Justification	Although shortening the duration of tuberculosis therapy is a global research priority, the GDG strongly recommends against the use of a less than 6-month FQ-containing regimen and for the use of the standard 6-month rifampicin-containing regimen. The main reason behind the recommendation not to use a FQ-containing regimen of less than 6 months is that there are significantly higher rates of relapse at 18-month follow-up among patients treated with this regimen compared to the standard 6-month regimen (2HRZE/4HR). This higher rate of relapse was found despite that fact that there were higher rates of 2-month culture conversion with the less than 6-month FQ-containing regimen. Additionally, the evidence showed no reduction in adverse events with the FQ-containing regimen and no difference in all-cause and TB-related mortality. An additional concern (although not addressed specifically in these data) with using FQs in drug-susceptible TB treatment, especially given higher rates of relapse in the FQ regimen, is that this may lead to a rise in FQ resistance and therefore to the loss of FQ as part of the drug-resistant TB regimen. This would be a very serious loss to the MDR-TB treatment armamentarium. Consequently, the relatively minor reduction in treatment duration (2 months) with no reduction in adverse events or mortality, combined with the increased risk of relapse at 18 months, leads the EG to support the standard 2HRZE/4HR regimen and recommend against the shorter FQ-containing regimen. The GDG also acknowledges that the comparator shorter FQ regimens varied with respect to the FQ used, the drug that the FQ replaced and the other drugs in the regimen. However, the EG still believes that all the FQ-based regimens at the doses tested had similar outcomes and those outcomes were inferior to the standard rifampicin-containing regimen.				
Subgroup considerations	None.				
Implementation considerations	There are no implementation concerns as the 6-month rifampicin-based regimen is the standard regimen for the treatment of drug-susceptible tuberculosis.				
Monitoring and evaluation	There are no new monitoring or evaluation concerns beyond the standard recommendations.				
Research priorities	Certain subgroups may do equally well with a shortened FQ-containing regimen (i.e. women, people with BMI greater than 18, people with non-severe, non-cavitary disease). Therefore, further research may be warranted into whether a 4-month FQ-containing regimen could be non-inferior to the standard regimen in these populations. Suggested areas for research are: the mechanisms that lead certain groups to be more likely to do worse with a shortened FQ-containing regimen; the biological mechanisms behind why TB persists and then relapses despite more rapid culture conversion with certain regimens; the determination of optimal dosing of FQ, since higher doses may affect outcomes; more qualitative research or systematic review on patient values and preferences with regard to TB treatment regimens.				

PICO 2

Question

Should a fixed-dose combination, versus separate drug formulations, be used for patients with active drug-susceptible TB disease?		
Population:	Patients with active drug-susceptible TB disease	Background:
Intervention:	Fixed-dose combination formulation (FDC)	
Comparison:	Separate drug formulations	
Main outcomes:	Failure/relapse (per protocol analysis), Albanna & Menzies; Treatment failure, Cochrane study; Relapse, Cochrane study; Death, Cochrane study; 2-month culture conversion, Albanna & Menzies; Sputum smear or culture conversion at end of treatment, Cochrane study; Adherence versus non-adherence to treatment, Albanna & Menzies; Serious adverse reactions from TB drugs, Albanna & Menzies; Serious adverse events, Cochrane study; Adverse events leading to discontinuation of treatment, Cochrane study; Patient satisfaction, Albanna & Menzies; Acquisition (or amplification) of drug resistance, Albanna & Menzies.	
Setting:	Albanna & Menzies: Many countries – mostly low- to middle-income countries. Cochrane: adolescents and adults with bacteriologically confirmed TB.	
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Increasing rates of TB drug resistance are a major global health concern. Fixed-dose combination formulations (FDCs) have long been recommended by WHO and may reduce rates of drug resistance by improving adherence and minimizing the risk that a patient may receive an incomplete treatment regimen. However, concerns remain about the efficacy of FDCs, especially regarding the bioavailability of rifampicin.	
Desirable Effects	How substantial are the desirable anticipated effects? ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Desirable anticipated effects:** The GDG decision on the degree of desirable anticipated effects is based on the balance of patient satisfaction and adherence. Patient satisfaction was higher in patients taking the FDCs. Two studies evaluated this outcome although how this evaluation was performed in these studies is not very clear. Patient adherence was slightly lower with FDCs but the difference was not significant and was not considered to be substantial enough to outweigh the effects of patient satisfaction. **Undesirable anticipated effects:** The review of evidence shows no significant difference in benefit or harm between the FDCs and separate drug formulations in terms of treatment failure, death, adherence or acquisition of drug resistance. There were slightly higher rates of acquired drug resistance and relapse among patients taking FDCs, although the differences were not significant. Rates of adverse events were not greater with the FDCs. There is general concern with the studies in this review in that FDCs or single drug formulations were not always used exclusively and uniformly throughout the entire treatment period. This may have caused inconsistencies in the results that may have masked a clear effect of one formulation over another. Regimens that used intermittent dosing were excluded from the analysis.	It is thought that the FDCs may improve patient adherence through reduction in pill burden, and may reduce drug resistance by preventing the patient from taking an incomplete regimen due to patient omission of medications and by reducing prescribing mistakes. However, these benefits were not supported by the data in these reviews. The slightly increased risk of acquired drug resistance may be biologically plausible in that decreased rifampicin bioavailability in FDCs may cause the loss of INH protection, leading to resistance mutations. Potential undesirable effects of FDCs include difficulty in adjusting the regimen in case of adverse events, inability to adjust individual medication dosing, and the risk of poor rifampicin bioavailability. However, FDCs provide programme benefits by making medication ordering easier and reduce the occurrence of stock-outs. FDCs are likely to facilitate more convenient programmatic administration of TB treatment for both patient and provider. The benefit-harm balance of FDCs may change under programme conditions.

<table>
<tr><th></th><th>Judgement</th><th>Research evidence</th><th>Additional considerations</th></tr>
<tr><td>Undesirable Effects</td><td>How substantial are the undesirable anticipated effects?
○ Large
○ Moderate
● Small
○ Trivial

○ Varies
○ Don't know</td><td colspan="2">Summary of findings:
<table>
<tr><th>Outcome</th><th>With separate drug formulations</th><th>With a FDC</th><th>Difference (95% CI)</th><th>Relative effect (RR) (95% CI)</th></tr>
<tr><td>Failure/relapse (per protocol analysis): Albanna & Menzies</td><td>31 per 1000</td><td>40 per 1000(31 to 53)</td><td>11 more per 1000 (from 1 fewer to 21 more)</td><td>RR 1.28 (0.99 to 1.70)</td></tr>
<tr><td>Treatment failure: Cochrane study</td><td>19 per 1000</td><td>24 per 1000 (15 to 37)</td><td>5 more per 1000 (from 3 fewer to 19 more)</td><td>RR 1.28 (0.82 to 2.00)</td></tr>
<tr><td>Relapse: Cochrane study</td><td>55 per 1000</td><td>71 per 1000 (55 to 91)</td><td>16 more per 1000 (from 0 fewer to 36 more)</td><td>RR 1.28 (1.00 to 1.64)</td></tr>
<tr><td>Death: Cochrane study</td><td>25 per 1000</td><td>24 per 1000 (17 to 34)</td><td>1 fewer per 1000 (from 8 fewer to 10 more)</td><td>RR 0.96 (0.67 to 1.39)</td></tr>
<tr><td>Acquisition (or amplification) of drug resistance: Albanna & Menzies</td><td>1 per 1000</td><td>1 per 1000 (0 to 4)</td><td>2 more per 1000 (from 1 fewer to 5 more)</td><td>RR 1.6 (0.5 to 5.4)</td></tr>
</table></td><td></td></tr>
<tr><td>Certainty of evidence</td><td>What is the overall certainty of the evidence of effects?
○ Very low
● Low
○ Moderate
○ High

○ No included studies</td><td>Overall, the quality of the evidence for the critical outcomes ranged from low to moderate, with most being of moderate quality.</td><td>The bioavailability of the drug formulations in FDCs were an ongoing concern. Studies in these reviews did not evaluate bioavailability of drugs in FDCs. However, previous studies did not indicate that the formulations used in these reviews had significant bioavailability issues. Additionally, when individual studies within the reviews were examined, there was no improvement in outcomes over time. Presumably formulations would have improved over time, so no improvement with better formulations indicates that the lack of superior treatment outcomes seen with the FDCs were not due to older, poorer formulations masking the effect of newer, better formulations. However, no pharmacokinetic (PK) studies were done, and it is known that the bioavailability of drugs, especially rifampin, in FDCs has historically been a concern. The bioavailability of FDCs versus single drug formulations remains unclear and controversial.

Programmes that receive drugs from quality-assured sources may not have as many complicating bioavailability issues.</td></tr>
<tr><td>Values</td><td>Is there important uncertainty about, or variability in, the extent to which people value the main outcomes?
○ Important uncertainty or variability
○ Possibly important uncertainty or variability
● Probably no important uncertainty or variability
○ No important uncertainty or variability</td><td></td><td></td></tr>
<tr><td>Balance of effects</td><td>Does the balance between desirable and undesirable effects favour the intervention or the comparison?
○ Favours the comparison
○ Probably favours the comparison
● Does not favour either the intervention or the comparison
○ Probably favours the intervention
○ Favours the intervention

○ Varies
○ Don't know</td><td>Justification of judgement: the GDG felt that the increase in patient satisfaction counterbalances the potential for relapse and adverse reactions.</td><td>Concerns with applying this review's evidence to current treatment circumstances are:

Many studies were done before the widespread use of HIV antiretroviral medications.

Many of the studies required the subjects to be AFB smear-positive, which could have limited the inclusion of HIV-positive persons.

The bioavailability of the component medications of the FDCs used in the studies is unclear.

Patients' comorbidities were not analysed.</td></tr>
</table>

	Judgement	Research evidence	Additional considerations
Resources required	How large are the resource requirements (costs)? ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence was identified.	
Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)? ○ Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Cost effectiveness	Does the cost-effectiveness of the intervention favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ No included studies	No research evidence was identified.	
Equity	What would be the impact on health equity? ○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	FDCs would be likely to lead to a reduction in stock-outs of TB medications, leading to increased health equity.
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	If NTPs are encouraged to use a new formulation, this may disrupt current manufacturing, production and TB drug dissemination chains. There is already wide experience with FDC use throughout the world.
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know	
Certainty of evidence	Very low	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies	
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should a fixed-dose combination, versus separate drug formulations, be used for patients with active drug-susceptible TB disease?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ●	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
Recommendation	The GDG suggests the use of FDCs or separate drug formulations in patients with drug-susceptible TB (conditional recommendation, low certainty in the evidence).				
Justification	Ascertaining the risks and benefits of FDCs versus separate formulations was complex, causing the GDG to be unable to recommend one over the other. Patient satisfaction was higher in patients taking FDCs but only two studies in the systematic review evaluated this and the method of evaluation was not clear. There was no inferiority with the FDCs compared with separate dose formulations in terms of treatment failure, death, adherence or acquisition of drug resistance. Separate formulations performed better on the basis of point estimates but these differences were not considered to be substantial by the GDG. The Cochrane review showed there may be a slightly higher risk of relapse among patients taking FDCs. Rates of adverse events were not greater with the FDCs. In general, it is thought that FDCs may improve patient adherence through reduction in pill burden and reduction in drug resistance by preventing the patient from taking an incomplete regimen due to patient omission of medications and by reducing prescribing mistakes. However, such benefits were not supported by the data in these reviews. The slightly increased risk of acquired drug resistance may be biologically plausible in that decreased rifampicin bioavailability in FDCs causes the loss of INH protection, leading to resistance mutations. The bioavailability of the drug formulations in the FDCs were an ongoing concern. Studies in these reviews did not evaluate bioavailability of drugs in FDCs, but previous studies did not indicate that the formulations used in these reviews had significant bioavailability issues. Additionally, when individual studies within the review were examined, there was no improvement in outcomes over time. Presumably formulations would have improved over time, so no temporal improvement suggests that the lack of better treatment outcomes seen with FDCs was not due to older, poorer formulations masking the effect of newer, better formulations. However, no PK studies were done, and it is known that the bioavailability of drugs, especially rifampin, in FDCs has historically been a concern. NTPs that receive drugs from quality-assured sources may not have as many complicating bioavailability issues. The bioavailability of FDCs versus separate dose formulations remains unclear and controversial. There is general concern about the systematic reviews presented to the GDG, in that FDCs or single-dose formulations were not always used exclusively and uniformly throughout the entire treatment period. This may have caused inconsistency in the results that may have masked a clear effect of one formulation over another. Regimens that used intermittent dosing were excluded from the analysis. Additional concerns with applying this review's evidence to current treatment circumstances are that many studies were done before the widespread use of HIV antiretroviral medications, many of the studies required the subjects to be AFB smear-positive, which could have limited the inclusion of HIV-positive persons, and patient comorbidities were not analysed. Potential undesirable effects of FDCs that were not included in the systematic review but that could impact their programmatic use include the difficulty in removing the offending drug in the case of adverse events and the inability to adjust individual medication dosing. However, FDCs may provide programme benefits by making medication ordering easier, reducing the occurrence of stock-outs, facilitating drug delivery and prescription preparation, reducing the need for additional health-care staff training on dosing and dispensing of medications, and contributing to a lower pill burden. It is likely that the true benefit-harm balance of the FDCs may change under programme conditions. In summary, the GDG believes that there is no clear advantage of FDCs over separate drug formulations or vice versa except with respect to greater patient satisfaction with FDCs and a reduced risk of relapse with separate dose formulations. The GDG felt that the increase in patient satisfaction counterbalances the small potential increase in relapse and other programmatic benefits of FDCs supporting the choice of FDCs over the separate dose formulations.				
Subgroup considerations	The reduced pill burden afforded by FDCs may be especially valuable in patients with comorbidities (notably HIV infection) and for pediatric patients (who may have particular difficulty in swallowing large amounts of medications). Patients with a specific medical condition such as intolerance for a specific TB drug, liver or renal malfunction may not benefit from an FDC, as they are more likely to require individual medication dose adjustment which can be done with separate formulations only.				
Implementation considerations	The inability to state clear guidelines for the preferred use of FDCs or separate drug formulations may confuse programmes concerning which drugs to purchase. This may affect drug manufacturing, production and supply chains. NTPs are encouraged to make decisions about which formulations to use on the basis of market availability, their treatment results and experience. However, whichever treatment regimen is chosen (particularly with the FDCs), the quality of drugs must be assured.				
Monitoring and evaluation					
Research priorities	Additional qualitative research could show the reasons why FDC formulations did not show a clear benefit. Therefore, suggested areas for research are: pharmacokinetic studies of the bioavailability of FDC versus separate drug formulation regimens; better development of weight banding categories for drug dosing (children and other special populations, particularly people living with HIV, would benefit the most from this); additional qualitative studies detailing medication adherence; additional work on FDC formulations to further decrease pill burden, especially among patients with co-morbidities.				

PICO 3

Question

Should daily dosing throughout treatment versus thrice-weekly dosing throughout treatment be used for treatment of drug-susceptible pulmonary tuberculosis?		
Population:	Patients with drug-susceptible pulmonary tuberculosis	Background:
Intervention:	Daily dosing throughout treatment	
Comparison:	Thrice-weekly dosing throughout treatment	
Main outcomes:	Risk of failure in drug-susceptible disease; Risk of relapse in drug-susceptible disease; Risk of acquired drug resistance in drug-susceptible disease; Risk of failure in drug-susceptible disease or susceptibility unknown; Risk of relapse in drug-susceptible disease or susceptibility unknown; Risk of acquired drug resistance in drug-susceptible disease or susceptibility unknown.	
Setting:	Numerous countries, mainly low- and middle-income.	
Perspective:		

Assessment

<table>
<tr><th></th><th>Judgement</th><th>Research evidence</th><th>Additional considerations</th></tr>
<tr><td>Problem</td><td>Is the problem a priority?
○ No
○ Probably no
○ Probably yes
● Yes

○ Varies
○ Don't know</td><td>Intermittent dosing of tuberculosis medications (either throughout treatment or in the continuation phase only) may have the ability to improve treatment adherence. However, there are risks with intermittent dosing of poor treatment outcomes and the development of drug resistance.</td><td></td></tr>
<tr><td>Desirable Effects</td><td>How substantial are the desirable anticipated effects?
● Trivial
○ Small
○ Moderate
○ Large

○ Varies
○ Don't know</td><td>This review included pulmonary TB only. When thrice-weekly dosing throughout treatment was compared to daily dosing throughout, there were higher rates of treatment failure, relapse and acquired drug resistance both in drug-sensitive disease and when the strain sensitivity was unknown.
Adherence was not addressed adequately enough in the reviewed studies to be included as an outcome. However, in most studies included in the review, intermittent dosing used DOT while the use of DOT during daily dosing was variable.
Summary of findings:
<table>
<tr><th>Outcome</th><th>With daily dosing throughout treatment</th><th>With thrice weekly dosing throughout treatment</th><th>Difference (95% CI)</th><th>Relative effect (RR) (95% CI)</th></tr>
<tr><td>Risk of failure in drug-susceptible disease</td><td>10 per 1000</td><td>27 per 1000 (3 to 221)</td><td>17 more per 1000 (from 7 fewer to 211 more)</td><td>RR 2.6 (0.3 to 21.2)</td></tr>
<tr><td>Risk of relapse in drug-susceptible disease</td><td>30 per 1000</td><td>63 per 1000 (33 to 120)</td><td>33 more per 1000 (from 3 more to 90 more)</td><td>RR 2.1 (1.1 to 4.0)</td></tr>
<tr><td>Risk of acquired drug resistance in drug-susceptible disease</td><td>2 per 1000</td><td>23 per 1000 (5 to 109)</td><td>21 more per 1000 (from 3 more to 107 more)</td><td>RR 10.0 (2.1 to 46.7)</td></tr>
<tr><td>Risk of failure in drug-susceptible disease or susceptibility unknown</td><td>14 per 1000</td><td>50 per 1000 (16 to 172)</td><td>37 more per 1000 (from 3 more to 158 more)</td><td>RR 3.7 (1.2 to 12.6)</td></tr>
<tr><td>Risk of relapse in drug-susceptible disease or susceptibility unknown</td><td>34 per 1000</td><td>75 per 1000 (41 to 136)</td><td>41 more per 1000 (from 7 more to 102 more)</td><td>RR 2.2 (1.2 to 4.0)</td></tr>
<tr><td>Risk of acquired drug resistance in drug-susceptible disease or susceptibility unknown</td><td>2 per 1000</td><td>23 per 1000 (5 to 109)</td><td>21 more per 1000 (from 3 more to 107 more)</td><td>RR 10.0 (2.1 to 46.7)</td></tr>
</table></td><td>Possible anticipated benefits are less of a burden on the health-care system due to reduced need for DOT.</td></tr>
</table>

	Judgement	Research evidence	Additional considerations
Undesirable Effects	How substantial are the undesirable anticipated effects? ● Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know		
Certainty of evidence	What is the overall certainty of the evidence of effects? ● Very low ○ Low ○ Moderate ○ High ○ No included studies		
Values	Is there important uncertainty about, or variability in, the extent to which people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	The main outcomes assessed (treatment failure, treatment relapse and acquired drug resistance) would probably be of importance to all patients.	
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	Daily dosing is favoured.	
Resources required	How large are the resource requirements (costs)? ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence was identified.	
Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)? ○ Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Cost effectiveness	Does the cost-effectiveness of the intervention favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ No included studies	No research evidence was identified.	

	Judgement	Research evidence	Additional considerations
Equity	What would be the impact on health equity? ○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	Health equity would be increased with daily dosing and it would be reduced with dosing three times weekly. Certain populations would have inferior treatment for tuberculosis if intermittent dosing was used in the intensive phase. The problems created by intermittent dosing include requirements for different drug manufacturing and packaging and a reduced drug supply buffer, leading to an increased risk of TB medication stock-outs.	
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Daily treatment (the intervention) is acceptable to stakeholders. Thrice-weekly dosing is not acceptable to stakeholders, chiefly because of the concerns about equity outlined above. It is acknowledged that large countries, particularly India, use intermittent dosing frequently. However, the practice varies widely throughout India between daily and intermittent dosing. Given the findings in this review, all countries should be encouraged to use exclusively daily dosing in the intensive phase.	
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Daily treatment is believed to be feasible. However, there were no representatives from India (the largest user of thrice-weekly treatment) present on the GDG.	

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know	
Certainty of evidence	Very low	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies	
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should daily dosing throughout treatment versus thrice-weekly dosing throughout treatment be used for treatment of drug-susceptible pulmonary tuberculosis?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ●	Strong recommendation for the intervention ○
Recommendation	Recommendation 3a: The GDG suggests the use of daily dosing rather than three times weekly dosing in the intensive phase of treatment for drug-susceptible pulmonary tuberculosis in all patients (conditional recommendation, very low certainty in the evidence).				
Justification	There was hope that intermittent dosing of tuberculosis medications may have the ability to improve treatment adherence and to be less of a burden on the health-care system because of the reduced need for DOT. However, when thrice-weekly dosing throughout treatment is compared to daily dosing throughout treatment, there is a higher risk of treatment failure, relapse and acquired drug resistance in both drug-sensitive disease and when the strain sensitivity was unknown. This review included pulmonary TB only. Adherence was not addressed adequately enough in the reviewed studies for it to be included as an outcome. However, in most studies included in the review, intermittent dosing used DOT while the use of DOT during daily dosing was variable. The GDG also felt that health equity would be increased with daily dosing and would be reduced with three times weekly dosing. Certain populations would have inferior treatment for tuberculosis if intermittent dosing was used in the intensive phase. The problems created by intermittent dosing include requirements for different drug manufacturing and packaging and a reduced drug supply buffer, leading to an increased risk of TB medication stock-outs. Given the findings in this review, all countries are encouraged to use exclusively daily dosing in the intensive phase of treatment.				
Subgroup considerations	These recommendations apply to HIV-negative people as well as people living with HIV. The data used in this review was based on pulmonary TB patients. Children were not considered specifically in this review. However, there is no biologically plausible reason why these recommendations should not apply to children as well as adults. It is recommended that all children receive daily dosing of TB medications during the intensive phase of treatment, for the same reason as adults. See the 2014 WHO guideline Guidance for National Tuberculosis Programmes on the management of tuberculosis in children for recommendations on the daily dosing of children with drug-susceptible tuberculosis.				
Implementation considerations	There are no new implementation considerations because the recommended treatment is already widespread practice. India is the main exception since intermittent dosing is widespread in that country. These recommendations to use exclusively daily dosing in the intermittent phase of TB treatment will therefore probably have implications in India for drug procurement, practitioner training, change of programme practice and patient support.				
Monitoring and evaluation	There are no new monitoring or evaluation recommendations, as the standard of care (daily dosing of medications during the intensive phase of treatment) is being recommended.				
Research priorities	It may be appropriate to analyse the utility of 5 days of treatment per weeks versus 7 days of treatment in the intensive phase of treatment (i.e. sparing weekend dosing). Suggested areas for research are: research into the optimal duration of the intensive phase of treatment; outcomes of DOT versus self-administered treatment.				

PICO 4.1

Question

Should daily dosing during the intensive phase followed by thrice-weekly dosing during the continuation phase versus daily dosing throughout TB treatment be used for treatment of drug-susceptible pulmonary tuberculosis?

Population:	Patients with drug-susceptible pulmonary tuberculosis	Background:
Intervention:	Daily dosing during the intensive phase followed by thrice-weekly dosing during the continuation phase	
Comparison:	Daily dosing throughout TB treatment	
Main outcomes:	Risk of failure in drug-susceptible disease; Risk of relapse in drug-susceptible disease; Risk of acquired drug resistance in drug-susceptible disease; Risk of failure in drug-susceptible disease or susceptibility unknown; Risk of relapse in drug-susceptible disease or susceptibility unknown; Risk of acquired drug resistance in drug-susceptible disease or susceptibility unknown.	
Setting:	Numerous countries, mostly low- and middle income.	
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Intermittent dosing of tuberculosis medications (either throughout treatment or in the continuation phase only) may improve treatment adherence. However, there is a risk with intermittent dosing of poor treatment outcomes and the development of drug resistance.	
Desirable Effects	How substantial are the desirable anticipated effects? ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	This review included pulmonary TB only. When thrice-weekly dosing during the continuation phase only was compared to daily dosing throughout, there were higher rates of treatment failure and relapse in the patients that received thrice-weekly treatment during the continuation phase. Rates of acquired drug resistance did not differ. However, it was felt that, since the confidence intervals were very wide, the difference between the two treatments were not as substantial as when intermittent dosing during the intensive phase of treatment was examined (PICO 3).	
Undesirable Effects	How substantial are the undesirable anticipated effects? ○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	**Summary of findings:**	Treatment must be closely supervised if treatment with intermittent dosing is considered.

Outcome	With daily dosing throughout TB treatment	With daily dosing during the intensive phase followed by thrice-weekly dosing during the continuation phase	Difference (95% CI)	Relative effect (RR) (95% CI)
Risk of failure in drug-susceptible disease	10 per 1000	40 per 1000 (5 to 315)	29 more per 1000 (from 5 fewer to 304 more)	RR 3.8 (0.5 to 30.2)
Risk of relapse in drug-susceptible disease	30 per 1000	39 per 1000 (18 to 87)	9 more per 1000 (from 12 fewer to 57 more)	RR 1.3 (0.6 to 2.9)
Risk of acquired drug resistance in drug-susceptible disease	2 per 1000	1 per 1000 (0 to 13)	1 fewer per 1000 (from 2 fewer to 11 more)	RR 0.6 (0.1 to 5.7)
Risk of failure in drug-susceptible disease or susceptibility unknown	14 per 1000	20 per 1000 (5 to 74)	7 more per 1000 (from 8 fewer to 60 more)	RR 1.5 (0.4 to 5.4)
Risk of relapse in drug-susceptible disease or susceptibility unknown	34 per 1000	41 per 1000 (20 to 78)	7 more per 1000 (from 14 fewer to 44 more)	RR 1.2 (0.6 to 2.3)
Risk of acquired drug resistance in drug-susceptible disease or susceptibility unknown	2 per 1000	1 per 1000 (0 to 13)	1 fewer per 1000 (from 2 fewer to 11 more)	RR 0.6 (0.1 to 5.7)

	Judgement	Research evidence	Additional considerations
Certainty of evidence	What is the overall certainty of the evidence of effects? ● Very low ○ Low ○ Moderate ○ High ○ No included studies		
Values	Is there important uncertainty about, or variability in, the extent to which people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	The main outcomes assessed (treatment failure, treatment relapse and acquired drug resistance) would probably be of importance to all patients.	
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	Daily dosing is probably favoured.	
Resources required	How large are the resource requirements (costs)? ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence was identified.	
Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)? ○ Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Cost-effectiveness	Does the cost-effectiveness of the intervention favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ No included studies	No research evidence was identified.	
Equity	What would be the impact on health equity? ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Health equity would be increased with daily dosing and would be reduced with dosing three times weekly. Certain populations would have inferior treatment for tuberculosis if intermittent dosing in the continuation phase was used. The problems created by intermittent dosing include requirements for different drug manufacturing and packaging and a reduced drug supply buffer, leading to an increased risk of TB medication stock-outs.	

	Judgement	Research evidence	Additional considerations
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Daily treatment (the intervention) is acceptable to stakeholders. Three times weekly dosing during the continuation phase is not acceptable to stakeholders, chiefly because of the issues of equity outlined above. It is acknowledged that large countries, particularly India, use intermittent dosing frequently. However, practice varies widely throughout India between daily dosing and intermittent dosing. If intermittent dosing is considered, DOT must be done.	
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Daily treatment is believed to be feasible. However, there were no representatives from India (the largest user of thrice-weekly treatment) present on the GDG.	

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know	
Certainty of evidence	Very low	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies	
Cost- effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should daily dosing during the intensive phase followed by thrice-weekly dosing during the continuation phase versus daily dosing throughout TB treatment be used for treatment of drug-susceptible pulmonary tuberculosis?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ●	Strong recommendation for the intervention ○
Recommendation	The GDG suggests the use of daily dosing over twice-weekly or thrice-weekly dosing in the continuation phase of treatment for drug-susceptible pulmonary tuberculosis (conditional recommendation, very low certainty in the evidence).				
Justification	There was hope that intermittent dosing of tuberculosis medications may improve treatment adherence and may be less of a burden on the health-care system due to the reduced need for DOT. However, when thrice-weekly dosing in the continuation phase of treatment is compared to daily dosing throughout treatment, there is a higher risk of treatment failure and relapse. If thrice-weekly dosing during the continuation phase is used, then DOT must be adhered to. This review included pulmonary TB only. Adherence was not addressed adequately enough in the reviewed studies to be included as an outcome. However, in most studies included in the review, intermittent dosing used DOT while the use of DOT during daily dosing was variable. The GDG also felt that health equity would be increased with daily dosing and would be reduced with three times weekly dosing. Certain populations would have inferior treatment for tuberculosis if intermittent dosing in the intensive phase were to be used. The problems created by intermittent dosing include requirements for different drug manufacturing and packaging and a reduced drug supply buffer, leading to an increased risk of TB medication stock-outs. Given the findings in this review, all countries are encouraged to use daily dosing in the continuation phase of treatment.				
Subgroup considerations	No additional considerations beyond those outlined in PICO 3.				
Implementation considerations	No additional considerations beyond those outlined in PICO 3.				
Monitoring and evaluation	If thrice-weekly dosing during the continuation phase of treatment is used, then DOT must be adhered to.				
Research priorities	Additional research may show a benefit for thrice-weekly dosing in the continuation phase, as effect differences seen in this review between thrice-weekly dosing in the continuation phase and daily dosing during the continuation phase are small.				

PICO 4.2

Question

Should daily dosing throughout TB treatment versus daily dosing in the intensive phase followed by twice-weekly dosing in the continuation phase of TB treatment be used for treatment of drug-susceptible pulmonary tuberculosis?

Population:	Patients with drug-susceptible pulmonary tuberculosis	Background:
Intervention:	Daily dosing throughout TB treatment	
Comparison:	Daily dosing in the intensive phase followed by twice-weekly dosing in the continuation phase of TB treatment	
Main outcomes:	Risk of failure in drug-susceptible disease: Johnston; Risk of relapse in drug-susceptible disease, Johnston; Risk of acquired drug resistance in drug-susceptible disease, Johnston; Risk of failure in drug-susceptible disease or susceptibility unknown, Johnston; Risk of Relapse in drug-susceptible disease or susceptibility unknown, Johnston; Risk of acquired drug resistance in drug-susceptible disease or susceptibility unknown, Johnston.	
Setting:	Numerous countries, mostly LMIC.	
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Intermittent dosing of tuberculosis medications (either throughout treatment or in the continuation phase only) may improve treatment adherence. However, there is the risk with intermittent dosing of poor treatment outcomes and the development of drug resistance.	
Desirable Effects	How substantial are the desirable anticipated effects? ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Twice-weekly dosing in the continuation phase, versus daily dosing throughout, showed an increase risk of treatment failure and relapse. Acquired drug resistance did not differ. The rest of the findings regarding twice-weekly dosing in the continuation phase are the same as stated in the discussion surrounding thrice-weekly dosing in the continuation phase.	
Undesirable Effects	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	**Summary of findings:**	

Outcome	With daily dosing throughout TB treatment	With daily dosing in the intensive phase followed by twice weekly dosing in the continuation phase of TB treatment	Difference (95% CI)	Relative effect (RR) (95% CI)
Risk of failure in drug-susceptible disease (Johnston)	10 per 1000	41 per 1000 (5 to 179)	30 more per 1000 (from 5 fewer to 169 more)	RR 3.9 (0.5 to 17.2)
Risk of relapse in drug-susceptible disease (Johnston)	30 per 1000	51 per 1000(27 to 102)	21 more per 1000 (from 3 fewer to 72 more)	RR 1.7 (0.9 to 3.4)
Risk of acquired drug resistance in drug-susceptible disease (Johnston)	2 per 1000	2 per 1000 (0 to 12)	0 fewer per 1000 (from 2 fewer to 9 more)	RR 1.0 (0.2 to 5.0)
Risk of failure in drug-susceptible disease or susceptibility unknown (Johnston)	14 per 1000	41 per 1000 (14 to 120)	27 more per 1000 (from 0 fewer to 106 more)	RR 3.0 (1.0 to 8.8)
Risk of relapse in drug-susceptible disease or susceptibility unknown (Johnston)	34 per 1000	61 per 1000 (34 to 112)	27 more per 1000 (from 0 fewer to 78 more)	RR 1.8 (1.0 to 3.3)
Risk of acquired drug resistance in drug-susceptible disease or susceptibility unknown (Johnston)	2 per 1000	2 per 1000 (0 to 12)	0 fewer per 1000 (from 2 fewer to 9 more)	RR 1.0 (0.2 to 5.0)

	Judgement	Research evidence	Additional considerations
Certainty of evidence	What is the overall certainty of the evidence of effects? ○ Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Values	Is there important uncertainty about, or variability in, the extent to which people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence was identified.	
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	No research evidence was identified.	
Resources required	How large are the resource requirements (costs)? ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence was identified.	
Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)? ○ Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Cost-effectiveness	Does the cost-effectiveness of the intervention favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ No included studies	No research evidence was identified.	

	Judgement	Research evidence	Additional considerations
Equity	What would be the impact on health equity? ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	

Summary of judgments

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know	
Certainty of evidence	Very low	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies	
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should daily dosing throughout TB treatment versus daily dosing in the intensive phase followed by twice-weekly dosing in the continuation phase of TB treatment be used for treatment of drug-susceptible pulmonary tuberculosis?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ●	Strong recommendation for the intervention ○
Recommendation	The GDG suggests the use of daily dosing over twice-weekly or thrice-weekly dosing in the continuation phase of treatment for drug-susceptible pulmonary tuberculosis (conditional recommendation, very low certainty in the evidence).				
Justification					
Subgroup considerations					
Implementation considerations					
Monitoring and evaluation					
Research priorities					

PICO 5

Question

Should antiretrovirals started during TB treatment versus antiretrovirals started at the end of TB treatment be used for tuberculosis patients co-infected with HIV?		
Population:	Tuberculosis patients co-infected with HIV	Background:
Intervention:	Antiretrovirals started during TB treatment	
Comparison:	Antiretrovirals started at the end of TB treatment	
Main outcomes:	Adherence versus non-adherence to treatment; Successful treatment outcome (cure/completed treatment) versus failure/relapse/death; No severe adverse reactions from TB drugs versus severe drug reaction; No substantial cost versus substantial cost to patient; No substantial cost versus substantial cost to health-care system; Acquisition (or amplification) of drug resistance; Reduction of hospital stay; Reduction of clinical complications.	
Setting:		
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	
Desirable Effects	How substantial are the desirable anticipated effects? ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	No research evidence was identified.	
Undesirable Effects	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know		
Certainty of evidence	What is the overall certainty of the evidence of effects? ○ Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Values	Is there important uncertainty about, or variability in, the extent to which people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence was identified.	
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	No research evidence was identified.	

	Judgement	Research evidence	Additional considerations
Resources required	How large are the resource requirements (costs)? ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence was identified.	
Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)? ○ Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Cost-effectiveness	Does the cost-effectiveness of the intervention favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ No included studies	No research evidence was identified.	
Equity	What would be the impact on health equity? ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know	
Certainty of evidence	Very low	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies	
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should antiretrovirals started during TB treatment versus antiretrovirals started at the end of TB treatment be used for tuberculosis patients co-infected with HIV?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ●
Recommendation	HIV antiretroviral medications should be started in all TB patients living with HIV regardless of their CD4 count (strong recommendation, high quality of evidence). TB treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment (strong recommendation, high quality of evidence). HIV-positive patients with profound immunosuppression (e.g. CD4 counts less than 50 cells/mm3) should receive ART within the first 2 weeks of initiating TB treatment. From: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infections (WHO, 2016).				
Justification					
Subgroup considerations					
Implementation considerations					
Monitoring and evaluation					
Research priorities					

PICO 6

Question

Should a treatment period greater than 8 months versus a treatment period of 6 months be used for patients with pulmonary drug-susceptible tuberculosis co-infected with HIV?

Population:	Patients with pulmonary drug-susceptible tuberculosis co-infected with HIV	Background:
Intervention:	A treatment period greater than 8 months	
Comparison:	A treatment period of 6 months	
Main outcomes:	Failure, relapse, death	
Setting:	From a systematic review of randomized trials plus controlled observational studies (i.e. retrospective or prospective cohort studies).	
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	People co-infected with HIV and TB have greater risks of relapse and mortality. A systematic review and meta-analysis (Khan FA et al., CID 2010) found a trend towards higher rates of relapse if rifampicin were used for only 6 months (compared to a period greater than or equal to 8 months) or if ART was not used. However, in the face of WHO recommendations that all people with TB should also be treated with ART, the question of the duration of TB treatment needs to be revisited.	
Desirable Effects	How substantial are the desirable anticipated effects? ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Many of the studies included in this review were conducted before the HIV antiretroviral medications became available. During the review, the data were also broken down in a subgroup analysis comparing persons who were treated with ART and those who were not. When people who were not on HIV antiretrovirals were examined, relapse rates were significantly higher among persons who received treatment with regimens that contained 6 months of rifampicin, as opposed to those who received a treatment regimen greater than or equal to 8 months of rifampicin. However, when people received at least some treatment with ART, these differences disappeared. Rates of failure and death did not differ between people treated with 6 months of rifampicin versus those treated with rifampicin for a period greater than or equal to 8 months. This was true whether or not patients were on ART. However, it is unclear from these data whether the observed cases were true relapse as opposed to reinfection. Possible undesirable effects include: The extension of treatment to 8 months from 6 months has the additional burden of 2 months more of medication Patients may face increased stigma if they are on the longer treatment and others find out that the longer duration of TB treatment is the regimen for people living with HIV (PLWH). There is a greater risk of drug-drug interactions with a longer treatment regimen.	In the studies analysed for these guidelines, the patients not on ART were driving the relapse rates.
Undesirable Effects	How substantial are the undesirable anticipated effects? ○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	**Summary of findings:** Failure: 44 per 1000 vs 35 per 1000 (18 to 66); Difference: 9 fewer per 1000 (from 22 more to 26 fewer); Relative effect (RR) (95% CI): RR 0.8 (0.4 to 1.5) Relapse: 68 per 1000 vs 164 per 1000 (82 to 341); Difference: 96 more per 1000 (from 14 more to 273 more); Relative effect (RR) (95% CI): RR 2.4 (1.2 to 5.0) Death: 140 per 1000 vs 126 per 1000 (70 to 224); Difference: 14 fewer per 1000 (from 70 fewer to 84 more); Relative effect (RR) (95% CI): RR 0.9 (0.5 to 1.6)	
Certainty of evidence	What is the overall certainty of the evidence of effects? ● Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	

	Judgement	Research evidence	Additional considerations
Values	Is there important uncertainty about, or variability in, the extent to which people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence was identified.	
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? ○ Favours the comparison ● Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	No research evidence was identified.	
Resources required	How large are the resource requirements (costs)? ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence was identified.	
Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)? ○ Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Cost-effectiveness	Does the cost-effectiveness of the intervention favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ No included studies	No research evidence was identified.	
Equity	What would be the impact on health equity? ○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	

	Judgement	Research evidence	Additional considerations
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know	
Certainty of evidence	Very low	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies	
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should a treatment period greater than 8 months versus a treatment period of 6 months be used for patients with pulmonary drug-susceptible tuberculosis co-infected with HIV?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ●	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
Recommendation	The GDG suggests that patients with drug-susceptible pulmonary TB who are living with HIV should receive 6 months of treatment rather than extended treatment of 8 months or more (conditional recommendation/very low quality of evidence).				
Justification	All people living with HIV, especially those with TB, should be receiving ART. Therefore, PLWH co-infected with drug-susceptible TB should only require 6 months of rifampicin-containing TB treatment (see PICO 6 and the WHO publications The use of antiretroviral drugs for treating and preventing HIV infection [2016] and WHO policy on collaborative TB/HIV activities: guidelines for National Programmes and other stakeholders [2012]). However, conditions may justify deviating from this recommendation (i.e. extending treatment). Such conditions include situations when people fail to receive ART, or when people have severe TB disease, very low CD4 counts or other immunocompromising conditions. While PLWH should ideally always be on ART, in reality people do not receive ART for a variety of reasons. Adverse consequences of an extended period of TB treatment include the burden of an additional 2 months of medications and the increased risk of drug-drug interactions with prolonged treatment. When the subgroup of people who were not being treated with HIV antiretrovirals was examined, relapse rates were significantly higher among persons who received treatment with regimens that contained 6 months of rifampicin, as opposed to those who received greater than or equal to 8 months of treatment with rifampicin. When people received at least some treatment with ART, these differences disappeared. Rates of failure and death did not differ between people treated with 6 months of rifampicin versus greater than or equal to 8 months of rifampicin. This held true whether or not they were on ART. It should be noted that it is unclear from these data whether the observed cases were true relapse – as opposed to reinfection – and many of these studies (and the evidence for prolonging TB treatment) were conducted before the availability of HIV antiretroviral medications. Possible undesirable effects of an extended duration of TB treatment include the additional burden of 2 months more of medications and a greater risk of drug-drug interactions.				
Subgroup considerations					
Implementation considerations					
Monitoring and evaluation					
Research priorities	Suggested areas for research are: the factors that may cause people, especially PLWH, not to respond well to TB treatment (i.e. starting ART late, low CD4 counts, etc.); exploration and description of etiological factors leading to higher death rates and rates of adverse events in HIV/TB co-infected persons.				

PICO 7

Question

Should adjuvent corticosteroids versus TB treatment without corticosteroids be used for tuberculous pericarditis?		
Population:	Patients with tuberculous pericarditis	Background:
Intervention:	Treatment with adjuvent corticosteroids	
Comparison:	TB treatment without corticosteroids	
Main outcomes:	Death; Treatment adherence; Constrictive pericarditis.	
Setting:		
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	There is controversy concerning the effectiveness of adjunctive corticosteroids in reducing mortality in tuberculous pericarditis.	
Desirable Effects	How substantial are the desirable anticipated effects? ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Review of the data showed a benefit to steroid treatment with regard to death, constrictive pericarditis and treatment adherence. However, when the studies were considered individually, the largest (1400 patients) and most recent study – i.e. the IMPI study (Mayosi BM et al. Prednisolone and Mycobacterium indicus pranii in tuberculous pericarditis. N Engl J Med. 2014) – showed no benefit to steroids. However, HIV infection complicates these findings. In the IMPI study, 67% of subjects were HIV-positive and only 14% were on ART. In another smaller study of 58 subjects, in which all were HIV-positive, steroids reduced mortality (two other studies took place before the HIV era and one study had half of their subjects infected with HIV, but mortality was not analysed, although the other outcomes were). These immunosuppressed patients may have had a different benefit from steroids when compared to HIV-negative persons or people living with HIV(PLWH) who are on ART. In the IMPI study, there was a supplemental analysis of only the HIV-negative patients, and a small mortality benefit was shown with steroid treatment. Several other issues were raised regarding the analysis. A random-effects model was used in this analysis, which led to an unexpected finding that the relative risk of death was lower in the steroid treatment arm, despite the fact that similar numbers and proportions of patients in both the steroid and placebo arms had this outcome. When a fixed-effects model was applied, the difference in mortality tended to disappear. However, upon extensive discussion it was determined that the random-effects model was the most appropriate model to use, and so the findings stand. There was also a concern that publication bias may play a role in these results. Most of the studies were published in 2000 and before, so there was probably more of a publication bias at that time towards studies with positive findings. The undesirable effects were dictated by the increased rates of cancer in the steroid-treated group. These cancers were seen in the IMPI study, and were almost all HIV-related cancers (particularly Karposi sarcoma). Concerns still also exists in that the cancer findings in the IMPI study were also complicated by the fact that many patients who received steroids were also treated with immunotherapy (M. indicus pranii), the effects of which are unknown. Adjuvent corticosteroids compared to TB treatment without corticosteroids for tuberculous pericarditis	However, selective use of glucocorticoids in patients who are at the highest risk for inflammatory complications might be appropriate. Such patients might include those with large pericardial effusions, those with high levels of inflammatory cells or markers in pericardial fluid, or those with early signs of constriction (ATS guidelines, 2016).
Undesirable Effects	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know		

Outcomes	No of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with TB treatment without corticosteroids	Risk difference with adjuvent corticosteroids
Death	1779 (5 RCTs)	(⊕⊕◯◯) LOW 1,2	RR 0.54 (0.23 to 1.26)	161 per 1000	74 fewer per 1000 (124 fewer to 42 more)
Treatment adherence	1795 (2 RCTs)	(⊕◯◯◯) VERY LOW 1,3	RR 0.91 (0.75 to 1.12)	865 per 1000	78 fewer per 1000 (216 fewer to 104 more)
Constrictive pericarditis	1515 (3 RCTs)	(⊕⊕◯◯) LOW 2	RR 0.72 (0.32 to 1.58)	75 per 1000	21 fewer per 1000 (51 fewer to 43 more)

	Judgement	Research evidence	Additional considerations
Certainty of evidence	What is the overall certainty of the evidence of effects? ● Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Values	Is there important uncertainty about, or variability in, the extent to which people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	No research evidence was identified.	
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	No research evidence was identified.	
Resources required	How large are the resource requirements (costs)? ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence was identified.	
Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)? ○ Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Cost-effectiveness	Does the cost-effectiveness of the intervention favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ No included studies	No research evidence was identified.	

	Judgement	Research evidence	Additional considerations
Equity	What would be the impact on health equity? ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		Dexamethasone may not be available in some settings due to its IV requirements. If an oral steroid formulation is not available in these cases, this would lead to inequity.
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know	
Certainty of evidence	Very low	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies	
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should adjuvent corticosteroids versus TB treatment without corticosteroids be used for tuberculous pericarditis?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ●	Strong recommendation for the intervention ○
Recommendation	The GDG suggests initial adjunctive corticosteroid treatment may be used in patients with tuberculous pericarditis (conditional recommendation, very low certainty in the evidence).				
Justification	The panel felt that the benefit in constrictive pericarditis, even if the latest and largest study did not show a reduction in mortality, outweighed the potential harms of corticosteroid treatment. Review of the data showed a benefit to steroid treatment with regards to death, constrictive pericarditis and treatment adherence. However, when the studies were considered individually, the largest (1400 patients) and most recent study – i.e. the IMPI study (Mayosi BM et al. Prednisolone and Mycobacterium indicus pranii in tuberculous pericarditis. N Engl J Med. 2014) – showed no benefit to steroids. However, HIV infection complicates these findings. In the IMPI study, 67% of subjects were HIV-positive and only 14% were on ART. In another smaller study of 58 subjects, in which all were HIV-positive, steroids reduced mortality (the other studies did not address HIV and mortality). These immunosuppressed patients may have had a different benefit from steroids when compared to HIV-negative persons or PLWH who are on ART. In the IMPI study, there was a supplemental analysis of just the HIV negative patients, and a small mortality benefit was shown with steroid treatment. Several other issues were raised regarding the analysis. A random-effects model was used in this analysis, which led to an unexpected finding where the relative risk of death was lower in the steroid treatment arm, despite the fact that similar numbers and proportions of patients in both the steroid and placebo arms had this outcome. When a fixed-effects model was applied, the difference in mortality tended to disappear. However, upon extensive discussion it was determined that the random-effects model was the most appropriate model to use, and so the findings stand. There was also a concern that publication bias may play a role in these results. Most of the studies were published in the year 2000 and before, so there was probably more of a publication bias at that time towards studies with positive findings.				
Subgroup considerations	PLWH: In one study an increase in HIV-related cancers was observed. However, this increase appears to be caused by co-administration of immunotherapy (M. indicus pranii).				
Implementation considerations	Practitioners should give oral steroids if IV formulations are not available.				
Monitoring and evaluation					
Research priorities	Suggested areas for research are: different effects of steroids on people who are HIV-positive or not or who are being treated with ART or not; the relationship between steroid treatment and cancer risk.				

PICO 8

Question

Should adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6-8 weeks versus TB treatment without corticosteroids be used for tuberculous meningitis?		
Population:	Patients with tuberculous meningitis	Background:
Intervention:	Adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6-8 weeks	
Comparison:	TB treatment without corticosteroids	
Main outcomes:	Mortality; Death or severe disability; Relapse; Adverse events.	
Setting:		
Perspective:		

Assessment

<table>
<tr><th></th><th>Judgement</th><th>Research evidence</th><th>Additional considerations</th></tr>
<tr><td>Problem</td><td>Is the problem a priority?
○ No
○ Probably no
○ Probably yes
● Yes

○ Varies
○ Don't know</td><td>Tuberculous meningitis is a serious form of extrapulmonary TB that leads to high rates of death and severe disability. Steroids have been used in the treatment of tuberculous meningitis, but their role has been controversial.</td><td></td></tr>
<tr><td>Desirable Effects</td><td>How substantial are the desirable anticipated effects?
○ Trivial
○ Small
○ Moderate
● Large

○ Varies
○ Don't know</td><td>Analysis of the data shows statistically significantly lower rates of mortality or severe disability , and relapse in patients treated with steroids. The mortality benefit increased with increasing TB meningitis stage (i.e. increasing severity of disease). Additionally, rates of adverse events and severe adverse events were lower in the patients receiving steroids. All 8 of the episodes of severe hepatitis (one of which was fatal) occurred in the placebo arm.
There were no substantial undesirable anticipated effects due to steroid treatment.</td><td></td></tr>
<tr><td>Undesirable Effects</td><td>How substantial are the undesirable anticipated effects?
○ Large
○ Moderate
○ Small
● Trivial

○ Varies
○ Don't know</td><td>Summary of findings:
<table>
<tr><th>Outcome</th><th>With TB treatment without corticosteroids</th><th>With adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6-8 weeks</th><th>Difference (95% CI)</th><th>Relative effect (RR) (95% CI)</th></tr>
<tr><td>Mortality</td><td>348 per 1000</td><td>250 per 1000 (181 to 348)</td><td>97 fewer per 1000 (from 0 fewer to 167 fewer)</td><td>RR 0.72 (0.52 to 1.00)</td></tr>
<tr><td>Death or severe disability</td><td>489 per 1000</td><td>391 per 1000 (327 to 474)</td><td>98 fewer per 1000 (from 15 fewer to 161 fewer)</td><td>RR 0.80 (0.67 to 0.97)</td></tr>
<tr><td>Relapse</td><td>159 per 1000</td><td>134 per 1000 (92 to 198)</td><td>26 fewer per 1000 (from 38 more to 67 fewer)</td><td>RR 0.84 (0.58 to 1.24)</td></tr>
</table></td><td></td></tr>
<tr><td>Certainty of evidence</td><td>What is the overall certainty of the evidence of effects?
○ Very low
○ Low
● Moderate
○ High

○ No included studies</td><td>No research evidence was identified.</td><td>Usually, the overall certainty of evidence is graded on the basis of the lowest grade of the outcome evidence. In this case, the outcome of "relapse" is graded as low certainty of evidence. However, because the evidence for relapse is in the same direction as all the other evidence (and so therefore would not affect the overall decision) the overall certainty of evidence should not be downgraded to the level of the evidence of relapse (i.e. low).</td></tr>
</table>

	Judgement	Research evidence	Additional considerations
Values	Is there important uncertainty about, or variability in, the extent to which people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	No research evidence was identified.	
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ● Favours the intervention ○ Varies ○ Don't know	No research evidence was identified.	
Resources required	How large are the resource requirements (costs)? ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence was identified.	
Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)? ○ Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Cost-effectiveness	Does the cost-effectiveness of the intervention favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ No included studies	No research evidence was identified.	
Equity	What would be the impact on health equity? ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	Dexamethasone may not be available in some settings due to its IV requirements. If an oral steroid formulation is not available in these cases, this would lead to inequity.
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	

	Judgement	Research evidence	Additional considerations
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	Practitioners should give oral steroids if IV formulations are not available.

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know	
Certainty of evidence	Very low	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies	
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6-8 weeks versus TB treatment without corticosteroids be used for tuberculous meningitis?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ●
Recommendation	The GDG recommends that initial adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6-8 weeks should be used for patients with tuberculous meningitis (strong recommendation, moderate certainty in the evidence).				
Justification	Analysis of the data shows statistically significantly lower rates of mortality or severe disability, and relapse in patients treated with steroids. Additionally, rates of adverse events and severe adverse events, including severe hepatitis, were lower in the patients receiving steroids.				
Subgroup considerations	Steroids should be given regardless of the severity of meningitis				
Implementation considerations	Practitioners should give oral steroids if IV formulations are not available.				
Monitoring and evaluation					
Research priorities	Suggested areas for research are: the optimal steroid dose for TB meningitis (including among different formulations); the optimal steroid duration for TB meningitis, and whether this duration differs between different grades of meningitis.				

PICO 9

Question

Should empiric re-treatment with the 5 first-line drugs HRZES (WHO category II regimen) be used for patients with a previous history of treatment, with first-line anti-TB drugs being considered for re-treatment (due to treatment interruption or recurrence) in the absence of INH and RIF resistance testing?

Population:	Patients with a previous history of treatment with first-line anti-TB drugs being considered for re-treatment (due to treatment interruption or recurrence) in the absence of INH and RIF resistance testing	Background:
Intervention:	Empiric re-treatment with the 5 first-line drugs HRZES (WHO category 2 regimen)	
Comparison:	No comparator was defined for this comparison	
Main outcomes:	Adherence versus non-adherence to treatment; Successful treatment outcome (cure/completed treatment) versus failure/relapse/death; No severe adverse reactions from TB drugs versus severe drug reaction; No substantial cost versus substantial cost to patient; No substantial cost versus substantial cost to health-care system; Acquisition (or amplification) of drug resistance; Reduction of hospital stay; Reduction of clinical complications.	
Setting:		
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	
Desirable Effects	How substantial are the desirable anticipated effects? ○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	No research evidence was identified.	
Undesirable Effects	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know		
Certainty of evidence	What is the overall certainty of the evidence of effects? ○ Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Values	Is there important uncertainty about, or variability in, the extent to which people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence was identified.	

	Judgement	Research evidence	Additional considerations
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	No research evidence was identified.	
Resources required	How large are the resource requirements (costs)? ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence was identified.	
Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)? ○ Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Cost-effectiveness	Does the cost-effectiveness of the intervention favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ No included studies	No research evidence was identified.	
Equity	What would be the impact on health equity? ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know	
Certainty of evidence	Very low	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the interven-tion or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies	
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the interven-tion or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should empiric re-treatment with the 5 first-line drugs HRZES (WHO category II regimen) be used for patients with a previous history of treatment, with first-line anti-TB drugs being considered for re-treatment (due to treatment interruption or recurrence) in the absence of INH and RIF resistance testing?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
Recommendation	The GDG recommends that TB patients who require retreatment for TB should be referred for drug-susceptibility testing and that the category II regimen should no longer be prescribed (ungraded good practice statement).				
Justification	In persons who require retreatment for TB due to treatment interruption or recurrence of disease, drug susceptibility testing (DST) should be carried out and category II treatment should not be used. There are several reasons why category II should no longer be used. With the advent of widespread DST, the standard of care is to perform a DST on people who have had treatment interruption or recurrence of disease and then to treat accordingly. Not doing this, and instead empirically treating with the substandard category II regimen, perpetuates treatment inequity (especially in low- to middle-income countries), delays proper treatment for drug-resistant tuberculosis (which fuels drug resistance and leads to worse outcomes for the patient and for the community) and, if patients have drug-sensitive disease, exposes them unnecessarily to the toxicities of streptomycin. One of the basic tenets of TB treatment is that one drug should not be added to an unsuccessful regimen. Adding streptomycin to the previously unsuccessful regimen of INH, rifampicin, ethambutol and PZA violates this principle and fuels the development of drug resistance and the loss of streptomycin as a second-line agent in MDR-TB treatment. Patients who have failed treatment may have done so because of drug resistance. Use of category II in these patients runs contrary to the WHO treatment principle that any patient who has failed treatment should be started on an empirical MDR-TB regimen (Treatment of tuberculosis: guidelines, fourth edition. World Health Organization, 2010) and will only accelerate drug resistance. In patients who have had treatment interruption, the reason for that interruption should be addressed, whether it be medication stock-outs, side-effects of medicines, the need for greater patient or provider education, etc. The data for this review demonstrated that the empiric use of category II in patients requiring retreatment for their TB disease led to unacceptably low rates of treatment success (median treatment success rates of 68%). In addition, when patients with known INH resistance who were treated with category II were examined, acquired drug resistance rates were significantly higher than in those who received an RZE regimen. Adverse events were not sufficiently well recorded in the literature to be analysed. The GDG expressed concern regarding treatment of patients with INH mono-resistant TB. Xpert® MTB/RIF is the most common method for drug susceptibility testing, but it lacks the current ability to test for INH resistance. Patients with INH resistance are at a higher risk of developing additional drug resistance. Providers must be vigilant about the possibility of INH resistance and, if it is suspected, they must test for INH susceptibility and treat accordingly, although category II should never be used. Further WHO guidance on treatment for patients with INH mono-resistance, particularly addressing the use of fluoroquinolones, is upcoming.				
Subgroup considerations					
Implementation considerations	Patients eligible for retreatment should be referred for a rapid molecular test or DST to determine at least the INH and RIF resistance status. Based on the drug susceptibility profile, a standard treatment regimen can be repeated if no resistance is documented, or a MDR-TB regimen will be prescribed according to WHO's recently published MDR-TB treatment guidelines.				
Monitoring and evaluation					
Research priorities					

PICO 10.1

Question

Should self-administered treatment versus directly observed treatment be used for TB patients?		
Population:	TB patients	Background:
Intervention:	Self-administered treatment (SAT)	
Comparison:	Directly observed treatment (DOT)	
Main outcomes:	Mortality - cohort studies; Mortality - RCTs; Treatment success - cohort studies; Treatment success - RCTs; Completion - cohort studies; Completion - RCTs; Cure - cohort studies; Cure - RCTs; Failure - cohort studies; Failure - RCTs; Loss to follow-up – cohort studies; Loss to follow-up - RCTs; Relapse – cohort studies; Relapse - RCTs; Adherence – cohort studies; Adherence - RCTs; Smear conversion - cohort studies; Smear conversion - RCTs; Acquisition of drug resistance.	
Setting:		
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	DOT is defined as any person observing the patient taking medications in real time. It may include real-time video recording.
Desirable Effects	How substantial are the desirable anticipated effects? ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	SAT is considered the intervention. Results from RCTs were considered preferentially. Patients on SAT had slightly lower mortality rates and lower relapse rates but had higher rates of loss to follow-up and higher rates of acquired drug resistance. Patients who were on DOT had better rates of treatment success, cure, treatment completion, 2-month sputum conversion, and had better adherence.	The GDG focused preferentially on randomized control trial data. DOT included any form of observation of administration of treatment. Some patients were "double counted" in treatment success and in cure or treatment completion. In these studies, DOT was administered at a daily health clinic or was home-administered. Adherence definitions varied, but in general it was defined as taking > 90% of medications.
Undesirable Effects	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	**Summary of findings:**	

Outcome	With directly observed treatment (DOT)	With self administered treatment (SAT)	Difference (95% CI)	Relative effect (RR) (95% CI)
Mortality - Cohort studies	33 per 1000	0 per 1000 (0 to 0)	20 more per 1000 (from 0 fewer to 40 more)	not estimable
Mortality - RCTs	45 per 1000	0 per 1000 (0 to 0)	10 fewer per 1000 (from 30 fewer to 10 more)	0.73 (0.45-1.19)
Treatment success - Cohort studies	744 per 1000	588 per 1000 (536 to 655)	156 fewer per 1000 (from 89 fewer to 208 fewer)	RR 0.79 (0.72 to 0.88)
Treatment success - RCTs	746 per 1000	701 per 1000 (664 to 731)	45 fewer per 1000 (from 15 fewer to 82 fewer)	RR 0.94 (0.89 to 0.98)
Completion - Cohort studies	262 per 1000	0 per 1000 (0 to 0)	20 more per 1000 (from 40 fewer to 80 more)	not estimable
Completion - RCTs	234 per 1000	185 per 1000 (131 to 260)	49 fewer per 1000 (from 26 more to 103 fewer)	RR 0.79 (0.56 to 1.11)

	Judgement	Research evidence	Additional considerations
Certainty of evidence	What is the overall certainty of the evidence of effects? ○ Very low ● Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Values	Is there important uncertainty about, or variability in, the extent to which people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence was identified.	
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? ○ Favours the comparison ● Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	DOT is comparison	
Equity	What would be the impact on health equity? ○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	SAT is treatment intervention.	DOT definition broadened to include any person who observes the patient taking the medications in real time. This does not have to be a health care worker (HCW), but could be friend, relative, etc. Other patient-related factors (e.g. daily wage workers) may prevent access to DOT. The feeling of being "watched over" may be disempowering for patients. It may be stigmatizing to have an HCW coming to a patient's house. Other forms of DOT (e.g. administered by an emotionally supportive relative or close friend) may be more acceptable but may also be stigmatizing.
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	SAT is treatment intervention.	See comments on stigma, above.
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	SAT is treatment intervention.	

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know	
Certainty of evidence	Very low	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the interven-tion or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should self-administered treatment versus directly observed treatment be used for TB treatment?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ●	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
Recommendation	The GDG suggests either directly observed treatment (DOT) or self-administered treatment (SAT) (conditional recom-mendation, low certainty of evidence).				
Justification	If SAT is used, it must be used in conjunction with proper medical care, including patient counselling and education on the disease and its treatment.				
Subgroup considerations					
Implementation consider-ations	DOT may refer to observation by relatives and other caregivers. The systematic review defined DOT as any form of directly observed treatment by a health worker, social worker, relative or neighbour.				
Monitoring and evaluation					
Research priorities					

PICO 10.2

Question

Should directly observed treatment at different locations versus clinic or routine care be used for TB treatment?		
Population:	Patients undergoing TB treatment	Background:
Intervention:	DOT at different locations	
Comparison:	DOT at health facility/clinic or unsupervised treatment	
Main outcomes:	Mortality - cohorts (home/community versus clinic); Mortality - RCTs (community versus clinic); Success - cohorts (home/community versus clinic); Success - RCTs (home/community versus clinic); Completion - cohort studies (home/community versus clinic); Completion- RCTs (community versus clinic); Cure - cohort studies (home/community versus clinic); Cure - RCTs (home/community versus clinic); Failure – cohort studies (home/community versus clinic); Failure - RCTs (home versus community); Failure - RCTs (community versus clinic); Loss to follow-up - cohorts (home/community versus clinic); Loss to follow-up - RCTs (home/community versus clinic); Adherence - cohort studies (home/community versus clinic); Sputum conversion (2nd month) - cohort studies (home/community versus clinic); Sputum conversion (2nd month) - RCTs (home/community versus clinic); Unfavourable outcome (community versus clinic).	
Setting:		
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	
Desirable Effects	How substantial are the desirable anticipated effects? ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	The GDG focused on the data presented from RCTs, when available. This question compared community/home DOT versus clinic DOT. In general, these locations were grouped by distance, with community/home DOT being closer to the patient, and clinic-based DOT being more distant. There were some instances of community-based DOT being provided by health-care workers. Community/home-based DOT had higher rates of treatment success, cure, treatment completion and 2-month sputum conversion. It also had lower rates of mortality and overall lower rates of unfavourable outcomes. However, community-based DOT also had higher rates of loss to follow-up and lower adherence rates.	

	Judgement	Research evidence	Additional considerations
Undesirable Effects	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	**Summary of findings:**	

Outcome	With clinic or routine care	With DOT at different locations	Difference (95% CI)	Relative effect (RR) (95% CI)
Mortality - cohorts (home/community versus clinic)	45 per 1000	0 per 1000 (0 to 0)	0 fewer per 1000 (from 10 fewer to 20 more)	not estimable
Mortality - RCTs (community versus clinic)	110 per 1000	40 per 1000 (7 to 256)	70 fewer per 1000 (from 103 fewer to 146 more)	RR 0.36 (0.06 to 2.33)
Success - cohorts (home/community versus clinic)	791 per 1000	870 per 1000 (838 to 901)	79 more per 1000 (from 47 more to 111 more)	RR 1.10 (1.06 to 1.14)
Success - RCTs (home/community versus clinic)	840 per 1000	874 per 1000 (840 to 916)	34 more per 1000 (from 0 fewer to 76 more)	RR 1.04 (1.00 to 1.09)
Completion - cohort studies (home/community versus clinic)	170 per 1000	158 per 1000 (95 to 264)	12 fewer per 1000 (from 75 fewer to 94 more)	RR 0.93 (0.56 to 1.55)
Completion - RCTs (community versus clinic)	34 per 1000	98 per 1000 (39 to 248)	64 more per 1000 (from 5 more to 215 more)	RR 2.92 (1.15 to 7.41)
Cure - cohort studies (home/community versus clinic)	665 per 1000	738 per 1000 (659 to 825)	73 more per 1000 (from 7 fewer to 160 more)	RR 1.11 (0.99 to 1.24)
Cure - RCTs (home/community versus clinic)	602 per 1000	608 per 1000 (554 to 674)	6 more per 1000 (from 48 fewer to 72 more)	RR 1.01 (0.92 to 1.12)
Failure - cohort studies (home/community versus clinic)	39 per 1000	0 per 1000 (0 to 0)	10 fewer per 1000 (from 30 fewer to 0 fewer)	not estimable
Failure - RCTs (home versus community)	2 per 1000	2 per 1000 (0 to 24)	0 fewer per 1000 (from 1 fewer to 23 more)	RR 1.00 (0.06 to 16.00)
Failure - RCTs (community versus clinic)	13 per 1000	9 per 1000 (2 to 49)	4 fewer per 1000 (from 12 fewer to 36 more)	RR 0.68 (0.13 to 3.69)
Loss to follow-up - cohorts (home/community versus clinic)	113 per 1000	67 per 1000 (44 to 99)	46 fewer per 1000 (from 14 fewer to 69 fewer)	RR 0.59 (0.39 to 0.88)
Loss to follow-up - RCTs (home/community versus clinic)	134 per 1000	139 per 1000 (45 to 427)	5 more per 1000 (from 88 fewer to 293 more)	RR 1.04 (0.34 to 3.19)
Adherence - cohort studies (home/community versus clinic)	933 per 1000	868 per 1000 (719 to 1000)	65 fewer per 1000 (from 112 more to 215 fewer)	RR 0.93 (0.77 to 1.12)
Sputum conversion (2nd month) - cohort studies (home/community versus clinic)	866 per 1000	995 per 1000 (883 to 1000)	130 more per 1000 (from 17 more to 251 more)	RR 1.15 (1.02 to 1.29)
Sputum conversion (2nd month) - RCTs (home/community versus clinic)	694 per 1000	757 per 1000 (687 to 847)	62 more per 1000 (from 7 fewer to 153 more)	RR 1.09 (0.99 to 1.22)

Certainty of evidence	What is the overall certainty of the evidence of effects? ○ Very low ○ Low ● Moderate ○ High ○ No included studies	No research evidence was identified.	
Values	Is there important uncertainty about, or variability in, the extent to which people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence was identified.	

	Judgement	Research evidence	Additional considerations
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	No research evidence was identified.	
Equity	What would be the impact on health equity? ○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	As per previous discussion on DOT versus self-administered treatment (SAT)	
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	There is probably more acceptability and accessibility with community/home based-DOT than with other forms of DOT. Stigma may continue to be a concern. However, given complex family social dynamics, family members may not always be the best people to monitor treatment. Evidence from another PICO question showed that loss to follow-up is higher and adherence is lower if a family member is administering DOT.
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	Training of local staff will still be needed since family members cannot be the only options for care. Patients will still need psychosocial support and social service support even if family members are providing DOT.

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know	
Certainty of evidence	Very low	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should directly observed treatment at different locations versus clinic or routine care be used for TB treatment?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ●	Strong recommendation for the intervention ○
Recommendation	The GDG suggests community-based or home-based DOT over clinic-based or hospital-based DOT (conditional recommendation, moderate certainty in the evidence).				
Justification	Following the meeting the Steering Group asked for further clarification of the data relating to home/community-based DOT versus SAT. Additional analysis directly comparing home/community-based DOT versus SAT (cohort studies only, see corresponding evidence table) showed higher rates of treatment success and treatment adherence and lower rates of loss to follow-up with home/community-based DOT. Comparison of health facility-based DOT versus SAT (both RCTs and cohort studies, see corresponding evidence table) showed no difference in outcomes between these two methods. These analyses led to the recommendation that community/home-based DOT is the preferred option rather than health facility-based DOT or SAT.				
Subgroup considerations					
Implementation considerations	Community/home-based DOT should be done in combination with psychosocial support. Careful identification and training of persons conducting DOT is required. There is a need to define community-based DOT (this should not be confused with community clinics).				
Monitoring and evaluation					
Research priorities					

PICO 10.3

Question

Should different directly observed treatment providers versus standard providers be used for TB treatment (2)?		
Population:	Patients undergoing TB treatment (2)	Background:
Intervention:	Different DOT providers	
Comparison:	Standard providers (health-care workers, or HCW) or unsupervised treatment	
Main outcomes:	Mortality - family DOT versus HCW; Mortality - lay provider versus HCW; Success - family versus HCW; Success - lay provider versus HCW; Completion - cohort studies; Cure - family versus HCW; Cure - lay provider versus HCW; Failure - family versus HCW; Failure - lay provider versus HCW; Loss to follow-up - family versus HCW; Loss to follow-up - lay provider versus HCW; Adherence - family versus HCW (village doctor).	
Setting:		
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	
Desirable Effects	How substantial are the desirable anticipated effects? ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	In this analysis, family members were compared to HCW and lay providers were compared to HCW. Among family providers, compared to HCW, there were higher rates of mortality, loss to follow-up, failure and default, and lower rates of successful treatment, cure and adherence among patients who had DOT administered by family members. Among lay providers compared to HCW, there were higher rates of success and cure and lower mortality and failure among patients who had DOT administered by a lay person compared to an HCW.	

<table>
<tr><th></th><th>Judgement</th><th>Research evidence</th><th>Additional considerations</th></tr>
<tr><td>Undesirable Effects</td><td>How substantial are the undesirable anticipated effects?
○ Large
● Moderate
○ Small
○ Trivial

○ Varies
○ Don't know</td><td>Summary of findings:
<table>
<tr><th>Outcome</th><th>With standard providers</th><th>With different DOT providers</th><th>Difference (95% CI)</th><th>Relative effect (RR) (95% CI)</th></tr>
<tr><td>Mortality - family DOT versus HCW</td><td>119 per 1000</td><td>125 per 1000 (108 to 144)</td><td>6 more per 1000 (from 11 fewer to 25 more)</td><td>RR 1.05 (0.91 to 1.21)</td></tr>
<tr><td>Mortality - lay provider versus HCW</td><td>52 per 1000</td><td>38 per 1000 (24 to 59)</td><td>14 fewer per 1000 (from 7 more to 28 fewer)</td><td>RR 0.73 (0.47 to 1.13)</td></tr>
<tr><td>Success - family versus HCW</td><td>723 per 1000</td><td>615 per 1000 (485 to 767)</td><td>109 fewer per 1000 (from 43 more to 239 fewer)</td><td>RR 0.85 (0.67 to 1.06)</td></tr>
<tr><td>Success - lay provider versus HCW</td><td>763 per 1000</td><td>832 per 1000 (710 to 969)</td><td>69 more per 1000 (from 53 fewer to 206 more)</td><td>RR 1.09 (0.93 to 1.27)</td></tr>
<tr><td>Completion - cohort studies</td><td>365 per 1000</td><td>354 per 1000 (339 to 372)</td><td>11 fewer per 1000 (from 7 more to 26 fewer)</td><td>RR 0.97 (0.93 to 1.02)</td></tr>
<tr><td>Cure - family versus HCW</td><td>473 per 1000</td><td>246 per 1000 (76 to 785)</td><td>227 fewer per 1000 (from 312 more to 397 fewer)</td><td>RR 0.52 (0.16 to 1.66)</td></tr>
<tr><td>Cure - lay provider versus HCW</td><td>744 per 1000</td><td>811 per 1000 (603 to 1000)</td><td>67 more per 1000 (from 141 fewer to 350 more)</td><td>RR 1.09 (0.81 to 1.47)</td></tr>
<tr><td>Failure - family versus HCW</td><td>8 per 1000</td><td>0 per 1000 (0 to 0)</td><td>10 more per 1000 (from 0 fewer to 10 more)</td><td>not estimable</td></tr>
<tr><td>Failure - lay provider versus HCW</td><td>43 per 1000</td><td>20 per 1000 (7 to 56)</td><td>23 fewer per 1000 (from 13 more to 36 fewer)</td><td>RR 0.47 (0.17 to 1.29)</td></tr>
<tr><td>Loss to follow-up - family versus HCW</td><td>54 per 1000</td><td>80 per 1000 (66 to 98)</td><td>26 more per 1000 (from 11 more to 44 more)</td><td>RR 1.48 (1.21 to 1.81)</td></tr>
<tr><td>Loss to follow-up - Cohort studies</td><td>100 per 1000</td><td>75 per 1000 (42 to 132)</td><td>25 fewer per 1000 (from 32 more to 58 fewer)</td><td>RR 0.75 (0.42 to 1.32)</td></tr>
<tr><td>Adherence - Cohort studies</td><td>944 per 1000</td><td>812 per 1000 (746 to 887)</td><td>132 fewer per 1000 (from 57 fewer to 198 fewer)</td><td>RR 0.86 (0.79 to 0.94)</td></tr>
</table></td><td></td></tr>
<tr><td>Certainty of evidence</td><td>What is the overall certainty of the evidence of effects?
● Very low
○ Low
○ Moderate
○ High

○ No included studies</td><td>No research evidence was identified.</td><td></td></tr>
<tr><td>Values</td><td>Is there important uncertainty about, or variability in, the extent to which people value the main outcomes?
○ Important uncertainty or variability
○ Possibly important uncertainty or variability
● Probably no important uncertainty or variability
○ No important uncertainty or variability</td><td>No research evidence was identified.</td><td></td></tr>
<tr><td>Balance of effects</td><td>Does the balance between desirable and undesirable effects favour the intervention or the comparison?
○ Favours the comparison
● Probably favours the comparison
○ Does not favour either the intervention or the comparison
○ Probably favours the intervention
○ Favours the intervention

○ Varies
○ Don't know</td><td>Comparison is DOT being provided by standard providers (HCW).</td><td></td></tr>
</table>

	Judgement	Research evidence	Additional considerations
Resources required	How large are the resource requirements (costs)? ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No research evidence was identified.	
Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)? ○ Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Cost-effectiveness	Does the cost-effectiveness of the intervention favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ No included studies	No research evidence was identified.	
Equity	What would be the impact on health equity? ○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	As per previous DOT discussion.	
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	Family-based providers may have lower stigma, as their provision of DOT to the patient is less obvious to other people, such as neighbours.
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		Feasibility may be reduced with health-care workers in the community because it requires an increased number of health-care workers placed in the community, with an increased associated costs.

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know	
Certainty of evidence	Very low	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies	
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should different directly observed treatment providers versus standard providers be used for TB treatment (2)?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ●	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
Recommendation	The GDG suggests the use of health-care providers or trained lay providers, rather than family members, to administer DOT (conditional recommendation, very low certainty in the evidence).				
Justification	Following the meeting, the Steering Group asked for further clarification of the data surrounding different providers delivering DOT versus self-administered treatment (SAT). Additional analysis directly comparing HCW provided DOT versus SAT (RCTs and cohort studies, see corresponding evidence table) showed higher rates of treatment completion with SAT but higher rates of cure and adherence and lower rates of relapse and acquisition of drug resistance with HCW DOT. Comparison of lay provider-supplied DOT versus SAT, which included both RCTs and cohort studies (see corresponding evidence table) showed lower rates of treatment completion but higher rates of cure with a lay provider DOT. Comparison of family-provided DOT versus SAT showed higher rates of treatment success and lower rates of loss to follow-up with family-provided DOT compared with SAT (see corresponding evidence tables). These analyses led to the recommendation that DOT should be administered by trained lay providers or health-care workers. This is recommended over DOT administered by family members or unsupervised treatment.				
Subgroup considerations					
Implementation considerations					
Monitoring and evaluation					
Research priorities					

PICO 10.4

Question

Should self-administered treatment versus directly observed treatment be used for TB/HIV patients?		
Population:	TB/HIV patients	Background:
Intervention:	Self-administered treatment (SAT)	
Comparison:	DOT	
Main outcomes:	Mortality - cohort studies; Success - cohort studies; Completion - cohort studies; Cure - cohort studies; Failure - cohort studies; Loss to follow-up - cohort studies; Relapse - cohort studies.	
Setting:		
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	
Desirable Effects	How substantial are the desirable anticipated effects? ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Only cohort studies were available for this review. Self-administered treatment (SAT) is the intervention. TB/HIV co-infected patients on SAT had lower rates of treatment success, treatment completion and cure. They had higher rates of mortality, treatment failure and loss to follow-up. **Summary of findings:**	
Undesirable Effects	How substantial are the undesirable anticipated effects? ● Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know		
Certainty of evidence	What is the overall certainty of the evidence of effects? ● Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Values	Is there important uncertainty about, or variability in, the extent to which people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence was identified.	

Outcome	With DOT	With SAT	Difference (95% CI)	Relative effect (RR) (95% CI)
Mortality - cohort studies	67 per 1000	185 per 1000 (102 to 336)	117 more per 1000 (from 34 more to 269 more)	RR 2.74 (1.51 to 4.99)
Success - cohort studies	821 per 1000	337 per 1000 (238 to 484)	484 fewer per 1000 (from 337 fewer to 583 fewer)	RR 0.41 (0.29 to 0.59)
Completion - cohort studies	250 per 1000	25 per 1000 (3 to 190)	225 fewer per 1000 (from 60 fewer to 248 fewer)	RR 0.10 (0.01 to 0.76)
Cure - cohort studies	586 per 1000	234 per 1000 (170 to 322)	352 fewer per 1000 (from 264 fewer to 416 fewer)	RR 0.40 (0.29 to 0.55)
Failure - cohort studies	198 per 1000	634 per 1000 (418 to 962)	436 more per 1000 (from 220 more to 764 more)	RR 3.20 (2.11 to 4.86)
Loss to follow-up - cohort studies	171 per 1000	331 per 1000 (89 to 1000)	160 more per 1000 (from 82 fewer to 1000 more)	RR 1.94 (0.52 to 7.17)
Relapse - cohort studies	20 per 1000	18 per 1000 (3 to 124)	2 fewer per 1000 (from 17 fewer to 105 more)	RR 0.90 (0.13 to 6.28)

	Judgement	Research evidence	Additional considerations
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? ● Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	DOT is the comparison.	
Equity	What would be the impact on health equity? ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		DOT definition broadened to include any person who observes the patient taking the medications in real time. This does not have to be a health care worker (HCW), but could be friend, relative, etc. Other patient-related factors (daily wage workers, etc.) may prevent access to DOT. The feeling of being "watched over" may be disempowering for patients. It may be stigmatizing to have an HCW coming to a patient's house. Other forms of DOT (e.g. administered by an emotionally supportive relative or close friend) may be more acceptable but may also be stigmatizing.
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	The possibility of increased drug-drug interactions between TB and HIV medications may make DOT (and the increased patient support) more acceptable to stakeholders.
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know	
Certainty of evidence	Very low	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should self-administered treatment versus directly observed treatment be used for TB/HIV patients?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ●	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
Recommendation	The GDG suggests the use of DOT rather than self-administered treatment (SAT) in HIV-infected patients with TB (conditional recommendation, very low certainty of evidence).				
Justification	The GDG felt that HIV-positive people as a subgroup benefited more from DOT than the general TB population. The reasons for this are unclear but increased rates of drug-drug interactions and more severe disease in this cohort may cause DOT to offer a significant advantage over SAT.				
Subgroup considerations					
Implementation considerations					
Monitoring and evaluation					
Research priorities					

PICO 10.5

Question

Should incentives and enablers versus none be used for TB treatment?		
Population:	Patients receiving TB treatment	Background:
Intervention:	Incentives and enablers	
Comparison:	None	
Main outcomes:	Mortality - cohort studies; Mortality - RCTs; Treatment success - cohort studies; Treatment success - RCTs; Treatment completion - cohort studies; Treatment completion - RCTs; Cure - cohort studies; Cure - RCTs; Treatment failure - cohort studies; Treatment failure - RCTs; Loss to follow-up - cohort studies; Loss to follow-up - RCTs; Acquisition of resistance; Sputum conversion rate - RCTs.	
Setting:		
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		
Desirable Effects	How substantial are the desirable anticipated effects? ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Data from the RCT were preferentially considered. There were higher rate of treatment success, completion and sputum conversion with incentives/enablers. There were lower rate of treatment failure and loss to follow-up with incentives/enablers.	Examples of incentives and enablers included food, food vouchers, food supplements, financial support, transport subsidies, living allowance, housing incentives, and financial bonus if study objectives met. All but one of the studies were in low- to middle-income countries, so presumably these incentives were of significant value for the subjects. Food may be given as an incentive but it may also biologically improve outcomes through a reduction in malnutrition and consequent improvement in immune function. It should be noted that outcomes were exclusive, so cure may appear to be lower if treatment completion is higher. Treatment success is therefore probably the most reliable outcome.
Undesirable Effects	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	**Summary of findings:**	
Certainty of evidence	What is the overall certainty of the evidence of effects? ○ Very low ○ Low ● Moderate ○ High ○ No included studies	No research evidence was identified.	

Summary of findings:

Outcome	With none	With incentives and enablers	Difference (95% CI)	Relative effect (RR) (95% CI)
Mortality - RCTs	68 per 1000	-7 per 1000 (-3 to 2)	1 fewer per 1000 (from 40 fewer to 30 more)	risk difference (%) -0.10 (-0.04 to 0.03)
Treatment success - RCTs	714 per 1000	764 per 1000 (735 to 792)	50 more per 1000 (from 21 more to 79 more)	RR 1.07 (1.03 to 1.11)
Treatment completion - RCTs	361 per 1000	444 per 1000 (416 to 473)	83 more per 1000 (from 54 more to 112 more)	RR 1.23 (1.15 to 1.31)
Cure - RCTs	357 per 1000	328 per 1000 (303 to 360)	29 fewer per 1000 (from 4 more to 54 fewer)	RR 0.92 (0.85 to 1.01)
Treatment failure - RCTs	57 per 1000	38 per 1000 (28 to 50)	19 fewer per 1000 (from 7 fewer to 28 fewer)	RR 0.66 (0.50 to 0.87)
Loss to follow up - RCTs	102 per 1000	75 per 1000 (61 to 92)	26 fewer per 1000 (from 10 fewer to 41 fewer)	RR 0.74 (0.60 to 0.90)
Sputum conversion rate - RCTs	806 per 1000	975 per 1000 (822 to 1000)	169 more per 1000 (from 16 more to 346 more)	RR 1.21 (1.02 to 1.43)

	Judgement	Research evidence	Additional considerations
Values	Is there important uncertainty about, or variability in, the extent to which people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence was identified.	
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	No research evidence was identified.	
Equity	What would be the impact on health equity? ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	No research evidence was identified.	These incentives were usually given to the most vulnerable groups, so health equity was improved. However, if the incentives are not applied equitably, health disparities may be increased. The distribution of incentives and enablers is likely to depend on the country context. Incentives and enablers may have different effects within countries and between countries.
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	There may be reluctance on the part of implementers (e.g. governments, health partners) to pay for incentives. Implementers may be more willing to pay for incentives/enablers for particularly high-risk smaller subgroups (e.g. patients with MDR-TB). One of the components of WHO's END TB Strategy is to provide "social protection and poverty alleviation" for patients with tuberculosis. The strategy specifically calls for measures to "alleviate the burden of income loss and non-medical costs of seeking and staying in care". Included in these suggested protections are social welfare payments, vouchers and food packages. The benefit of incentives and enablers found in this review supports these components of the END TB Strategy (See: WHO END TB Strategy, http://www.who.int/tb/post2015_strategy/en/).
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	Incentives and enablers may not be feasible in all settings if the implementers are reluctant to pay for such programmes. Feasibility may also vary according to the type of the proposed incentive. In order to distribute the incentives and enablers, a government and/or NGO infrastructure would need to be in place, including anti-fraud mechanisms and appropriate accounting to ensure that incentives are distributed equitably and to the people who need them the most.

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know	
Certainty of evidence	Very low	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the interven-tion or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should incentives and enablers vs. none be used for TB treatment?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ●	Strong recommendation for the intervention ○
Recommendation	The GDG suggests that incentives and enablers* be provided to patients on tuberculosis treatment (conditional recommendation, moderate certainty in the evidence). *Incentives and enablers include different types of material support such as food, transportation subsidies or living allowances.				
Justification					
Subgroup considerations					
Implementation considerations	Countries should choose incentives that are the most appropriate to their situation.				
Monitoring and evaluation	Programmes should attempt to measure whether the provision of incentives improves programme performance.				
Research priorities	Suggested areas for research are: incentives that are best suited to specific populations; incentives that are most effective in low- and middle-income countries: analysis of the cost effectiveness of different types of incentives.				

PICO 10.6

Question

Should psychological interventions versus none be used for TB treatment?		
Population:	TB patients	Background:
Intervention:	Psychological interventions	
Comparison:	None	
Main outcomes:	Mortality - cohort studies; Success - RCTs (ETOH cessation counseling); Treatment completion - cohort studies (support groups); Treatment completion - RCTs (support groups); Cure - RCTs (support groups); Failure - cohort studies (support groups); Failure - RCTs (support groups); Loss to follow-up - cohort studies (support groups); Loss to follow-up - RCTs (support groups).	
Setting:		
Perspective:		

Assessment

<table>
<tr><th></th><th>Judgement</th><th>Research evidence</th><th>Additional considerations</th></tr>
<tr><td>Problem</td><td>Is the problem a priority?
○ No
○ Probably no
○ Probably yes
● Yes

○ Varies
○ Don't know</td><td>No research evidence was identified.</td><td></td></tr>
<tr><td>Desirable Effects</td><td>How substantial are the desirable anticipated effects?
○ Trivial
○ Small
● Moderate
○ Large

○ Varies
○ Don't know</td><td>Based on data from RCTs, patients who had access to support groups had higher rates of treatment completion and cure and lower rates of treatment failure and loss to follow-up.

Summary of findings:
<table>
<tr><th>Outcome</th><th>With none</th><th>With psychological interventions</th><th>Difference (95% CI)</th><th>Relative effect (RR) (95% CI)</th></tr>
<tr><td>Mortality - cohort studies</td><td>94 per 1000</td><td>172 per 1000 (68 to 437)</td><td>78 more per 1000 (from 26 fewer to 343 more)</td><td>RR 1.83 (0.72 to 4.66)</td></tr>
<tr><td>Success - RCTs (ETOH cessation counseling)</td><td>798 per 1000</td><td>870 per 1000 (766 to 982)</td><td>72 more per 1000 (from 32 fewer to 184 more)</td><td>RR 1.09 (0.96 to 1.23)</td></tr>
<tr><td>Treatment completion - cohort studies (support groups)</td><td>469 per 1000</td><td>689 per 1000 (506 to 938)</td><td>220 more per 1000 (from 38 more to 469 more)</td><td>RR 1.47 (1.08 to 2.00)</td></tr>
<tr><td>Treatment completion - RCTs (support groups)</td><td>814 per 1000</td><td>977 per 1000 (838 to 1000)</td><td>163 more per 1000 (from 24 more to 317 more)</td><td>RR 1.20 (1.03 to 1.39)</td></tr>
<tr><td>Cure - RCTs (support groups)</td><td>814 per 1000</td><td>928 per 1000 (790 to 1000)</td><td>114 more per 1000 (from 24 fewer to 285 more)</td><td>RR 1.14 (0.97 to 1.35)</td></tr>
<tr><td>Failure - cohort studies (support groups)</td><td>16 per 1000</td><td>0 per 1000 (0 to 0)</td><td>20 fewer per 1000 (from 60 fewer to 30 more)</td><td>not estimable</td></tr>
<tr><td>Failure - RCTs (support groups)</td><td>116 per 1000</td><td>0 per 1000 (0 to 0)</td><td>1 fewer per 1000 (from 2 fewer to 0 fewer)</td><td>not estimable</td></tr>
<tr><td>Loss to follow-up - cohort studies (support groups)</td><td>406 per 1000</td><td>126 per 1000 (61 to 256)</td><td>280 fewer per 1000 (from 150 fewer to 345 fewer)</td><td>RR 0.31 (0.15 to 0.63)</td></tr>
<tr><td>Loss to follow-up - RCTs (support groups)</td><td>47 per 1000</td><td>23 per 1000 (2 to 247)</td><td>23 fewer per 1000 (from 44 fewer to 200 more)</td><td>RR 0.50 (0.05 to 5.31)</td></tr>
</table></td><td>One RCT included alcohol cessation counselling as the intervention.</td></tr>
<tr><td>Undesirable Effects</td><td>How substantial are the undesirable anticipated effects?
○ Large
○ Moderate
○ Small
● Trivial

○ Varies
○ Don't know</td><td></td><td>The panel did not believe that the increased mortality seen in the cohort study had plausible results due to the following reasons:
There were concerns about confounding due to severity of illness in the support groups.
Allocation of patients to the support groups (the TB clubs) was based on where they lived so it was not randomized.
Within this cohort study, the control group had substantially more patients lost to follow-up (40%), so many patient outcomes are unclear and this degree of loss to follow-up may make the study invalid.
Causes of mortality in the two groups were not described, so causal relationship could not be determined.</td></tr>
</table>

	Judgement	Research evidence	Additional considerations
Certainty of evidence	What is the overall certainty of the evidence of effects? ○ Very low ● Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Values	Is there important uncertainty about, or variability in, the extent to which people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence was identified.	
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	No research evidence was identified.	
Equity	What would be the impact on health equity? ○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	The range of types of psychological support is very broad and may not be represented adequately in this review. Within this review, counselling sessions and peer support were included. Equity will be increased if the support is targeted at the most marginalized populations.
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know	
Certainty of evidence	Very low	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the interven-tion or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should psychological interventions versus none be used for TB treatment?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ●	Strong recommendation for the intervention ○
Recommendation	The GDG suggests that psychological support* should be provided to patients with TB (conditional recommendation, low certainty of evidence).				
Justification	*Psychological support includes counselling sessions and peer-group support.				
Subgroup considerations					
Implementation consider-ations					
Monitoring and evaluation					
Research priorities	Suggested area for research is: what type of psychological support is most appropriate?				

PICO 10.7

Question

Should additional patient education and counselling versus routine care be used for TB treatment?		
Population:	Patients on TB treatment	Background:
Intervention:	Additional patient education and counselling	
Comparison:	Routine care	
Main outcomes:	Mortality - RCTs; Treatment success; Treatment completion; Cure; Failure; Loss to follow-up; Adherence - RCT; Adherence - cohort studies.	
Setting:		
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	
Desirable Effects	How substantial are the desirable anticipated effects? ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	Patients who received education and counselling had better treatment success, treatment completion, cure and adherence rates. They had lower rates of loss to follow-up. It should be noted in this case that "counselling" refers to educational counselling and not psychological counselling. **Summary of findings:**	
Undesirable Effects	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		
Certainty of evidence	What is the overall certainty of the evidence of effects? ○ Very low ○ Low ● Moderate ○ High ○ No included studies	The certainty of the evidence would usually be the grade of the lowest ranked outcome (in this case very low or low). However, in this instance the evidence was graded as having overall a moderate certainty because the outcomes with very low or low certainty were not determined by the GDG as being critical outcomes. Two of the critical outcomes were rated as moderate and all the effects point in the same direction (i.e. in support of patient education).	

Outcome	With routine care	With additional patient education and counselling	Difference (95% CI)	Relative effect (RR) (95% CI)
Mortality - RCTs	40 per 1000	33 per 1000 (14 to 83)	7 fewer per 1000 (from 27 fewer to 42 more)	RR 0.83 (0.34 to 2.05)
Treatment success	426 per 1000	596 per 1000 (383 to 924)	170 more per 1000 (from 43 fewer to 498 more)	RR 1.40 (0.90 to 2.17)
Treatment completion	420 per 1000	718 per 1000 (554 to 932)	298 more per 1000 (from 134 more to 512 more)	RR 1.71 (1.32 to 2.22)
Cure	395 per 1000	849 per 1000 (624 to 1000)	454 more per 1000 (from 229 more to 759 more)	RR 2.15 (1.58 to 2.92)
Failure	49 per 1000	61 per 1000 (12 to 315)	11 more per 1000 (from 38 fewer to 266 more)	RR 1.23 (0.24 to 6.38)
Loss to follow-up	494 per 1000	242 per 1000 (104 to 578)	252 fewer per 1000 (from 84 more to 390 fewer)	RR 0.49 (0.21 to 1.17)
Adherence - RCT	293 per 1000	536 per 1000 (334 to 856)	243 more per 1000 (from 41 more to 563 more)	RR 1.83 (1.14 to 2.92)
Adherence - cohort studies	783 per 1000	948 per 1000 (823 to 1000)	164 more per 1000 (from 39 more to 313 more)	RR 1.21 (1.05 to 1.40)

	Judgement	Research evidence	Additional considerations
Values	Is there important uncertainty about, or variability in, the extent to which people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence was identified.	
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ● Favours the intervention ○ Varies ○ Don't know	No research evidence was identified.	
Equity	What would be the impact on health equity? ○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	It is important to make sure that education and counselling are done in a culturally appropriate manner. Specific marginalized populations may require special educational efforts.
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	Staff time needs to be freed up for this intervention and staff should be appropriately trained to provide health education. As staff time increases for this, it is necessary to ensure that staff time for other key activities is not affected.

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know	
Certainty of evidence	Very low	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the interven-tion or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should additional patient education and counselling versus routine care be used for TB treatment?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ●
Recommendation	The GDG recommends additional patient education and counselling for patients with TB (strong recommendation, moderate certainty of evidence).				
Justification					
Subgroup considerations					
Implementation consider-ations					
Monitoring and evaluation					
Research priorities					

PICO 10.8

Question

Should staff education versus none be used for TB treatment?		
Population:	Patients on TB treatment	Background:
Intervention:	Staff education	
Comparison:	None	
Main outcomes:	Mortality - cohort studies; Mortality - RCTs; Treatment success - cohort studies; Treatment success - RCTs; Completion - RCTs; Cure - RCTs; Treatment failure - cohort studies; Treatment failure - RCTs; Loss to follow-up - cohort studies; Loss to follow-up – RCTs.	
Setting:		
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	
Desirable Effects	How substantial are the desirable anticipated effects? ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	There were higher rates of treatment success, slightly lower rates of mortality and lower rates of loss to follow-up with staff education. **Summary of findings:**	
Undesirable Effects	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know		
Certainty of evidence	What is the overall certainty of the evidence of effects? ○ Very low ● Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	

Outcome	With none	With staff education	Difference (95% CI)	Relative effect (RR) (95% CI)
Mortality - cohort studies	0 per 1000	0 per 1000 (0 to 0)	0 fewer per 1000 (from 30 more to 30 fewer)	not estimable
Mortality - RCTs	50 per 1000	38 per 1000 (22 to 66)	12 fewer per 1000 (from 16 more to 28 fewer)	RR 0.76 (0.44 to 1.31)
Treatment success - cohort studies	693 per 1000	929 per 1000 (797 to 1000)	236 more per 1000 (from 104 more to 381 more)	RR 1.34 (1.15 to 1.55)
Treatment success - RCTs	634 per 1000	653 per 1000 (602 to 710)	19 more per 1000 (from 32 fewer to 76 more)	RR 1.03 (0.95 to 1.12)
Completion - RCTs	310 per 1000	282 per 1000 (195 to 405)	28 fewer per 1000 (from 96 more to 115 fewer)	RR 0.91 (0.63 to 1.31)
Cure - RCTs	454 per 1000	490 per 1000 (390 to 617)	36 more per 1000 (from 64 fewer to 163 more)	RR 1.08 (0.86 to 1.36)
Treatment failure - cohort studies	0 per 1000	0 per 1000 (0 to 0)	0 fewer per 1000 (from 30 more to 30 fewer)	not estimable
Treatment failure - RCTs	9 per 1000	0 per 1000 (0 to 0)	0 fewer per 1000 (from 10 fewer to 20 more)	not estimable
Loss to follow-up - cohort studies	178 per 1000	0 per 1000 (0 to 0)	180 fewer per 1000 (from 260 fewer to 100 fewer)	not estimable
Loss to follow-up - RCTs	77 per 1000	57 per 1000 (28 to 115)	20 fewer per 1000 (from 38 more to 50 fewer)	RR 0.74 (0.36 to 1.49)

	Judgement	Research evidence	Additional considerations
Values	Is there important uncertainty about, or variability in, the extent to which people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	No research evidence was identified.	
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	No research evidence was identified.	
Equity	What would be the impact on health equity? ○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	Training of staff may not be possible with all health-care workers in all communities. All health-care workers, regardless of their place in the health-care structure, need to have equal access to education. Patient equity may increase with increased staff education. With better staff education, treatment of patients should improve as health-care providers understand the disease better and place less stigma on patients.
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	Training and resources are required to train health staff adequately.

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know	
Certainty of evidence	Very low	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the interven-tion or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should staff education vs. none be used for TB treatment?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ●	Strong recommendation for the intervention ○
Recommendation	The GDG suggests that staff education should be used to optimize the treatment of patients with TB (conditional recommendation, low certainty of evidence).				
Justification					
Subgroup considerations					
Implementation considerations					
Monitoring and evaluation					
Research priorities					

PICO 10.9.1

Question

Should mobile telephone interventions versus. none be used for TB treatment?		
Population:	TB patients	Background:
Intervention:	Mobile health interventions	
Comparison:	None	
Main outcomes:	Mortality - cohort studies (video DOT versus in-person DOT); Treatment success - RCTs (telephone reminders); Completion - cohort studies (video DOT versus in-person DOT); Completion - RCTs (telephone reminders); Cure - cohort studies (telephone reminder); Cure - RCTs (telephone reminders); Failure (telephone reminders); Sputum/culture conversion at 2 months - cohort studies (telephone reminders); Sputum/culture conversion at 2 months - RCTs (telephone reminders); Poor outcome (telephone reminders); Poor outcome (medication monitor); Poor outcome (combined medication monitor and telephone reminders); Loss to follow-up (telephone reminders); Loss to follow-up (medication monitor); Loss to follow-up (combined medication monitor and telephone reminders); Poor adherence (telephone reminders); Poor adherence (medication monitor); Poor adherence (telephone reminder and medication monitor).	
Setting:		
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	
Desirable Effects	How substantial are the desirable anticipated effects? ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	The mobile telephone interventions could be SMS reminders, telephone calls or video observed treatment (VOT). Since VOT was examined only by cohort studies, VOT was considered separately. Otherwise, RCT data were considered preferentially. For telephone reminders (SMS and telephone calls), there were higher rates of successful treatment outcomes and cure, and lower rates of treatment failure with telephone reminders as opposed to no intervention. Telephone reminders marginally lowered 2-month sputum conversion rates. It should be noted however, that these data are based on only one RCT.	

<table>
<tr><th></th><th>Judgement</th><th>Research evidence</th><th>Additional considerations</th></tr>
<tr><td>Undesirable Effects</td><td>How substantial are the undesirable anticipated effects?
○ Large
○ Moderate
○ Small
● Trivial

○ Varies
○ Don't know</td><td>Summary of findings:
<table>
<tr><th>Outcome</th><th>With none</th><th>With mobile health interventions</th><th>Difference (95% CI)</th><th>Relative effect (RR) (95% CI)</th></tr>
<tr><td>Treatment success - RCTs (telephone reminders)</td><td>882 per 1000</td><td>935 per 1000 (768 to 1000)</td><td>53 more per 1000 (from 115 fewer to 265 more)</td><td>RR 1.06 (0.87 to 1.30)</td></tr>
<tr><td>Completion - RCTs (telephone reminders)</td><td>194 per 1000</td><td>0 per 1000 (0 to 0)</td><td>190 fewer per 1000 (from 340 fewer to 50 fewer)</td><td>not estimable</td></tr>
<tr><td>Cure - cohort studies (telephone reminder)</td><td>323 per 1000</td><td>749 per 1000 (517 to 1000)</td><td>426 more per 1000 (from 194 more to 762 more)</td><td>RR 2.32 (1.60 to 3.36)</td></tr>
<tr><td>Cure - RCTs (telephone reminders)</td><td>580 per 1000</td><td>992 per 1000 (783 to 1000)</td><td>412 more per 1000 (from 203 more to 679 more)</td><td>RR 1.71 (1.35 to 2.17)</td></tr>
<tr><td>Failure (telephone reminders)</td><td>120 per 1000</td><td>0 per 1000 (0 to 0)</td><td>120 fewer per 1000 (from 220 fewer to 20 fewer)</td><td>not estimable</td></tr>
<tr><td>Sputum/culture conversion at 2 months - Cohort studies (telephone reminders)</td><td>385 per 1000</td><td>624 per 1000 (420 to 933)</td><td>239 more per 1000 (from 35 more to 547 more)</td><td>RR 1.62 (1.09 to 2.42)</td></tr>
<tr><td>Sputum/culture conversion at 2 months - RCTs (telephone reminders)</td><td>750 per 1000</td><td>712 per 1000 (383 to 1000)</td><td>38 fewer per 1000 (from 368 fewer to 570 more)</td><td>RR 0.95 (0.51 to 1.76)</td></tr>
</table></td><td></td></tr>
<tr><td>Certainty of evidence</td><td>What is the overall certainty of the evidence of effects?
● Very low
○ Low
○ Moderate
○ High

○ No included studies</td><td>No research evidence was identified.</td><td></td></tr>
<tr><td>Values</td><td>Is there important uncertainty about, or variability in, the extent to which people value the main outcomes?
○ Important uncertainty or variability
○ Possibly important uncertainty or variability
● Probably no important uncertainty or variability
○ No important uncertainty or variability</td><td>No research evidence was identified.</td><td></td></tr>
<tr><td>Balance of effects</td><td>Does the balance between desirable and undesirable effects favour the intervention or the comparison?
○ Favours the comparison
○ Probably favours the comparison
○ Does not favour either the intervention or the comparison
● Probably favours the intervention
○ Favours the intervention

○ Varies
○ Don't know</td><td>No research evidence was identified.</td><td></td></tr>
<tr><td>Equity</td><td>What would be the impact on health equity?
○ Reduced
○ Probably reduced
○ Probably no impact
○ Probably increased
○ Increased

● Varies
○ Don't know</td><td>No research evidence was identified.</td><td>These interventions may increase equity if travel to a clinic or to the patient's home is reduced.
These interventions may decrease ability of patients to participate if the patients are in an area with limited communication infrastructure.</td></tr>
</table>

	Judgement	Research evidence	Additional considerations
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No research evidence was identified.	There may be trepidation about using new technology. There are significant privacy issues surrounding security of telephone data. Encryption and other privacy technology will need to be considered. HCWs may not like the use of this intervention if their fee structure is lower when telephone communication is used.
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No research evidence was identified.	Feasibility depends on the communication infrastructure, telephone availability and connection costs.

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know	
Certainty of evidence	Very low	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should mobile health interventions versus none be used for TB treatment?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ●	Strong recommendation for the intervention ○
Recommendation	The GDG suggests that mobile telephone interventions should be used with patients undergoing TB treatment (conditional recommendation, very low certainty in the evidence).				
Justification	Patient support and the ability to interact with HCWs should be preserved.				
Subgroup considerations					
Implementation considerations					
Monitoring and evaluation					
Research priorities	Research into the effectiveness of video DOT in low- to middle-income countries is encouraged since existing data are from high-income countries.				

PICO 10.9.2

Question

Should video observed treatment versus DOT be used for TB treatment?		
Population:	TB patients	Background:
Intervention:	Video observed treatment (VOT)	
Comparison:	DOT	
Main outcomes:	Mortality - cohort studies (VOT versus in-person DOT); Treatment success - RCTs (telephone reminders); Completion - cohort studies (VOT versus in-person DOT); Completion - RCTs (telephone reminders); Cure - cohort studies (telephone reminder); Cure - RCTs (telephone reminders); Failure (telephone reminders); Sputum/culture conversion at 2 months - cohort studies (telephone reminders); Sputum/culture conversion at 2 months - RCTs (telephone reminders); Poor outcome (telephone reminders); Poor outcome (medication monitor); Poor outcome (combined medication monitor and telephone reminders); Loss to follow-up (telephone reminders); Loss to follow-up (medication monitor); Loss to follow-up (combined medication monitor and telephone reminders); Poor adherence (telephone reminders); Poor adherence (medication monitor); Poor adherence (telephone reminder and medication monitor);	
Setting:		
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	
Desirable Effects	How substantial are the desirable anticipated effects? ● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	For VOT there were only cohort studies. These studies were from high-income countries. There were no data from low- and middle-income countries. Patients whose treatment included VOT had minimally higher mortality than those using regular DOT but, due to the rarity of mortality events, these findings may not be significant. The GDG expressed concerns at the uncertainty of evidence surrounding the use of VOT. This uncertainty fueled the conditional recommendation for this intervention.	There is concern at the indirectness of evidence for VOT, given that the studies were done in low-burden countries. There are many varieties of VOT, so many different options are likely to be available to TB programmes. VOT may be particularly useful in low- and middle-income countries where the health-care system is overburdened.
Undesirable Effects	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	**Summary of findings:** Outcome / With none / With mobile health interventions / Difference (95% CI) / Relative effect (RR) (95% CI) Mortality - cohort studies (VOT versus in-person DOT) / 9 per 1000 / 16 per 1000 (2 to 155) / 7 more per 1000 (from 7 fewer to 146 more) / RR 1.80 (0.19 to 17.00) Completion - cohort studies (VOT versus in-person DOT) / 709 per 1000 / 830 per 1000 (560 to 1000) / 121 more per 1000 (from 149 fewer to 511 more) / RR 1.17 (0.79 to 1.72)	
Certainty of evidence	What is the overall certainty of the evidence of effects? ● Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	

	Judgement	Research evidence	Additional considerations
Values	Is there important uncertainty about, or variability in, the extent to which people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence was identified.	
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ● Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	No research evidence was identified.	
Equity	What would be the impact on health equity? ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	No research evidence was identified.	See mobile technology intervention.
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No research evidence was identified.	See mobile technology intervention.
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	No research evidence was identified.	See mobile technology intervention.

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know	
Certainty of evidence	Very low	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the interven-tion or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should video observed treatment versus DOT be used for TB treatment?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ●	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
Recommendation	The GDG suggests that VOT or DOT could be used in patients undergoing TB treatment (conditional recommendation, very low certainty of evidence).				
Justification					
Subgroup considerations					
Implementation consider-ations	Other support should be provided together with VOT.				
Monitoring and evaluation					
Research priorities	Suggested areas for research are: efficacy of VOT in low- and middle-income countries; utilization of data from other medical programmes that use telephone technology (especially the in the field of HIV).				

PICO 10.10

Question

Should reminders and tracers versus none be used for TB treatment?		
Population:	TB patients	Background:
Intervention:	Reminders and tracers	
Comparison:	none	
Main outcomes:	Mortality - cohort studies; Mortality - RCTs; Treatment success - cohort studies; Treatment success - RCTs; Treatment completion - cohort studies; Treatment completion - RCT; Cure - cohort studies; Failure - cohort studies; Loss to follow-up - cohort studies; Loss to follow-up - RCTs; Adherence; Sputum/culture conversion at 2 months; Development of drug resistance - cohort studies.	
Setting:		
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		
Desirable Effects	How substantial are the desirable anticipated effects? ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	Data from RCTs showed: There were higher rates of treatment success, treatment adherence, and 2-month sputum conversion with reminders/tracers. There were lower rates of mortality and loss to follow-up with reminders/tracers.	Higher rates of culture conversion benefit the community by decreasing the spread of TB.

	Judgement	Research evidence	Additional considerations
Undesirable Effects	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	**Reminders and tracers compared to none for TB treatment**	

Outcomes	No of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with none	Risk difference with reminders and tracers
Mortality - cohort studies	406825 (3 observational studies)	(⊕◯◯◯) VERY LOW 1,2	not estimable	80 per 1000	80 fewer per 1000 (80 fewer to 80 fewer)
Mortality - RCTs	480 (1 RCT)	(⊕⊕◯◯) LOW 2,3	RR 0.38 (0.10 to 1.40)	33 per 1000	21 fewer per 1000 (30 fewer to 13 more)
Treatment success - cohort studies	406825 (3 observational studies)	(⊕◯◯◯) VERY LOW 1,2,4	RR 1.03 (0.89 to 1.20)	764 per 1000	23 more per 1000 (84 fewer to 153 more)
Treatment success - RCTs	778 (4 RCTs)	(⊕⊕◯◯) LOW 4,5	RR 1.12 (1.01 to 1.26)	779 per 1000	93 more per 1000 (8 more to 203 more)
Treatment completion - cohort studies	405673 (1 observational study)	(⊕⊕◯◯) LOW	RR 1.29 (1.27 to 1.32)	88 per 1000	25 more per 1000 (24 more to 28 more)
Treatment completion - RCT	252 (2 RCTs)	(⊕◯◯◯) VERY LOW 2,4,6	not estimable	728 per 1000	728 fewer per 1000 (728 fewer to 728 fewer)
Cure - cohort studies	405815 (2 observational studies)	(⊕◯◯◯) VERY LOW 1,2,4	RR 1.28 (0.59 to 2.79)	676 per 1000	189 more per 1000 (277 fewer to 1,210 more)
Failure - cohort studies	406825 (3 observational studies)	(⊕◯◯◯) VERY LOW 1	not estimable	21 per 1000	21 fewer per 1000 (21 fewer to 21 fewer)
Loss to follow-up - cohort studies	408081 (4 observational studies)	(⊕◯◯◯) VERY LOW 1,2,4	not estimable	83 per 1000	83 fewer per 1000 (83 fewer to 83 fewer)
Loss to follow-up - RCTs	671 (2 RCTs)	(⊕⊕◯◯) LOW 2,3	RR 0.23 (0.03 to 1.58)	114 per 1000	88 fewer per 1000 (111 fewer to 66 more)
Adherence	747 (2 RCTs)	(⊕⊕⊕◯) MODERATE 6	RR 1.41 (1.14 to 1.76)	470 per 1000	193 more per 1000 (66 more to 357 more)
Sputum/culture conversion at 2 months	495 (2 RCTs)	(⊕⊕⊕◯) MODERATE 5	RR 1.26 (1.14 to 1.40)	669 per 1000	174 more per 1000 (94 more to 268 more)
Development of drug resistance - cohort studies	405673 (1 observational study)	(⊕⊕◯◯) LOW	RR 0.50 (0.45 to 0.55)	6 per 1000	3 fewer per 1000 (4 fewer to 3 fewer)

Certainty of evidence	What is the overall certainty of the evidence of effects? ● Very low ○ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	
Values	Is there important uncertainty about, or variability in, the extent to which people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence was identified.	
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	No research evidence was identified.	

	Judgement	Research evidence	Additional considerations
Equity	What would be the impact on health equity? ○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	Health equity would be increased unless the patient lives in an area that cannot be reached by a communication network.
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know	
Certainty of evidence	Very low	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should reminders and tracers versus none be used for TB treatment?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ●	Strong recommendation for the intervention ○
Recommendation	The GDG suggests that reminders or tracers* should be used for patients on tuberculosis treatment (conditional recommendation, very low certainty of evidence).				
Justification	Reminders or tracers include text messages, telephone calls, medicine monitors or home visits.				
Subgroup considerations					
Implementation considerations	Multiple organizations have initiated programmes like these, so TB programmes may find it helpful to collaborate and communicate with other medical service delivery programmes that have already set up the infrastructure.				
Monitoring and evaluation					
Research priorities					

PICO 10.11

Question

Should mixed patient case management interventions versus none be used for TB treatment?		
Population:	TB patients	Background:
Intervention:	Mixed case management interventions	
Comparison:	none	
Main outcomes:	Mortality - cohort studies (enhanced DOT versus SAT); Mortality - cohort studies (enhanced DOT versus DOT); Mortality - RCTs (mixed interventions versus SAT); Mortality - RCTs (enhanced DOT versus DOT); Treatment success - cohort studies (enhanced DOT versus SAT); Treatment success - cohort studies (enhanced DOT versus DOT); Treatment success - RCTs (enhanced DOT versus SAT); Treatment success - RCTs (enhanced DOT versus DOT); Treatment completion - cohort studies (enhanced DOT versus SAT); Treatment completion - cohort studies (enhanced DOT versus DOT); Treatment completion - RCTs (enhanced DOT versus SAT); Treatment completion - RCTs (enhanced DOT versus DOT); Cure - cohort studies (enhanced DOT versus DOT); Cure - RCTs (enhanced DOT versus DOT); Cure - cohort studies (enhanced DOT versus SAT); Cure - RCTs (enhanced DOT versus SAT); Cure - RCTs (mixed case management versus SAT); Failure - cohort studies (enhanced DOT versus DOT); Failure - cohort studies (enhanced DOT versus SAT); Failure - RCTs (mixed case management versus SAT); Failure - RCTs (enhanced DOT versus DOT); Loss to follow-up - cohort studies (enhanced DOT versus DOT); Loss to follow-up - RCTs (enhanced DOT versus DOT); Loss to follow-up - cohort studies (enhanced DOT versus SAT); Loss to follow-up - RCTs (mixed case management versus SAT); Relapse - cohort studies (enhanced DOT versus SAT); Adherence (enhanced DOT versus DOT); Adherence (mixed case management versus SAT); Sputum smear conversion rate (2nd month) - RCTs (enhanced DOT versus SAT); Acquired drug resistance - cohort studies (enhanced DOT versus SAT).	
Setting:		
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No research evidence was identified.	
Desirable Effects	How substantial are the desirable anticipated effects? ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	In this review, enhanced DOT was compared to DOT (or SAT) without any other services. Enhanced DOT was DOT combined with some form of incentive or reminder or patient education. There is a lot of variation surrounding what "enhanced" means. Mixed interventions were a combination of some forms of support, whether incentives, reminders or patient education. Data from the RCTs showed: When enhanced DOT was compared to DOT alone, enhanced DOT had higher rates of treatment success, treatment completion, cure and adherence, and lower rates of mortality and loss to follow-up. There was a minimal increase in risk of failure with enhanced DOT. When enhanced DOT was compared to SAT, enhanced DOT had higher rates of treatment success, treatment completion, cure and 2-month sputum conversion. When mixed patient support interventions were compared to SAT, mixed patient support interventions had higher rates of cure and adherence, and lower rates of mortality and loss to follow-up.	

	Judgement	Research evidence	Additional considerations
Undesirable Effects	How substantial are the undesirable anticipated effects? ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	**Summary of findings:**	

Outcome	With none	With mixed case management interventions	Difference (95% CI)	Relative effect (RR) (95% CI)
Mortality - cohort studies (enhanced DOT versus SAT)	49 per 1000	0 per 1000 (0 to 0)	50 fewer per 1000 (from 130 fewer to 30 more)	not estimable
Mortality - cohort studies (enhanced DOT versus DOT)	49 per 1000	46 per 1000 (31 to 66)	3 fewer per 1000 (from 17 more to 18 fewer)	RR 0.93 (0.64 to 1.35)
Mortality - RCTs (mixed interventions versus SAT)	81 per 1000	71 per 1000 (35 to 141)	10 fewer per 1000 (from 45 fewer to 60 more)	RR 0.88 (0.44 to 1.75)
Mortality - RCTs (enhanced DOT versus DOT)	34 per 1000	15 per 1000 (8 to 31)	18 fewer per 1000 (from 3 fewer to 26 fewer)	RR 0.46 (0.23 to 0.91)
Treatment success - cohort studies (enhanced DOT versus SAT)	695 per 1000	848 per 1000 (806 to 883)	153 more per 1000 (from 111 more to 188 more)	RR 1.22 (1.16 to 1.27)
Treatment success - Cohort studies (enhanced DOT versus DOT)	716 per 1000	910 per 1000 (781 to 1000)	193 more per 1000 (from 64 more to 351 more)	RR 1.27 (1.09 to 1.49)
Treatment success - RCTs (enhanced DOT versus SAT)	688 per 1000	935 per 1000 (729 to 1000)	248 more per 1000 (from 41 more to 516 more)	RR 1.36 (1.06 to 1.75)
Treatment success - RCTs (enhanced DOT versus DOT)	748 per 1000	868 per 1000 (830 to 913)	120 more per 1000 (from 82 more to 165 more)	RR 1.16 (1.11 to 1.22)
Treatment completion - cohort studies (enhanced DOT versus SAT)	304 per 1000	560 per 1000 (462 to 672)	255 more per 1000 (from 158 more to 368 more)	RR 1.84 (1.52 to 2.21)
Treatment completion - cohort studies (enhanced DOT versus DOT)	411 per 1000	349 per 1000 (214 to 567)	62 fewer per 1000 (from 156 more to 197 fewer)	RR 0.85 (0.52 to 1.38)
Treatment completion - RCTs (enhanced DOT versus SAT)	688 per 1000	969 per 1000 (763 to 1000)	282 more per 1000 (from 76 more to 543 more)	RR 1.41 (1.11 to 1.79)
Treatment completion - RCTs (enhanced DOT versus DOT)	71 per 1000	59 per 1000 (41 to 84)	12 fewer per 1000 (from 13 more to 30 fewer)	RR 0.83 (0.58 to 1.19)
Cure - cohort studies (enhanced DOT versus DOT)	339 per 1000	479 per 1000 (227 to 1000)	139 more per 1000 (from 112 fewer to 665 more)	RR 1.41 (0.67 to 2.96)
Cure - RCTs (enhanced DOT versus DOT)	699 per 1000	832 per 1000 (790 to 881)	133 more per 1000 (from 91 more to 182 more)	RR 1.19 (1.13 to 1.26)
Cure - cohort studies (enhanced DOT versus SAT)	708 per 1000	1000 per 1000 (722 to 1000)	297 more per 1000 (from 14 more to 700 more)	RR 1.42 (1.02 to 1.99)
Cure - RCTs (enhanced DOT versus SAT)	688 per 1000	935 per 1000 (729 to 1000)	248 more per 1000 (from 41 more to 516 more)	RR 1.36 (1.06 to 1.75)
Cure - RCTs (mixed case management versus SAT)	678 per 1000	780 per 1000 (698 to 875)	102 more per 1000 (from 20 more to 197 more)	RR 1.15 (1.03 to 1.29)
Failure - cohort studies (enhanced DOT versus DOT)	8 per 1000	5 per 1000 (2 to 15)	3 fewer per 1000 (from 6 fewer to 6 more)	RR 0.64 (0.23 to 1.77)
Failure - cohort studies (enhanced DOT versus SAT)	4 per 1000	0 per 1000 (0 to 0)	0 fewer per 1000 (from 20 fewer to 10 more)	not estimable
Failure - RCTs (mixed case management versus SAT)	49 per 1000	47 per 1000 (9 to 249)	2 fewer per 1000 (from 40 fewer to 200 more)	RR 0.96 (0.18 to 5.05)
Failure - RCTs (enhanced DOT versus DOT)	8 per 1000	15 per 1000 (6 to 41)	7 more per 1000 (from 2 fewer to 33 more)	RR 1.91 (0.72 to 5.07)
Loss to follow-up - cohort studies (enhanced DOT versus DOT)	167 per 1000	79 per 1000 (23 to 269)	89 fewer per 1000 (from 102 more to 144 fewer)	RR 0.47 (0.14 to 1.61)
Loss to follow-up - RCTs (enhanced DOT versus DOT)	179 per 1000	68 per 1000 (45 to 102)	111 fewer per 1000 (from 77 fewer to 134 fewer)	RR 0.38 (0.25 to 0.57)
Loss to follow-up - cohort studies (enhanced DOT versus SAT)	269 per 1000	164 per 1000 (86 to 306)	105 fewer per 1000 (from 38 more to 183 fewer)	RR 0.61 (0.32 to 1.14)
Loss to follow-up - RCTs (mixed case management versus SAT)	186 per 1000	108 per 1000 (67 to 173)	78 fewer per 1000 (from 13 fewer to 119 fewer)	RR 0.58 (0.36 to 0.93)
Relapse - cohort studies (enhanced DOT versus SAT)	13 per 1000	0 per 1000 (0 to 0)	10 more per 1000 (from 30 more to 10 fewer)	not estimable
Adherence (enhanced DOT versus DOT)	760 per 1000	798 per 1000 (646 to 988)	38 more per 1000 (from 114 fewer to 228 more)	RR 1.05 (0.85 to 1.30)
Adherence (mixed case management versus SAT)	571 per 1000	709 per 1000 (509 to 983)	137 more per 1000 (from 63 fewer to 411 more)	RR 1.24 (0.89 to 1.72)
Sputum smear conversion rate (2nd month) - RCTs (enhanced DOT versus SAT)	531 per 1000	877 per 1000 (616 to 1000)	345 more per 1000 (from 85 more to 712 more)	RR 1.65 (1.16 to 2.34)
Acquired drug resistance - Cohort studies (enhanced DOT versus SAT)	9 per 1000	0 per 1000 (0 to 0)	10 more per 1000 (from 30 more to 10 fewer)	not estimable

	Judgement	Research evidence	Additional considerations
Certainty of evidence	What is the overall certainty of the evidence of effects? ○ Very low ● Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	Because all the effects point in the same direction and the majority of the outcomes of interest are graded as having moderate or low certainty of evidence, the outcomes graded as moderate certainty drive the overall evidence grade. Therefore, instead of grading the evidence at the lowest grade of the outcome of interest (mortality at a grade of very low), the preponderance of moderate certainty of evidence improves the overall evidence grade to low. The GDG also believed that the quality of the mortality data should not affect the overall data grading to a great degree because the mortality data was weak due to rarity of events and a large confidence interval.
Values	Is there important uncertainty about, or variability in, the extent to which people value the main outcomes? ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	No research evidence was identified.	
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ● Favours the intervention ○ Varies ○ Don't know	No research evidence was identified.	
Equity	What would be the impact on health equity? ○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	The same financial concerns apply here as outlined in the section on incentives/enablers.
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know	
Certainty of evidence	Very low	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the interven-tion or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

Should mixed case management interventions versus none be used for TB treatment?

Type of recommendation	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ●	Strong recommendation for the intervention ○
Recommendation	The GDG suggests that a combination of DOT or organized self-administered treatment (SAT) plus other treatment adherence interventions* should be provided instead of DOT alone or SAT (conditional recommendation, low certainty of evidence).				
Justification	*Other treatment adherence interventions include: relevant DOT provider, staff education, digital health reminders (SMS, telephone calls), different types of social support such as material support for the patient (e.g. financial incentives, food, transport subsidies), and health education or psychological support.				
Subgroup considerations					
Implementation consider-ations					
Monitoring and evaluation					
Research priorities					

PICO 11

Question

Should decentralized treatment and care versus centralized treatment and care be used for patients on MDR-TB treatment?		
Population:	Patients on MDR-TB treatment	Background:
Intervention:	Decentralized treatment and care	
Comparison:	Centralized treatment and care	
Main outcomes:	Treatment success versus treatment failure/death/loss to follow-up; Loss to follow-up versus treatment success/treatment failure/death; Death versus treatment success/treatment failure/loss to follow-up; Treatment failure versus treatment success/death/loss to follow-up.	
Setting:	Countries which have decentralized treatment and care for patients with multi-drug resistant tuberculosis.	
Perspective:		

Assessment

	Judgement	Research evidence	Additional considerations
Problem	Is the problem a priority? ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	WHO recommendations from 2011 state that patients with MDR-TB should be treated mainly in an ambulatory setting rather than in a system based mainly in the hospital. This is an update of that guidance.	As Xpert rolls out more patients will be diagnosed in decentralized centres, requiring more treatment in decentralized areas.
Desirable Effects	How substantial are the desirable anticipated effects? ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	Decentralized care was defined as care in the local community where the patient lives provided by non-specialized or periphery health centres, by community health workers or nurses, by non-specialized doctors, community volunteers or treatment supporters. There may have been a brief phase of initial hospitalization up to 1 month. Care could occur at local venues or at the patient's home or workplace. Treatment and care included DOT and patient support, and injections during the intensive phase. Centralized care was defined as treatment and care provided solely by specialized DR-TB centres or teams. This care was usually delivered by specialist doctors or nurses and could include centralized outpatient clinics (outpatient facilities located at or near the site of the centralized hospital). The care was defined as inpatient care for the duration of the intensive phase of treatment or until culture smear conversion. After that, patients could have received decentralized care. Both HIV-negative and HIV-positive persons were included in the studies examined. However, the studies did not stratify patients on the basis of HIV status. Treatment success and loss to follow-up improved with decentralized care versus centralized care. The risk of death and treatment failure showed minimal difference between patients undergoing decentralized care or centralized care. There were limited data on adverse reactions, adherence, acquired drug resistance and cost. No studies examined injections during the intensive phase or support for co-morbidities. The study by Narita et al. was excluded from sensitivity analysis due to concerns that it was very different from the other studies. For instance, it was conducted in the USA in the 1990s and the patients selected for hospitalized care in the study were failing their treatment or were non-adherent. The results of this study differed significantly from the other studies and had wide confidence intervals. Exclusion of this study did not significantly affect the treatment success or risk of death.	The GDG expressed concern that health-care workers may have selected patients that they thought might have a worse prognosis into the centralized care groups. None of the studies controlled for this risk of bias.

<table>
<tr><th></th><th>Judgement</th><th>Research evidence</th><th>Additional considerations</th></tr>
<tr><td>Undesirable Effects</td><td>How substantial are the undesirable anticipated effects?
○ Large
○ Moderate
○ Small
● Trivial

○ Varies
○ Don't know</td><td>Decentralized treatment and care compared to centralized treatment and care of patients on MDR-TB treatment
<table>
<tr><th>Outcomes</th><th>No of participants (studies) Follow-up</th><th>Quality of the evidence (GRADE)</th><th>Relative effect (95% CI)</th><th colspan="2">Anticipated absolute effects</th></tr>
<tr><th></th><th></th><th></th><th></th><th>Risk with centralized treatment and care</th><th>Risk difference with decentralized treatment and care</th></tr>
<tr><td>Treatment success versus treatment failure/death/loss to follow-up</td><td>3405 (5 observational studies)</td><td>(⊕◯◯◯) VERY LOW 1,2,3,4</td><td>RR 1.13 (1.01 to 1.27)</td><td>573 per 1000</td><td>74 more per 1000 (6 more to 155 more)</td></tr>
<tr><td>Loss to follow-up versus treatment success/treatment failure/death</td><td>3276 (4 observational studies)</td><td>(⊕◯◯◯) VERY LOW 1,2,3,4</td><td>RR 0.66 (0.38 to 1.13)</td><td>222 per 1000</td><td>76 fewer per 1000 (138 fewer to 29 more)</td></tr>
<tr><td>Death versus treatment success/treatment failure/loss to follow-up</td><td>2754 (4 observational studies)</td><td>(⊕◯◯◯) VERY LOW 1,2,3,4</td><td>RR 1.01 (0.67 to 1.53)</td><td>172 per 1000</td><td>2 more per 1000 (57 fewer to 91 more)</td></tr>
<tr><td>Treatment failure versus treatment success/death/loss to follow-up</td><td>2693 (3 observational studies)</td><td>(⊕◯◯◯) VERY LOW 1,2,3,4</td><td>RR 1.07 (0.48 to 2.40)</td><td>42 per 1000</td><td>3 more per 1000 (22 fewer to 59 more)</td></tr>
</table></td><td></td></tr>
<tr><td>Certainty of evidence</td><td>What is the overall certainty of the evidence of effects?
● Very low
○ Low
○ Moderate
○ High

○ No included studies</td><td>No research evidence was identified.</td><td></td></tr>
<tr><td>Values</td><td>Is there important uncertainty about, or variability in, the extent to which people value the main outcomes?
○ Important uncertainty or variability
○ Possibly important uncertainty or variability
● Probably no important uncertainty or variability
○ No important uncertainty or variability</td><td>No research evidence was identified.</td><td></td></tr>
<tr><td>Balance of effects</td><td>Does the balance between desirable and undesirable effects favour the intervention or the comparison?
○ Favours the comparison
○ Probably favours the comparison
○ Does not favour either the intervention or the comparison
● Probably favours the intervention
○ Favours the intervention

○ Varies
○ Don't know</td><td>No research evidence was identified.</td><td></td></tr>
</table>

<table>
<tr><th></th><th>Judgement</th><th>Research evidence</th><th>Additional considerations</th></tr>
<tr><td>Resources required</td><td>How large are the resource requirements (costs)?
○ Large costs
○ Moderate costs
○ Negligible costs and savings
○ Moderate savings
○ Large savings

● Varies
○ Don't know</td><td>No research evidence was identified.</td><td>The cost estimates were based on limited studies. This would be an area for further research.
Although hospitalization is generally thought of as being more expensive than outpatient care, good outpatient programmes have significant costs as well. These costs in outpatient programmes may vary significantly depending on the services provided.
A cost-saving measure with decentralized care may be that patients are able to access treatment faster. Treating patients before they are very ill and require more medical care, and making public health savings by treating people before TB can be transmitted to contacts could be benefits of decentralized care.
The resource requirements probably vary because country programmes are highly variable and so the costs of these programmes in different countries are variable.</td></tr>
<tr><td>Certainty of evidence of required resources</td><td>What is the certainty of the evidence of resource requirements (costs)?
● Very low
○ Low
○ Moderate
○ High

○ No included studies</td><td>Of the eight studies eligible for inclusion in the review, three (two modelling studies and one cohort study) reported on treatment costs. Table 6 compares the treatment cost to the health-care system for one MDR-TB patient in the decentralized and centralized setting. The two modelling studies showed significant cost savings using a decentralized compared with a centralized model. Whereas, the study by Kerschberger et al showed similar treatment costs for both treatment models.
Treatment cost to the health-care system for one MDR-TB patient in decentralized and centralized care settings (in US$)
<table>
<tr><th>Study</th><th>Study design</th><th>Country</th><th>Description of decentralized care</th><th>Cost of decentralized care</th><th>Description of centralized care</th><th>Cost of centralized care</th></tr>
<tr><td>Musa 2015</td><td>Modelling</td><td>Nigeria</td><td>Home-based care for entire duration of treatment</td><td>$1535</td><td>Hospital-based care for intensive phase then home-based care for continuation phase</td><td>$2095</td></tr>
<tr><td>Sinanovic 2015</td><td>Modelling</td><td>South Africa</td><td>Primary health-care clinic for entire duration of treatment</td><td>$7753</td><td>Hospital-based care for intensive phase (until 4-month culture conversion) then clinic-based care</td><td>$13,432</td></tr>
<tr><td>Kerschberger 2016</td><td>Retrospective cohort</td><td>Swaziland</td><td>Home-based care for entire duration of treatment</td><td>$13,361</td><td>Clinic-based care for intensive phase then home-based care for continuation phase</td><td>$13,006</td></tr>
</table></td><td></td></tr>
<tr><td>Cost-effectiveness</td><td>Does the cost-effectiveness of the intervention favour the intervention or the comparison?
○ Favours the comparison
○ Probably favours the comparison
○ Does not favour either the intervention or the comparison
● Probably favours the intervention
○ Favours the intervention

○ Varies
○ No included studies</td><td>No research evidence was identified.</td><td></td></tr>
</table>

	Judgement	Research evidence	Additional considerations
Equity	What would be the impact on health equity? ○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	
Acceptability	Is the intervention acceptable to key stakeholders? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	
Feasibility	Is the intervention feasible to implement? ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	In some places it may be illegal to treat MDR-TB patients in a decentralized setting. These legal issues need to be addressed.

Summary of judgements

	Judgement							Implications
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know	
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know	
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know	
Certainty of evidence	Very low	Low	Moderate	High			No included studies	
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability				
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know	
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies	
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies	
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know	
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know	
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know	

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