Evidence reviews to support the update of NICE guidance on Tuberculosis: clinical diagnosis and management of tuberculosis and measures for its prevention and control

**Review 2: Effectiveness and cost-effectiveness of case management strategies to increase the uptake of, or adherence to, treatment for people with active or latent TB**

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FINAL REPORT

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Declaration of authors’ competing interests

No authors have any competing interests.

Abbreviations used in the report

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>BA</td>
<td>before-after (study)</td>
</tr>
<tr>
<td>CM</td>
<td>case management</td>
</tr>
<tr>
<td>CPH</td>
<td>Centre for Public Health (at NICE)</td>
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<tr>
<td>DOPT</td>
<td>directly observed preventive therapy</td>
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<tr>
<td>DOT</td>
<td>directly observed therapy</td>
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<tr>
<td>ECM</td>
<td>enhanced case management</td>
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<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>ICER</td>
<td>incremental cost-effectiveness ratio</td>
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<tr>
<td>IDU</td>
<td>injecting drug user</td>
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<tr>
<td>INH</td>
<td>isoniazid</td>
</tr>
<tr>
<td>LTBI</td>
<td>latent tuberculosis infection</td>
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<tr>
<td>MDR-TB</td>
<td>multidrug-resistant tuberculosis</td>
</tr>
<tr>
<td>NA</td>
<td>not applicable</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
</tr>
<tr>
<td>NR</td>
<td>not reported</td>
</tr>
<tr>
<td>nRCT</td>
<td>non-randomised controlled trial</td>
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<tr>
<td>NS</td>
<td>not significant</td>
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<tr>
<td>OR</td>
<td>odds ratio</td>
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<tr>
<td>QA</td>
<td>quality assessment</td>
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<td>QALY</td>
<td>quality-adjusted life year</td>
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<td>RCT</td>
<td>randomised controlled trial</td>
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<tr>
<td>RR</td>
<td>risk ratio (relative risk)</td>
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<tr>
<td>SAT</td>
<td>self-administered therapy</td>
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<td>TB</td>
<td>tuberculosis</td>
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</table>
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1 Executive summary

This report presents the findings of a systematic review commissioned by the NICE Centre for Public Health to support the development of updated guidance on tuberculosis. The review questions are:

- What case management strategies and interventions are effective and cost effective in increasing the uptake of, or adherence to, treatment for people with active or latent TB?
- What is known from studies of case management interventions about the barriers to uptake and adherence to treatment for active or latent TB?

We searched a range of database sources from 1993 to 2013. We included outcome evaluations, cost-effectiveness studies or studies reporting views about an intervention, where the intervention involved a case manager working with individual patients (including directly observed therapy), in order to increase uptake of or adherence to treatment. Quality assessment and data extraction were carried out using standardised forms from the NICE methods manual. Data were synthesized narratively.

Thirty studies were included in the review (13 effectiveness studies, 16 cost-effectiveness studies, and two views studies, with one study in two categories). Seven studies were rated high quality (++) and fifteen medium (+) and fifteen low (–).

The findings of the studies are summarised in the evidence statements below.

**Evidence statement 1: effectiveness of case management and DOT for patients with active TB on treatment adherence and completion**

There is weak evidence from one (–) US study\(^1\) that a videophone DOT intervention achieves similar rates of adherence to TB treatment as standard DOT (95% against 97.5%).

There is weak evidence from one (–) South Korean study\(^2\) that a service-level intervention involving intensified supervision of staff to improve case management practice achieves improved rates of follow-up X-rays (intervention 90.8% against control 80.2%, significance NR), sputum smear and culture tests (97.6% against 70.2%, significance NR), drug collection rates (87.9% against 77.1%, \(p<0.01\)), delays in drug collection of 7 days or more (4.7% against 12.2%, \(p<0.01\)), treatment completion rates (78.8% against 65.2%, \(p<0.01\)), and treatment success (75.2% against 45.8%, \(p<0.01\)).

There is strong evidence from one (++) Australian study\(^3\) that family-based DOT does not lead to higher adherence (RR 1.04 (0.88–1.23)) than standard treatment with self-administered therapy. There was a non-statistically-significant trend towards improved treatment completion (RR 2.7 (0.66–14.2)).
Applicability

The evidence is directly applicable to people in the UK. This is because there are no obvious differences in the population, context or setting of the studies compared to the UK context.

1 DeMaio et al., 2001 (–)
2 Jin et al., 1993 (–)
3 MacIntyre et al., 2003 (++)

Evidence statement 2: effectiveness of case management and DOT for drug users on treatment uptake, adherence and completion

There is weak evidence from one US study (–)\(^1\) that a policy of directly observed preventive therapy (DOPT) showed a non-statistically-significant trend towards lower rates of TB among drug users compared to self-administered preventive therapy (one-group RR 0.4 (0.04-4.8)).

There is conflicting evidence from two (++) US studies\(^2,3\) as to whether DOPT leads to higher adherence rates than SAT among drug users. There is strong evidence from one (++) US study\(^4\) that DOPT does not lead to higher completion rates, or adherence rates, than usual care with SAT among drug users (completion 80% against 79%; adherence 82% against 90% (for 80% adherence), 80% against 77% (for 90% adherence)). However, DOPT did lead to higher adherence rates than usual care for 100% adherence (77% against 10%, p<0.001), and to higher adherence rates than a peer support intervention (80% against 51% (for 90% adherence), p < 0.001; 77% against 6% (for 100% adherence), p<0.001).

There is strong evidence from one (++) US study\(^2\) that DOPT combined with methadone treatment leads to higher rates of TB treatment completion among heroin-dependent injecting drug users than usual care with SAT (77.1% against 13.1%, p < 0.0001). However, an additional case management component with counselling and service access did not increase the effectiveness of the basic intervention (59.5% completion).

There is strong evidence from one (++) US study\(^4\) that either outreach DOPT with incentives or on-site DOPT with incentives improve adherence among drug users more than outreach DOPT alone, but outreach DOPT with incentives is not significantly different from on-site DOPT with incentives (OR for outreach DOPT with incentive vs outreach DOPT alone 29.7 (56.5–134.5); OR for on-site DOPT with incentive vs outreach DOPT alone 39.7 (58.7–134.5)).

There is strong evidence from one (++) Estonian study\(^5\) that an intervention involving incentives, scheduling visits and reminders, and providing transport, increases attendance at a TB clinic among drug users (57.1% against 30.4%, p = 0.004).

Applicability
The evidence is partially applicable to people in the UK who use drugs. This is because the populations of drug users in the studies, or the services available to them, may differ from those in the UK.

1 Graham et al., 1996 (–)
2 Batki et al., 2002 (++)
3 Chaisson et al., 2001 (++))
4 Malotte et al., 2001 (++)
5 Rüütel et al., 2011 (++)

**Evidence statement 3: effectiveness of DOT for people with latent TB infection on treatment completion**

There is medium evidence from one (+) study conducted in multiple countries (not the UK)\(^1\) that DOT leads to higher treatment completion rates and lower risk of active TB than self-administered therapy (completion 82.1% against 69.0%, \(p < 0.001\); risk of active TB adjusted hazard ratio 0.38 (0.15-0.99), \(p = 0.05\)). However, the regimens used in this study differed between groups.

**Applicability**

The evidence is directly applicable to people in the UK. This is because there are no obvious differences in the population, context or setting of the studies compared to the UK context.

1 Sterling et al., 2011 (+)

**Evidence statement 4: effectiveness of case management and observed drug collection for migrants or new entrants on treatment uptake and completion**

There is weak evidence from one (–) US study\(^1\) that cultural case management, including culturally tailored education and support by trained peers, leads to higher uptake of treatment (88% against 73%, \(p<0.001\)) and completion of treatment (82% against 37%, \(p<0.001\)) for LTBI among refugee populations.

There is weak evidence from one (–) Italian study\(^2\) that requiring immigrants to attend clinic sites to collect drugs for LTBI treatment leads to lower rates of treatment completion (7.3% against 26%, \(p=0.006\)).

**Applicability**

The evidence is partially applicable to immigrants to the UK. This is because the populations of migrants in the studies, or the policies in place around immigration, may differ from those in the UK.

1 Goldberg et al., 2004 (–)
Evidence statement 5: effectiveness of DOT for people with HIV on treatment completion

There is medium evidence from one (+) US study\(^1\) that DOT leads to higher rates of treatment completion than SAT for LTBI treatment among people with HIV (93% against 61%, \(p < 0.001\)). However, this study also involved a change in regimen.

Applicability

The evidence is directly applicable to people in the UK. Despite differences in the broader healthcare context in the USA, there are no obvious differences in the population, context or setting of the study compared to the UK context.

\(^1\) Narita et al., 2002 (+)

Evidence statement 6: effectiveness of education and tracking for homeless people on treatment completion

There is strong evidence from one (++) US study\(^1\) that an education programme and active tracking of defaulters, with DOT and incentives, leads to higher rates of completion of LTBI treatment among homeless people than DOT and incentives alone (adjusted OR 3.01 (2.15-4.20), \(p < 0.001\)).

Applicability

The evidence is partly applicable to people in the UK. This is because the population of homeless people in the study, or the services available to them, may differ from those in the UK.

\(^1\) Nyamathi et al., 2006 (++)

Evidence statement 7: cost-effectiveness of DOT, increased outpatient care, and Find and Treat for patients with active TB

There is medium evidence from five (3 + and 2 –) cost-effectiveness studies\(^1-5\) that directly observed therapy for active TB incurs lower net costs than self-administered therapy, when the cost savings resulting from reduced treatment failure are taken into account. Relative net cost savings from DOT in these studies\(^1,4-5\) range from US$1,788 to US$16,370 per patient treated (with other studies reporting a relative cost per death averted of US$1,234\(^2\), and a relative cost per patient cured of US$2,783\(^3\)).

However, there is weak evidence from one (–) cost-effectiveness study\(^6\) that DOT is more costly than SAT for patients at low risk of default (incremental cost of US$919 per patient treated, US$40,260 per patient cured). There is also moderate evidence
from one (+) study that a policy of universal DOT is more costly than a policy of partial DOT (incremental cost of US$24,064 per patient cured).³

There is medium evidence from one (+) cost-effectiveness study⁷ that a Find and Treat service which combines mobile screening for high-risk populations with enhanced case management support has an incremental cost-effectiveness compared to usual care of £6,400 per QALY (£18,000 per QALY for mobile screening and £4,100 per QALY for enhanced case management).

There is weak evidence from one (−) cost-effectiveness study that a policy of increased outpatient care for TB is less costly than usual care (cost savings of US$10,804 for smear-positive patients, US$9,028 for smear-negative per patient cured), although the addition of DOT and incentives makes little difference to this.

There is weak evidence from one (−) cost-effectiveness study⁹ that remote DOT via videophone has an incremental cost-effectiveness of Aus$1.32 per day of observation, compared to in-person DOT.

Evidence statement 8: Cost-effectiveness of screening and DOT for drug users

There is weak evidence from three (1 +¹ and 2 −²,³) cost-effectiveness studies that programmes for drug users which include screening and directly observed prophylactic therapy have lower relative net costs than no intervention, with net cost savings ranging from US$3,724 to US$30,770 per case averted, or from US$1,380 to US$3,590 per person treated¹⁻³.

Evidence statement 9: Cost-effectiveness of DOT for people with latent TB infection

There is weak evidence from one (−) cost-effectiveness study¹ that weekly isoniazid and rifapentine under DOT is cost saving compared to no intervention, while twice-weekly isoniazid under DOT has an incremental cost-effectiveness ratio of $7,879 per QALY compared to no intervention.
Evidence statement 10: Cost-effectiveness of screening, LTBI treatment and DOPT for new entrants

There is good evidence from one (++) study¹ that a screening and LTBI treatment programme for new entrants to the USA is cost saving compared to no intervention, and that reminders by phone, post or home visiting are also cost saving. However, this study finds the incremental cost of DOPT compared to the combination of all these interventions to be over US$100,000 per QALY.

¹ Porco et al., 2006 (++)

Evidence statement 11: Cost-effectiveness of DOPT for neonates exposed to TB

There is weak evidence from one (–) cost-effectiveness study¹ that directly observed preventive therapy has an incremental cost-effectiveness of US$21,710,000 per death prevented compared to no intervention, substantially greater than parent-administered therapy.

¹ Berkowitz et al., 2006 (–)

Evidence statement 12: Qualitative evidence on interventions to promote adherence to treatment for TB or LTBI

There is weak evidence from one (–) UK study¹ that a link worker for marginalized people with TB or LTBI is viewed positively by staff in other agencies. Participants report that the link worker increases understanding of TB among workers in different services, facilitates service users’ access to different services and provides practical and emotional support.

There is medium evidence from one (+) Australian study² that a videophone DOT service is viewed positively by staff and patients. The privacy and convenience of the videophone DOT service were especially valued.

¹ Craig et al., 2008 (–)
² Wade et al., 2012 (+)
2 **Background**

Sub-optimal uptake of, and adherence to, tuberculosis treatment for people with active or latent TB can lead to increased morbidity and mortality, increased infectiousness, and the emergence of drug resistance.

A range of strategies may be employed to promote uptake of and/or adherence to treatment. This review focuses on case management approaches, including directly observed therapy. A separate review is also being conducted on education and support strategies.

Case management can be defined as any approach in which a named case manager co-ordinates care and management for a patient with suspected or confirmed TB. Enhanced case management (ECM) involves the case manager working alongside a multidisciplinary team to co-ordinate clinical and psychosocial care. Existing UK guidance (Story and Cocksedge, 2012) recommends ECM for all patients with clinically or socially complex needs. As well as specialist clinical care, ECM should also include outreach and advocacy work to address patients’ other needs (e.g. housing, substance misuse, welfare) within a flexible and responsive model of care.

Case management may include directly observed therapy (DOT), in which a trained health professional provides medication and observes the person swallowing every dose. Previous NICE public health guidance (PH37) recommends DOT for the following groups:

- all hard-to-reach children aged under 16;
- those who do not, or have previously not, adhered to treatment;
- those previously treated for TB;
- those with a history of homelessness, drug or alcohol misuse;
- those who are currently, or have been previously, in prison;
- those with a major psychiatric, memory or cognitive disorder;
- those in denial of the TB diagnosis;
- those who have multi-drug resistant TB; and
- those too ill to administer treatment.

Guidance from the Royal College of Nursing (Story and Cocksedge, 2012) recommends DOT for a similar range of populations, including in addition all children aged under 16 and those who request DOT. However, in previous NICE clinical guidance (CG117), DOT is recommended only for homeless people and those with a history of non-adherence.
3 Methods

This review was conducted according to the methods guidance set out in the current (third) edition of Methods for the Development of NICE Public Health Guidance (National Institute for Health and Care Excellence, 2012).

3.1 Review questions

The review questions are:

- What case management strategies and interventions are effective and cost effective in increasing the uptake of, or adherence to, treatment for people with active or latent TB?
- What is known from studies of case management interventions about the barriers to uptake and adherence to treatment for active or latent TB?

3.2 Searching

3.2.1 Database searches

The search strategy was designed through consultations with the CPH team and the Guideline Development Group. The following database sources were searched in October 2013 and searches were limited from 1993 to the most recent records (with the exception of the Conference Proceedings Citation Indexes, which were run from 2011 to the present).

- ASSIA
- British Nursing Index
- CINAHL
- Cochrane Database of Systematic Reviews
- Cochrane Health Technology Assessment database
- Conference Proceedings Citation Index-Science
- Conference Proceedings Citation Index-Social Science & Humanities
- Database of Abstracts of Reviews of Effectiveness
- Embase
- EPPI Centre Trials Register of Promoting Health Interventions
- ERIC
- HMIC
- Medline
- Medline In Process
- NHS Economic Evaluation Database
- OpenGrey
- Science Citation Index Expanded
- Social Policy and Practice
- Social Sciences Citation Index
- Sociological Abstracts

The search strategy took the following form:
(TB) AND (terms for uptake / adherence outcomes) AND (terms for case management interventions)

A filter was used to exclude studies on animals. No language restriction was placed on the searches, although non-English language studies were subsequently excluded during the screening process. The full database search records can be found in Appendix A.

3.2.2 Other searches

The following websites were also searched:
- British Infection Association via http://www.britishinfection.org/drupal/
- British Thoracic Society via http://www.brit-thoracic.org.uk/
- Campbell Collaboration via http://www.campbellcollaboration.org/
- Chartered Institute of Environmental Health via http://www.cieh.org/
- Cochrane Infectious Diseases Group Specialized Register via http://cidg.cochrane.org/specialized-register
- Department of Health, Social Services and Public Safety of Northern Ireland via http://www.dhsspsni.gov.uk/
- Health Protection Scotland via http://www.hps.scot.nhs.uk/
- Health Quality Improvement Partnership via http://www.hqip.org.uk/
- Infection Prevention Society via http://www.ips.uk.net/
- Local Government Association via http://www.local.gov.uk
- McMaster University Health Evidence via http://www.healthevidence.org/
- National Guideline Clearinghouse http://www.guideline.gov/
- NICE via http://www.nice.org.uk/
- Public Health Observatory via http://www.apho.org.uk/
- Stop TB UK via http://www.stoptbuk.org/
- Target Tuberculosis via http://www.targettb.org.uk
- TB Alert via http://www.tbalert.org

Google was searched using a simplified version of the search string, and the advanced search options to limit to PDFs or word document files. The first 100 search results were scanned for relevance. We searched PubMed using a time-limited search to identify any new items. We conducted backwards citation searching (one generation) for all items included on full text. We conducted forwards citation searching for all items included on full text, using Web of Science and Google Scholar for forward citation chasing. Finally, we searched BL Ethos (http://ethos.bl.uk/) to identify unpublished theses.

3.3 Screening
EPPI-Reviewer 4 software was used to manage data. The following inclusion criteria were applied:

1) Does the study measure uptake of, or adherence to, tuberculosis treatment as an outcome, or concern an intervention aiming to increase uptake or adherence?
2) Does the study present primary data regarding an intervention, either concerning outcomes or processes?
3) Was the study conducted in a country which is a current OECD member?¹
4) Does the intervention include case management (CM), defined as an intervention where a designated case manager works with an individual patient? (Purely educational or informational interventions were excluded. Interventions delivered by non-professionals without specific training in CM were excluded. Directly observed therapy, with or without other CM components, was included.)
5) Is the study report written in English?
6) Was the study either:
   (i) a prospective outcome evaluation (retrospective studies with no cost-effectiveness component were excluded, although studies with a prospective intervention group and a retrospective comparison were included);
   (ii) a cost-effectiveness study (either modelling or economic evaluation); or
   (iii) a qualitative study which reported views about an intervention? (Studies about views of TB in general, or about ongoing practice in TB treatment or TB services, were excluded.)

An initial random sample of 10% of titles and abstracts was screened by two reviewers independently and differences arising were resolved by discussion. Agreement at this stage was 98.7%, with Cohen’s kappa $\kappa=0.81$. This was deemed to be adequate agreement, and subsequent titles and abstracts were screened by a single reviewer. The full text of all references which met criteria, or where it was unclear if they met the criteria, was retrieved and re-screened to the same criteria by two reviewers independently and differences were resolved by discussion. Agreement on the full-text screening was 96.1% with $\kappa=0.92$.

### 3.4 Quality assessment, data extraction and synthesis

Review quality was assessed, and data extracted, using the tools in the third edition of the CPH methods manual (National Institute for Health and Clinical Excellence, 2012). Quality assessment and data extraction were conducted by one reviewer and comprehensively checked by a second reviewer. Data were synthesized narratively.

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¹ These are: Australia, Austria, Belgium, Canada, Chile, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Korea, Luxembourg, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, UK, USA.
4 Results

4.1 Flow of literature through the review
The searches returned a total of 3,796 unique records. After screening, 30 records were included in the review (13 effectiveness studies, 16 cost-effectiveness studies, and two views studies, with one study in two categories). Figure 1 shows the flow of literature through the review.

Figure 1. Flow of literature through the review
4.2 Results of quality assessment

4.2.1 Effectiveness studies

The results of quality assessment for the effectiveness studies are shown in Table 1. Six studies were rated high quality (++), two medium (+) and five low (–).

Table 1. Quality assessment of the effectiveness studies (N=13)

<table>
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<tr>
<th>Reference</th>
<th>Design</th>
<th>Population</th>
<th>Method of allocation to intervention/comparison</th>
<th>Outcomes</th>
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<td>RCT</td>
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<td>Chaisson et al., 2001</td>
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<td>+</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Key to questions:**

1.1 Is the source population or source area well described?
1.2 Is the eligible population or area representative of the source population or area?
1.3 Do the selected participants or areas represent the eligible population or area?
2.1 Allocation to intervention (or comparison). How was selection bias minimised?
2.2 Were interventions (and comparisons) well described and appropriate?
2.3 Was the allocation concealed?
2.4 Were participants and/or investigators blind to exposure and comparison?
2.5 Was the exposure to the intervention and comparison adequate?
2.6 Was contamination acceptably low?
2.7 Were other interventions similar in both groups?
2.8 Were all participants accounted for at study conclusion?
2.9 Did the setting reflect usual UK practice?
2.10 Did the intervention or control comparison reflect usual UK practice?
3.1 Were outcome measures reliable?
3.2 Were all outcome measurements complete?
3.3 Were all important outcomes assessed?
3.4 Were outcomes relevant?
3.5 Were there similar follow-up times in exposure and comparison groups?
3.6 Was follow-up time meaningful?
4.1 Were exposure and comparison groups similar at baseline? If not, were these adjusted?
4.2 Was Intention to Treat (ITT) analysis conducted?
4.3 Was the study sufficiently powered to detect an intervention effect (if one exists)?
4.4 Were the estimates of effect size given or calculable?
4.5 Were the analytical methods appropriate?
4.6 Was the precision of intervention effects given or calculable? Were they meaningful?
5.1 Are the study results internally valid? (i.e. unbiased)
5.2 Are the study results generalisable to the source population? (i.e. externally valid)

Key to sections 1-4:
++ The study has been designed/conducted in such a way as to minimise the risk of bias
+ Either the answer to the checklist question is not clear from the way the study is reported, or the study may not have addressed all potential sources of bias
– Significant sources of bias may persist
NR The study fails to report this particular question
NA Not applicable given the study design

Key to section 5:
++ All or most of the checklist criteria have been fulfilled; where they have not been, the conclusions are very unlikely to alter
+ Some of the checklist criteria have been fulfilled, where they have not, or not adequately described, the conclusions are unlikely to alter
– Few or no checklist criteria have been fulfilled and the conclusions are likely to alter
4.2.2 Cost-effectiveness studies

The results of quality assessment for the effectiveness studies are shown in Table 2. One study was rated as ‘not applicable’ on section 1 of the tool, and in line with the guidance on the tool, was not data-extracted or further considered in the review. One study was rated as having ‘minor limitations’ (++), five as having ‘potentially serious limitations’ (+) and nine as having ‘very serious limitations’ (–).

Table 2. Quality assessment of the cost-effectiveness studies (N=16)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Applicability</th>
<th>Overall judgment</th>
<th>Study limitations</th>
<th>Overall assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.1</td>
<td>1.2</td>
<td>1.3</td>
<td>1.4</td>
</tr>
<tr>
<td>Berkowitz et al., 2006</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Burman et al., 1997</td>
<td>NR</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Chaulk et al., 2000</td>
<td>NR</td>
<td>NR</td>
<td>+</td>
<td>NR</td>
</tr>
<tr>
<td>Gourevitch et al., 1998</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Holland et al., 2009</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Jit et al., 2011</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Migliori et al., 1999</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Moore et al., 1996</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Palmer et al.,</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Year</td>
<td>Perlman et al., 2001</td>
<td>Porco et al., 2006</td>
<td>Synder &amp; Chin, 1999a</td>
<td>Snyder et al., 1999b</td>
</tr>
<tr>
<td>---------</td>
<td>----------------------</td>
<td>------------------</td>
<td>---------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>1998</td>
<td>++ + + – + – – + Partly applicable</td>
<td>++ + + ++ – + ++ +</td>
<td>+ ++ + ++ + – – + Partly applicable</td>
<td>++ + ++ + – – + + + ++ – – +</td>
</tr>
<tr>
<td>1999</td>
<td>++ + + ++ + – ++ +</td>
<td>Directly applicable</td>
<td>++ ++ + ++ + + ++ +</td>
<td>Partly applicable</td>
</tr>
<tr>
<td>1999a</td>
<td>++ ++ + ++ + – – +</td>
<td>Partly applicable</td>
<td>++ ++ ++ + – – +</td>
<td>Partly applicable</td>
</tr>
<tr>
<td>1999b</td>
<td>++ ++ + ++ + – – +</td>
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<td>2001</td>
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<td>Partly applicable</td>
<td>++ + ++ + – – +</td>
<td>Partly applicable</td>
</tr>
<tr>
<td>2006</td>
<td>++ + + ++ + – ++ +</td>
<td>Directly applicable</td>
<td>++ ++ + ++ +</td>
<td>Partly applicable</td>
</tr>
</tbody>
</table>

Key to questions:

1.1 Is the study population appropriate for the topic being evaluated?
1.2 Are the interventions appropriate for the topic being evaluated?
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?
1.4 Was were the perspective(s) clearly stated and what were they?
1.5 Are all direct health effects on individuals included, and are all other effects included where they are material?
1.6 Are all future costs and outcomes discounted appropriately?
1.7 Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)?
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?
2.3 Are all important and relevant outcomes included?
2.4 Are the estimates of baseline outcomes from the best available source?
2.5 Are the estimates of relative ‘treatment’ effects from the best available source?
2.6 Are all important and relevant costs included?
2.7 Are the estimates of resource use from the best available source?
2.8 Are the unit costs of resources from the best available source?
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?
2.11 Is there any potential conflict of interest?
4.2.3 Views studies

The results of quality assessment for the views studies are shown in Table 3. One study was rated medium quality (+) and one low (–).

Table 3. Quality assessment of the views studies (N=2)

<table>
<thead>
<tr>
<th>Reference</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Craig et al., 2008</td>
<td>Y</td>
<td>Y</td>
<td>?</td>
<td>?</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>?</td>
<td>N</td>
<td>?</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>–</td>
</tr>
<tr>
<td>Wade et al., 2012</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

Key to questions:
1. Is a qualitative approach appropriate?
2. Is the study clear in what it seeks to do?
3. How defensible/rigorous is the research design/methodology?
4. How well was the data collection carried out?
5. Is the role of the researcher clearly described?
6. Is the context clearly described?
7. Were the methods reliable?
8. Is the data analysis sufficiently rigorous?
9. Is the data 'rich'?
10. Is the analysis reliable?
11. Are the findings convincing?
12. Are the findings relevant to the aims of the study?
13. Conclusions
14. How clear and coherent is the reporting of ethics?
### 4.3 Findings: effectiveness

This section presents the findings for the review of effectiveness. Table 4 summarizes the overall characteristics of the studies.

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Des.</th>
<th>QA</th>
<th>Country</th>
<th>Population</th>
<th>Intervention / comparison</th>
<th>Outcomes</th>
<th>Direction of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batki et al., 2002</td>
<td>RCT</td>
<td>++</td>
<td>USA</td>
<td>Drug users</td>
<td>DOPT, methadone, counselling / DOPT, methadone / usual care</td>
<td>Completion</td>
<td>Effective</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Active TB No difference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chaisson et al., 2001</td>
<td>RCT</td>
<td>++</td>
<td>USA</td>
<td>Drug users</td>
<td>DOPT / peer support / usual care</td>
<td>Adherence</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Completion No difference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DeMaio et al., 2001</td>
<td>BA</td>
<td>–</td>
<td>USA</td>
<td>Patients with active TB</td>
<td>Standard DOT / videophone DOT</td>
<td>Adherence</td>
<td>No difference</td>
</tr>
<tr>
<td>Goldberg et al., 2004</td>
<td>BA</td>
<td>–</td>
<td>USA</td>
<td>Refugees</td>
<td>Case management</td>
<td>Uptake</td>
<td>Effective</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Completion Effective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graham et al., 1996</td>
<td>BA</td>
<td>–</td>
<td>USA</td>
<td>Drug users</td>
<td>DOPT</td>
<td>TB</td>
<td>Effective</td>
</tr>
<tr>
<td>Jin et al., 1993</td>
<td>RCT</td>
<td>–</td>
<td>S Korea</td>
<td>Patients with active TB</td>
<td>Intensified supervision for staff / usual supervision</td>
<td>Tests performed</td>
<td>Effective</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adherence</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Completion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MacIntyre et al., 2003</td>
<td>RCT</td>
<td>++</td>
<td>Australia</td>
<td>Patients with active TB</td>
<td>Family-based DOT / usual care</td>
<td>Adherence</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Completion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malotte et al., 2001</td>
<td>RCT</td>
<td>++</td>
<td>USA</td>
<td>Drug users</td>
<td>Outreach DOPT, incentive / outreach DOPT alone / on-site DOPT, incentive</td>
<td>Adherence</td>
<td>Effective (incentive groups)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Completion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matteelli et al., 2000</td>
<td>RCT</td>
<td>–</td>
<td>Italy</td>
<td>Immigrants</td>
<td>Supervised drug collection / usual care</td>
<td>Completion</td>
<td>Adverse</td>
</tr>
<tr>
<td>Narita et al., 2002</td>
<td>BA</td>
<td>+</td>
<td>USA</td>
<td>HIV+ people with LTBI</td>
<td>DOT</td>
<td>Completion</td>
<td>Effective</td>
</tr>
<tr>
<td>Nyamathi et al., 2006</td>
<td>RCT</td>
<td>++</td>
<td>USA</td>
<td>Homeless people with LTBI</td>
<td>Education, tracking of defaulters, DOT, incentives / DOT, incentives</td>
<td>Knowledge</td>
<td>Effective</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Completion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rüütel et al. 2011</td>
<td>RCT</td>
<td>++</td>
<td>Estonia</td>
<td>Drug users</td>
<td>Active referral, incentive / passive referral</td>
<td>Attendance at TB clinic</td>
<td>Effective</td>
</tr>
<tr>
<td>Sterling et</td>
<td>RCT</td>
<td>+</td>
<td>Multi.</td>
<td>People with DOT / SAT</td>
<td></td>
<td>Completion</td>
<td>Effective</td>
</tr>
</tbody>
</table>
In this section the findings are characterized by the main population group included in the studies, namely:

- Patients with active TB (N=3 studies)
- Drug users (N=5)
- People with latent TB infection (general) (N=1)
- Migrants or new entrants (N=2)
- Patients with HIV (N=1)
- Homeless people (N=1)

In terms of the interventions evaluated, the majority of the studies focus exclusively on DOT alone, or DOT with incentives (N=8: Chaisson et al., 2001 (++); Graham et al., 1996 (–); MacIntyre et al., 2003 (++); Malotte et al., 2001 (++); Matteelli et al., 2000 (–); Narita et al., 2002 (+); Sterling et al., 2011 (+)). One study evaluates intensified supervision for clinical staff (Jin et al., 1993 (–)). Only three (Batki et al., 2002 (++); Goldberg et al., 2004 (–); Nyamathi et al., 2006 (++); Rüütel et al., 2011 (++)) evaluate an intervention which incorporates other elements of case management; moreover, of these, one focuses mainly on reminders (Rüütel et al., 2011 (++) and one on education and tracking of defaulters (Nyamathi et al., 2006 (++)), with only two investigating an approach which unambiguously fits the definition of ECM in current practice (Batki et al., 2002 (++); Goldberg et al., 2004 (–)).

4.3.1 Patients with active TB (N=3)

DeMaio and colleagues (2001 (–)) evaluated a telemedicine intervention for the delivery of directly observed therapy for TB by videophone in the USA. The study was very small (sample size N=6) and there was limited description of the methods, context or intervention. The study appears to have compared the same group of patients who received ‘standard’ DOT (presumably in person) at one time, and DOT using videophones installed in their homes at some other time. No information was provided on the sample, other than that patients with a history of injecting drug use were excluded. The study outcome was treatment adherence, defined as a completed DOT session.

The study found that patients were adherent to videophone DOT in 95% of cases, and standard DOT in 97.5% of cases. The authors argued that videophone DOT used much less staff time than standard DOT (3 minutes per visit as against 1 hour), but no data were provided to justify this claim.

Jin and colleagues (1993 (–)) evaluated a service-level intervention to improve TB treatment services in South Korea. The study used a cluster-randomised trial design, with only post-test outcome data reported, although there was limited detail provided on study methods. The settings were health centres in urban and rural areas. The intervention focused on clinical staff rather than on patients, and consisted of intensified supervision of staff by centre directors, and regular sessions for
discussions of the achievements of each member of staff, in order to improve their case management practice. (However, it is unclear what is meant by the latter – the focus of the study is entirely on the intervention with staff.) The comparison group were instructed to deliver services as normal, including regular supervision but not the intensified supervision received by the intervention group. The study outcomes were the number of follow-up patient examinations (X-ray and sputum smear and culture) performed, rates of drug collection and delays in drug collection, treatment completion, and treatment success defined by bacteriological conversion. (Given the nature of the outcomes, we have assumed that the population included consisted of those with active TB, but this is not explicitly stated.)

The study found positive effects of the intervention on all these outcomes. The intervention group performed more follow-up X-rays (intervention 90.8% against control 80.2%, significance NR) and sputum smear and culture tests (97.6% against 70.2%, significance NR); drug collection rates were higher in the intervention group (87.9% against 77.1%, p<0.01) and delays in drug collection of 7 days or more were lower (4.7% against 12.2%, p<0.01); treatment completion rates were higher (78.8% against 65.2%, p<0.01), as were treatment success rates (75.2% against 45.8%, p<0.01).

MacIntyre and colleagues (2003 (++) evaluated a family-based DOT intervention in new TB patients in Australia. The study used a quasi-randomised trial design, with alternating allocation of patients to intervention and control groups. The setting was urban healthcare clinics. The population was mostly foreign-born (89.6%) and spoke a first language other than English (81.5%); 26% were employed and 30% students. Patients with MDR-TB or HIV were excluded from the study. Patients in the intervention group were asked to nominate a family member; both the nominated family member and the patient received education, and the family member was trained to observe the patient’s daily treatment. Patients in the comparison group received usual care, including some element of education, but did not receive DOT as standard. The study outcomes were adherence, measured by urine testing of isoniazid levels and by electronic pill bottles, and treatment non-completion, measured by clinic attendance and drug collection rates.

The study found that only 58% of the intervention group actually received the intervention as planned, either due to refusal or due to not having a suitable family member. There was no significant difference between the groups in compliance as measured by urine testing, on either an intention-to-treat analysis (RR 1.04 (0.88–1.23)) or a per-protocol analysis (RR 0.96 (0.75–1.23)). However, a trend analysis of urinary isoniazid levels (intention-to-treat) showed significantly higher levels in the intervention group (p<0.05). Electronic pill bottle data were not analysed by treatment group, but showed higher levels of non-compliance (mean 13% of doses missed) than the urinary isoniazid outcome. Rates of treatment non-completion were lower in the intervention group (3.4% against 9.3%), but not significantly so (RR 2.7 (0.66–14.2)).

**Evidence statement 1: effectiveness of case management and DOT for patients with active TB on treatment adherence and completion**
There is weak evidence from one (−) US study\(^1\) that a videophone DOT intervention achieves similar rates of adherence to TB treatment as standard DOT (95% against 97.5%).

There is weak evidence from one (−) South Korean study\(^2\) that a service-level intervention involving intensified supervision of staff to improve case management practice achieves improved rates of follow-up X-rays (intervention 90.8% against control 80.2%, significance NR), sputum smear and culture tests (97.6% against 70.2%, significance NR), drug collection rates (87.9% against 77.1%, \(p<0.01\)), delays in drug collection of 7 days or more (4.7% against 12.2%, \(p<0.01\)), treatment completion rates (78.8% against 65.2%, \(p<0.01\)), and treatment success (75.2% against 45.8%, \(p<0.01\)).

There is strong evidence from one (++) Australian study\(^3\) that family-based DOT does not lead to higher adherence (RR 1.04 (0.88–1.23)) than standard treatment with self-administered therapy. There was a non-statistically-significant trend in this study towards improved treatment completion (RR 2.7 (0.66–14.2)).

**Applicability**

The evidence is directly applicable to people in the UK. This is because there are no obvious differences in the population, context or setting of the studies compared to the UK context.

1 DeMaio et al., 2001 (−)
2 Jin et al., 1993 (−)
3 MacIntyre et al., 2003 (++)

### 4.3.2 Drug users (\(N=5\))

Batki and colleagues (2002 (++)) evaluated an intervention for drug users implemented in a methadone clinic in the USA. The study used a randomised trial design. The population consisted of heroin-dependent injecting drug users with latent TB infection (excluding those who were pregnant, HIV-positive, or had evidence of liver disease). The intervention was a multi-component programme combining directly observed preventive therapy (limited details were provided on the DOPT component), methadone treatment, counselling twice monthly, and access to medical and social work services as necessary. A second ‘minimal’ intervention group received DOPT and methadone, but no other services. The comparison group received usual care, consisting of self-administered treatment for LTBI, and no methadone treatment (although participants in the intervention group could access methadone treatment elsewhere, and several did). The outcomes measured were treatment completion (defined as ≥80% of doses taken as measured by clinic records), duration of retention in therapy, and active TB.

The study found that more people completed therapy in the full intervention group (59.5% (43.6–75.3)) and in the minimal intervention group (77.1% (61.3–91.0)) than in
the comparison group (13.1% (3-23.7)); the difference between both intervention groups and the comparison group was significant (p<0.0001), but there was no significant difference between the two intervention groups. This was also the case for the retention outcome (mean duration of treatment in full intervention group 5.0 months (4.5–5.5), minimal group 5.7 months (5.4–6.0), comparison group 1.6 months (0.9–2.25) (p<0.0001)). There was one case of active TB in the minimal treatment group and one in the comparison group; neither of these had completed treatment.

Chaisson and colleagues (2001 (++)) evaluated two different interventions to improve adherence to preventive treatment among drug users. The study used a randomised controlled trial design. The setting was a public TB clinic in Baltimore, USA. One intervention consisted of directly observed preventive therapy, administered by a nurse, and the other of a peer support intervention in which participants attended monthly meetings with a trained peer counsellor and support group meetings, and self-administered therapy. The comparison group received usual care including self-administered therapy. The outcomes measured were treatment completion, adherence (at 100%, 90% and 80% levels) measured by observation for the DOPT group and self-report for the other groups, and validated by electronic pill bottles and urine testing for the non-DOPT groups.

The study found that in the DOPT group, 80% of patients completed therapy compared to 78% of the peer support group and 79% for the usual-care group (NS). In the DOPT group, 77% of patients took all doses as compared to 6% of the peer support group and 10% of the usual-care group (p<0.001 for the DOPT vs peer and DOPT vs usual-care comparisons, NS for peer vs usual care); 80% of DOPT patients took at least 90% of doses, as compared to 51% of the peer support group and 77% of the usual-care group (p<0.001 for DOPT vs peer, NS for DOPT vs usual care, significance NR for peer vs usual care); and 82% of DOPT patients took at least 80% of doses, as compared to 71% of the peer support group and 90% of the usual-care group (NS). By self-report, the number of doses missed was 17% in the peer group and 11% in the usual care group (NS); however, the number of doses taken as measured by urine testing was found to be 47% in the peer group and 55% in the usual-care group (NS); and by electronic pill bottle monitoring, 59% in the peer group and 49% in the usual-care group (p<0.001).

Graham and colleagues (1996 (–)) conducted a study of trends in TB and M. avium incidence among drug users in Baltimore, USA, which can also be interpreted as evidence of the effectiveness of DOT. The study used a one-group design. However, the timing of the intervention with respect to the outcomes is somewhat unclear: at some point the policy in place changed from self-administered chemoprophylaxis to DOPT, but it is unclear when this took place. The outcomes are incidence (cases per 1000 person-years) of TB and M. avium. However, full outcome data were not reported in the study, only risk ratios.

The study found that in years 4 to 5 of the study, presumably after DOPT was implemented, there was a non-significantly lower risk of TB compared to baseline (RR 0.4 (0.04-4.8)) but a significantly higher risk of M. avium (RR 7.3 (2.2-24.3)).
Malotte and colleagues (2001 (++)) compared the effectiveness of three different interventions to improve adherence to treatment for latent TB in people who injected drugs or used crack cocaine, in California. The study used a randomised controlled trial design. The setting was a ‘storefront’ facility conducting risk-reduction programmes for drug users. There were three groups in the study: condition 1 received DOT conducted by an outreach worker at a location chosen by the participant and a monetary incentive of US$5 per visit; condition 2 received the same DOT intervention as condition 1, but without the incentive; and condition 3 received DOT at the study site, with the US$5 incentive. The outcomes measured were treatment completion and the percentage of medications taken on time.

The study found that both the incentive conditions (1 and 3) led to significantly (p<0.001) higher rates of treatment completion than outreach DOT without an incentive (condition 2) (c1 52.8%; c2 3.6%; c3 60%; OR for c1 vs c2 29.7 (56.5–134.5), for c3 vs c2 39.7 (58.7–134.5)), as well as significantly (p<0.001) higher rates of medication taken on time (c1 72%, c2 12%, c3 69%). However, conditions 1 and 3 were not significantly different.

Rüütel and colleagues (2011 (++)) conducted an intervention among injecting drug users which, unlike the other interventions in this section, was mostly intended to increase uptake rather than adherence. The study used a randomised trial design. The setting was a methadone maintenance clinic in Estonia, and the participants were injecting drug users who had been tested for TB. Although described as ‘active case management’, the intervention was relatively minimal: study personnel scheduled visits to TB services for participants and reminded them to attend, and provided transportation if necessary. There was also an incentive (€6.40 in vouchers) for participants who returned for test reading. The outcome measured was attendance at the TB clinic.

The study found that a significantly higher (p=0.004) percentage of participants attended the clinic in the intervention group (57.1%) than in the control group (30.4%).

**Evidence statement 2: effectiveness of case management and DOT for drug users on treatment uptake, adherence and completion**

There is weak evidence from one US study (–)\(^1\) that a policy of directly observed preventive therapy (DOPT) showed a non-statistically-significant trend towards lower rates of TB among drug users compared to self-administered preventive therapy (one-group RR 0.4 (0.04-4.8)).

There is conflicting evidence from two (+++) US studies\(^2,3\) as to whether DOPT leads to higher adherence rates than SAT among drug users. There is strong evidence from one (+++) US study\(^3\) that DOPT does not lead to higher completion rates, or adherence rates, than usual care with SAT among drug users (completion 80% against 79%; adherence 82% against 90% (for 80% adherence), 80% against 77% (for 90% adherence)). However, DOPT did lead to higher adherence rates than usual care for 100% adherence (77% against 10%, p<0.001), and to higher adherence
rates than a peer support intervention (80% against 51% (for 90% adherence), p < 0.001; 77% against 6% (for 100% adherence), p<0.001).

There is strong evidence from one (+++) US study\(^2\) that DOPT combined with methadone treatment leads to higher rates of TB treatment completion among heroin-dependent injecting drug users than usual care with SAT (77.1% against 13.1%, p < 0.0001). However, an additional case management component with counselling and service access did not increase the effectiveness of the basic intervention (59.5% completion).

There is strong evidence from one (+++) US study\(^4\) that either outreach DOPT with incentives or on-site DOPT with incentives improve adherence among drug users more than outreach DOPT alone, but outreach DOPT with incentives is not significantly different from on-site DOPT with incentives (OR for outreach DOPT with incentive vs outreach DOPT alone 29.7 (56.5–134.5); OR for on-site DOPT with incentive vs outreach DOPT alone 39.7 (58.7–134.5)).

There is strong evidence from one (+++) Estonian study\(^5\) that an intervention involving incentives, scheduling visits and reminders, and providing transport, increases attendance at a TB clinic among drug users (57.1% against 30.4%, p = 0.004).

Applicability

The evidence is partially applicable to people in the UK who use drugs. This is because the populations of drug users in the studies, or the services available to them, may differ from those in the UK.

1 Graham et al., 1996 (–)
2 Batki et al., 2002 (++)
3 Chaisson et al., 2001 (+++)
4 Malotte et al., 2001 (++)
5 Rüütel et al., 2011 (++)

4.3.3 People with latent TB infection (N=1)

One study (Sterling et al., 2011 (+)) examines different regimens for people with latent TB infection. The study was carried out in several countries (USA, Canada, Brazil, and Spain) and compared combination therapy (isoniazid and rifapentine once weekly) under DOT with self-administered therapy (daily isoniazid). However, no details were reported on the context or delivery of DOT. The study used a randomised trial design with a large sample size (N=7,731). The relevant outcomes measured were treatment completion, TB incidence and death.

The study found that treatment completion rates were significantly higher in the DOT group than the SAT group (DOT 82.1%, SAT 69.0%, p<0.001). Incidence of TB was not significantly lower in the unadjusted analysis, but was significantly lower in the
intervention group after adjustment for baseline risk factors (adjusted hazard ratio 0.38 (0.15-0.99), p = 0.05). Risk of death did not differ significantly between groups.

**Evidence statement 3: effectiveness of DOT for people with latent TB infection on treatment completion**

There is medium evidence from one (+) study conducted in multiple countries (not the UK)\(^1\) that DOT leads to higher treatment completion rates and lower risk of active TB than self-administered therapy (completion 82.1% against 69.0%, p<0.001; risk of active TB adjusted hazard ratio 0.38 (0.15-0.99), p=0.05). However, the regimens used in this study differed between groups.

**Applicability**

The evidence is directly applicable to people in the UK. This is because there are no obvious differences in the population, context or setting of the studies compared to the UK context.

\(^1\) Sterling et al., 2011 (+)

### 4.3.4 Migrants or new entrants (N=2)

Two effectiveness studies focused on migrants or new entrants. Goldberg and colleagues (2004 (–)) investigated a case management programme for refugees arriving in Washington state, USA. The intervention used a one-group design comparing outcomes after the intervention to retrospective pre-test data. The intervention was a ‘cultural case management’ programme, focusing in particular on people from Somalia, the former Soviet states, and the former Yugoslavia (although people of some other national origins are also reported to have been included). Three case managers were recruited, one each from each of these groups, and were given training in TB by the staff of the refugee screening programme. The case management programme itself (which was delivered to 80% of the intervention participants) included home readings of TSTs, culturally tailored education, and referrals to other services such as housing and social services. Case managers also attempted to build trusting and supportive relationships with participants. The outcomes measured were treatment uptake (i.e. whether participants started treatment) and treatment completion.

The study found that intervention participants had significantly higher uptake of treatment than the retrospective pre-test group (88% against 73%, p<0.001), as well as treatment completion (82% against 37%, p<0.001). Subgroup analysis found that among participants from the former Yugoslavia and former Soviet Union there was a significant effect on both outcomes, while those from Somalia had higher completion rates but not higher uptake rates.

Matteelli and colleagues (2000 (–)) evaluated the impact of different treatment regimens for immigrants undergoing TB screening and LTBI treatment in Italy. The study used a randomised trial design. The study compared three groups: one
received ‘supervised’ treatment on a twice-weekly regimen, one unsupervised treatment on a twice-weekly regimen, and one unsupervised treatment on a daily regimen. However, very little information was provided on what constituted ‘supervision’ in this study: the authors report that participants had to report twice weekly to the clinical service sites to collect drugs, but there does not appear to have been any observation or other support. The outcomes measured were treatment completion and time to dropout.

The study found that the supervised treatment group had significantly lower rates of treatment completion than either of the unsupervised groups (7.3% against 26% or 41%, \( p=0.006 \) and \( p=0.001 \) respectively), as well as a significantly shorter mean time to dropout (3.8 weeks against 6 weeks or 6.2 weeks, \( p=0.003 \)).

<table>
<thead>
<tr>
<th>Evidence statement 4: effectiveness of case management and observed drug collection for migrants or new entrants on treatment uptake and completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is weak evidence from one (–) US study(^1) that cultural case management, including culturally tailored education and support by trained peers, leads to higher uptake of treatment (88% against 73%, ( p&lt;0.001 )) and completion of treatment (82% against 37%, ( p&lt;0.001 )) for LTBI among refugee populations.</td>
</tr>
<tr>
<td>There is weak evidence from one (–) Italian study(^2) that requiring immigrants to attend clinic sites to collect drugs for LTBI treatment leads to lower rates of treatment completion (7.3% against 26%, ( p=0.006 )).</td>
</tr>
</tbody>
</table>

Applicability

The evidence is partially applicable to immigrants to the UK. This is because the populations of migrants in the studies, or the policies in place around immigration, may differ from those in the UK.

\(^1\) Goldberg et al., 2004 (–)
\(^2\) Matteelli et al., 2000 (–)

4.3.5 Patients with HIV (\( N=1 \))

One study (Narita et al., 2002 (+)) focused on treatment of latent TB infection for HIV-infected patients. The study used a one-group design with retrospective pre-test data. The setting was community HIV clinics in Florida, USA. While the main focus of the study is on the change from isoniazid treatment to a regimen of rifamycin/pyrazinamide, there was also a change from self-administered therapy to DOT, and hence the study meets criteria for inclusion in this review; however, very few details of DOT were reported, other than that treatment was observed by clinic staff. The outcome measured was treatment completion.

The study found significantly higher rates of treatment completion after the change of regimen (93% against 61%, \( p < 0.001 \)).
Evidence statement 5: effectiveness of DOT for people with HIV on treatment completion

There is medium evidence from one (+) US study\(^1\) that DOT leads to higher rates of treatment completion than SAT for LTBI treatment among people with HIV (93% against 61%, \(p < 0.001\)). However, this study also involved a change in regimen.

Applicability

The evidence is directly applicable to people in the UK. Despite differences in the broader healthcare context in the USA, there are no obvious differences in the population, context or setting of the study compared to the UK context.

\(1\) Narita et al., 2002 (+)

4.3.6 Homeless people (\(N=1\))

One study (Nyamathi et al., 2006 (++)) focused on a case management intervention for homeless people with latent TB infection. The study used a randomised trial design. The setting was homeless emergency and recovery shelters in Los Angeles, USA. The intervention was delivered by a nurse and a trained outreach worker. The main component was an educational programme consisted of eight culturally tailored small-group sessions focusing on TB and HIV, self-esteem, communication skills, and problem-solving skills; they were also provided with information about services. Participants who missed a DOT dose were actively tracked and reintegrated into the programme where possible. Control participants received a single brief education session. Participants in both groups were required to report to the study clinic twice weekly for DOT, and received a $5 incentive for each visit, but control participants were not actively tracked. The outcomes were knowledge about TB and treatment completion.

The study found that the intervention led to significantly better knowledge about TB (intervention 3.8±3.5, control 2.0±4.2, \(p<0.01\)). It also led to higher rates of treatment completion (intervention 61.5%, control 39.3%, \(p<0.01\); a logistic regression model controlling for confounders produced an OR of 3.01 (2.15-4.20) in favour of the intervention group, \(p<0.001\)). Subgroup analyses indicated somewhat higher effect sizes among women (RR 1.94 (1.26-2.98)) than men (RR 1.46 (1.21-1.77)) and among people of white or Hispanic ethnicity (RR 2.32 (1.32-4.06)) than those of African-American ethnicity (RR 1.45 (1.22-1.74)), but all these subgroups showed a significant effect of the programme.

Evidence statement 6: effectiveness of education and tracking for homeless people on treatment completion

There is strong evidence from one (+++) US study\(^1\) that an education programme and active tracking of defaulters, with DOT and incentives, leads to higher rates of completion of LTBI treatment among homeless people than DOT and incentives alone (adjusted OR 3.01 (2.15-4.20), \(p<0.001\)).
Applicability

The evidence is partly applicable to people in the UK. This is because the population of homeless people in the study, or the services available to them, may differ from those in the UK.

1 Nyamathi et al., 2006 (++)

4.4 Findings: cost-effectiveness

This section presents the findings for the review of cost-effectiveness. Table 5 summarizes the overall characteristics of the studies. One study (Chaulk et al., 2000) was found at QA stage not to be applicable; in line with the methods guide, this study was not data-extracted or considered further in the analysis.

Table 5. Characteristics of the cost-effectiveness studies (N=15)

<table>
<thead>
<tr>
<th>Reference</th>
<th>QA</th>
<th>Population</th>
<th>Intervention / comparator</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berkowitz et al., 2006</td>
<td>–</td>
<td>Neonates exposed to TB</td>
<td>DOPT / parent-administered therapy</td>
<td>Cost per death averted</td>
</tr>
<tr>
<td>Burman et al., 1997</td>
<td>+</td>
<td>Patients with active TB</td>
<td>DOT / SAT</td>
<td>Net cost savings</td>
</tr>
<tr>
<td>Gourevitch et al., 1998</td>
<td>–</td>
<td>Drug users</td>
<td>DOPT / SAT</td>
<td>Net cost savings</td>
</tr>
<tr>
<td>Holland et al., 2009</td>
<td>–</td>
<td>People with LTBI</td>
<td>Four drug prophylaxis regimens, two DOT and two SAT</td>
<td>Net cost savings; cost per QALY</td>
</tr>
<tr>
<td>Jit et al., 2011</td>
<td>+</td>
<td>Patients with active TB from high-risk groups</td>
<td>Mobile screening and enhanced case management including DOT / usual care</td>
<td>Cost per QALY</td>
</tr>
<tr>
<td>Migliori et al., 1999</td>
<td>–</td>
<td>Patients with active TB</td>
<td>Changes to hospital policy; DOT; additional staffing; incentives</td>
<td>Cost per cure</td>
</tr>
<tr>
<td>Moore et al., 1996</td>
<td>+</td>
<td>Patients with active TB</td>
<td>DOT / conventional SAT / fixed-dose SAT</td>
<td>Cost per relapse averted; cost per death averted</td>
</tr>
<tr>
<td>Palmer et al., 1998</td>
<td>+</td>
<td>Patients with active TB</td>
<td>Universal DOT / partial DOT / SAT</td>
<td>Cost per cure</td>
</tr>
<tr>
<td>Perlman et al., 2001</td>
<td>–</td>
<td>Drug users</td>
<td>Screening; DOPT; enablers</td>
<td>Cost per case averted; net cost savings</td>
</tr>
<tr>
<td>Porco et al., 2006</td>
<td>++</td>
<td>Immigrants</td>
<td>Screening; active recruitment of immigrants; DOPT</td>
<td>Cost per QALY</td>
</tr>
<tr>
<td>Snyder &amp; Chin, 1999a</td>
<td>–</td>
<td>Patients with active TB at low risk of default</td>
<td>DOT / SAT</td>
<td>Cost per cure</td>
</tr>
<tr>
<td>Snyder et al., 1999b</td>
<td>+</td>
<td>Drug users</td>
<td>Screening; DOPT; enablers</td>
<td>Net cost savings</td>
</tr>
</tbody>
</table>
The findings below are categorized by population or setting type, in the following categories:

- Patients with active TB (N=9 studies)
- Drug users (N=3)
- People with latent TB infection (N=1)
- Migrants or new entrants (N=1)
- Neonates (N=1)

As with the effectiveness evidence, the focus of the majority of the cost-effectiveness studies (N=13) is DOT (with, in some cases, incentives and enablers); only two could be said to incorporate elements of ECM (Jit et al., 2011 (+); Porco et al., 2006 (++)).

The majority of the studies quantify cost-effectiveness in terms of net cost savings, i.e. the (healthcare) costs of the intervention compared to the healthcare costs of the cases of TB and drug-resistance averted by the intervention. Relatively few studies attempt to value health outcomes. We return to this point in the discussion below.

4.4.1 Patients with active TB (N=9 studies)

Burman and colleagues (1997 (+)) present a decision-analytic model to assess the cost-effectiveness of directly observed therapy in patients with active TB, compared to self-administered therapy. The cost data indicate that DOT was considered to be administered by nurses in a clinic setting or by home visits, although limited information was presented. The model considered the perspective of the programme as well as a broader healthcare system perspective, with a time horizon up to 2 years for some outcomes. Data were drawn from the records of a TB clinic in Denver, USA, as well as from the literature, with most data reflecting a USA setting. Adherence or compliance data were not considered in the model as such, and the treatment effect of DOT was drawn from a single retrospective one-group study measuring its impacts on failure and drug resistance. Findings were presented in the form of net costs, i.e. the costs of the programme less the treatment costs saved by reduced treatment failure and drug resistance.

This study found that DOT was cost saving relative to SAT, with net cost savings of US$909 per patient treated from a programme perspective (DOT net costs US$1,405, SAT $2,314), US$7,744 from a healthcare perspective (DOT net costs $2,785, SAT $10,529), and US$8,168 from a perspective which also takes into account the losses of patients’ time resulting both from DOT and from the
consequences of treatment failure and drug resistance (DOT net cost $3,999, SAT $12,167). Sensitivity analyses indicated that DOT retained this advantage across a range of assumptions about cost and drug efficacy; in particular, the relative failure rates would have to change substantially (a five-fold increase in DOT or a six-fold decrease in SAT) to overturn the advantage of DOT.

Jit and colleagues (2011 (+)) report a cost-effectiveness analysis of the Find and Treat service. This service combined a mobile radiography unit, which visits sites such as drug treatment services and homeless shelters, with an enhanced case management service in which staff members accompany clients to visits and appointments. There was also a broader awareness-raising component, again targeted at high-risk groups, and delivered by peer workers. (Thus, the mobile screening unit and the awareness-raising aimed to increase uptake of services, while the enhanced case management aimed to promote adherence to treatment among patients with active TB; we have categorised the study as a whole under the latter.) The Find and Treat service was compared to outcomes for patients who presented to usual TB services. The study used a discrete age cohort model to estimate the cost-effectiveness of the service, with data drawn from programme records and from the literature – including data on the effect of the intervention on treatment completion rates – over a time horizon of 5 years. Findings were presented in the form of cost per QALY (unlike the majority of the studies in this review, the healthcare costs of averted treatment failures were not taken into account in calculating the benefits of the intervention).

The study found that the incremental cost-effectiveness of the Find and Treat service was £6,400 per QALY. Separate analysis of the two components of the service found that the cost-effectiveness of the mobile screening service was £18,000 per QALY, and that of the enhanced case management programme £4,100 per QALY. Sensitivity analyses indicated that these ICERs would rise slightly under less favourable assumptions, with the most unfavourable combination of assumptions giving a cost-effectiveness of £10,000 per QALY for the service as a whole, £26,000 per QALY for mobile screening, and £6,800 per QALY for enhanced case management.

Migliori and colleagues (1999 (–)) report a cost-comparison study looking at the effects of different policies for management of patients with TB in Italy. Their main analysis compared two scenarios: scenario 1, based on current practice in Italy, and scenario 2, with a greater use of outpatient treatment. These scenarios were then considered in conjunction with DOT (limited information was provided on the delivery or setting of the DOT component), additional staffing, and/or food incentives for patients. The study appeared to use a healthcare perspective (the authors report also using a social perspective which included productivity loss, but this is not reported in any detail). Limited information was provided on the sources of the data, and in particular, the effectiveness data appeared to be assumed rather than derived from studies; the outcomes included in the model were also somewhat unclear. Findings were presented in the form of cost per cure; however, no incremental analysis of the data was presented in the report, limiting its value with respect to the DOT and incentive interventions.
The study findings for cost per cure (US$, smear-positive / smear-negative) in the base case scenario, using Italian population data on treatment success, are shown in Table 6.

Table 6. Findings from Migliori et al., 1999 (--), cost per cure (1997 prices), US$

<table>
<thead>
<tr>
<th></th>
<th>Scenario 1 (current practice)</th>
<th>Scenario 2 (more outpatient care)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alone</td>
<td>16,494 / 11,230</td>
<td>5,690 / 2,202</td>
</tr>
<tr>
<td>With DOT</td>
<td>16,703 / 11,438</td>
<td>5,946 / 2,448</td>
</tr>
<tr>
<td>With DOT + additional staff</td>
<td>17,105 / 11,838</td>
<td>6,437 / 2,920</td>
</tr>
<tr>
<td>With DOT + incentives</td>
<td>17,576 / 12,308</td>
<td>7,014 / 3,474</td>
</tr>
<tr>
<td>With DOT + additional staff + incentives</td>
<td>17,978 / 12,708</td>
<td>7,505 / 3,946</td>
</tr>
</tbody>
</table>

Sensitivity analyses on treatment success rates indicated that the cost per cure could vary from US$25,503 to US$14,181 for scenario 1 alone, and from $8,799 to $4,893 for scenario 2 alone, as treatment success varied between 50% and 90% for smear-positive patients; similar ranges were seen for smear-negative patients and for the other forms of the scenarios.

Moore and colleagues (1996 (+)) present a cost-effectiveness analysis of directly observed therapy for patients with TB. DOT was compared both to conventional self-administered therapy, and to fixed-dose combination therapy (also self-administered). In this study DOT was considered to be delivered by a registered nurse case worker and licenced practical nurse outreach worker, with each patient visiting the clinic once and then receiving 50 outreach visits. They used a decision-analytic model, with a healthcare perspective, with some outcomes considered up to 2 years. The data were generally drawn from the literature, and from clinic records; treatment effect data were based on several studies, most from the USA. Findings were presented in the form of costs per relapse averted and per life saved.

This study found that the cost per relapse averted was US$17,305 for conventional SAT, $15,446 for fixed-dose SAT, and $14,378 for DOT. The cost per life saved was $15,200 for conventional SAT, $14,068 for fixed-dose SAT, and $13,966 for DOT. Sensitivity analyses found that the relative cost-effectiveness of the three options was not sensitive to changes in the costs of managing TB. However, the results were more sensitive to changes in costs, with DOT and fixed-dose SAT of comparable cost-effectiveness if the direct cost of DOT increases by $100; sensitivity analyses showed the marginal cost per life saved of DOT ranging between $0 and approximately $1,350, and the marginal cost per relapse averted between $0 and approximately $450, as the cost of DOT ranges from $13,600 to $15,000. They were also sensitive to relatively small increases in the probability of incomplete DOT leading to relapse, with the marginal cost per life saved of DOT ranging between $0 and approximately $43 as the probability of relapse ranges between 0.27 and 0.30. They were also sensitive to variation in the probability of relapse with resistant TB for
fixed-dose combination therapy, with the marginal cost per life saved of DOT ranging between approximately $170 and $0 as this probability ranges between 0.001 and 0.0016.

Palmer and colleagues (1998 (+)) present a cost-effectiveness analysis of directly observed therapy, considering a scenario in which DOT is delivered to all patients, one in which it is delivered to only 15% of patients and the remainder have self-administered therapy, and one in which there is no DOT and all patients have SAT. Limited information is presented on the delivery or context of DOT, although it appears to be assumed that a health professional conducts the observations. The study used a decision-analytic model with data drawn from clinic records and from the literature, most from the USA, including data on treatment completion. The model was analysed from a healthcare perspective, with a horizon of 10 years. The findings were reported as cost per case cured.

The study found that the direct costs per cure were US$16,846 for the partial DOT strategy (15% of patients), $20,106 for the no DOT strategy, and $17,323 for universal (100%) DOT. The incremental cost-effectiveness of universal DOT compared to partial DOT was $24,064 per cure. Sensitivity analyses indicated that these results were not sensitive to changes in default rate, infection rate or hospital stay; however, they were somewhat sensitive to changes in outpatient costs, where a 20% decrease gave an incremental cost-effectiveness of $18,184 per cure, and a 20% increase $29,944.

Snyder and Chin (1999a (−)) focused specifically on people with active TB who are at low risk of default, to inform the decision to move from a policy where DOT is targeted at high-risk patients to a universal DOT policy. They defined low-risk patients as those with no history of homelessness, injecting drug use or imprisonment, and without HIV infection or drug-resistant TB. These patients currently receive SAT, and the analysis considered the effect of providing DOT for this population, including incentives (value US$25 per week); however, no information was provided on the provider or setting of DOT. The model used a healthcare perspective, with some outcomes considered up to a 2-year horizon. Cost data were drawn from Medi-Cal reimbursement rates, while data on DOT effectiveness and baseline probabilities were drawn from the previous study by Moore et al. (1996 (+)), described above; data on SAT, including treatment default rates, were drawn from clinical record data from California. The findings were presented in the form of cost per patient treated and per patient cured.

The study found that for this population, the direct costs of DOT per patient treated would be US$1,332 greater than SAT, and the net incremental cost of DOT including cost savings from treatment of relapses would be US$919 per patient treated; the net incremental cost per patient cured would be $40,260. Sensitivity analyses indicated that this result was sensitive to large changes in the default rate on SAT, with DOT becoming net-cost-saving at a SAT default rate of 32.2% (base case 1.7%), or in the relapse rate after completing SAT; however, it was not very sensitive to substantial changes in the effectiveness of DOT in preventing default.
Wade and colleagues (2012 (–)) investigate a telehealth programme for delivering DOT for active TB in South Australia. In this programme broadband connections and videophones were installed in patients’ homes, and nurses observed patients remotely. The evaluation compared this intervention to the previous model where nurses visited patients’ homes. (In fact some patients included in the telehealth arm were considered unsuitable for the videophone intervention, and continued to receive in-person DOT.) The study focused on establishing the cost per successful observation of each way of delivering DOT, and did not attempt to model the effects of this, for example on treatment completion or health state outcomes. The data populating the model come from the evaluation of the programme, which used a retrospective cohort design. The findings are presented in terms of cost per successful day of observation.

The study found that the telehealth intervention cost Aus$2,654 per care episode and in-person DOT Aus$2,589; incorporating the difference in successful days of observation per episode, the incremental cost-effectiveness of the telehealth intervention was Aus$1.32 per day of observation. Sensitivity analyses indicated that the telehealth intervention would be dominant (net-cost-saving) with increased numbers of patients using the service, or with increased travel time for the in-person DOT service, but would have a higher ICER with a higher percentage of non-compliant patients or lower staff salaries.

Weis and colleagues (1999 (–)) conducted a retrospective economic evaluation of the implementation of DOT in Tarrant County, Texas. In the earlier phase of data collection almost all patients received SAT, with treatment only observed if patients relapsed or acquired drug resistance. In the later phase almost all patients received DOT. The study used clinical record data on adherence and treatment failure to compare the cost-effectiveness of the two policies. The findings were reported in the form of the cost per patient treated, taking into account the costs of hospitalization resulting from treatment failures in each group.

The study found that DOT was substantially less costly once the reduction in treatment failure was taken into account, with total costs per patient treated of US$11,260 as against US$27,630 in the SAT group. (However, there were also differences in the regimen received, with greater use of intermittent therapy in the DOT group, such that the direct costs of medication and laboratory services were actually greater in the SAT group, even without taking further outcomes into account.)

Wilton and colleagues (2001 (–)) report a Monte Carlo model comparing DOT and ‘conventional therapy’ in the USA and South Africa (only the USA analysis is considered here, in line with our review inclusion criteria). Very little information was provided about the delivery or setting of DOT, and none about what ‘conventional therapy’ means, although it appears to be SAT. Data, including data on default rates, were drawn from the literature and from previous cost-effectiveness studies, including Moore et al.’s discussed above (Moore et al., 1996 (+)); for treatment effect data Moore et al. (1996 (+)) and another modelling study were cited, rather than research data, but the latter studies appear to have been populated with empirical
data. The analysis used a healthcare perspective, but the time horizon is unclear. The findings were presented in terms of net costs.

The study found that the total mean net cost of DOT was US$18,932, and of ‘conventional therapy’ US$20,720. Sensitivity analyses indicated that DOT remained more cost-effective when a different and more costly protocol for second-line treatment was included.

**Evidence statement 7: cost-effectiveness of DOT, increased outpatient care, and Find and Treat for patients with active TB**

There is medium evidence from five (3 + and 2 −) cost-effectiveness studies1−5 that directly observed therapy for active TB incurs lower net costs than self-administered therapy, when the cost savings resulting from reduced treatment failure are taken into account. Relative net cost savings from DOT in these studies1,4−5 range from US$1,788 to US$16,370 per patient treated (with other studies reporting a relative cost per death averted of US$1,2342, and a relative cost per patient cured of US$2,7833).

However, there is weak evidence from one (−) cost-effectiveness study6 that DOT is more costly than SAT for patients at low risk of default (incremental cost of US$919 per patient treated, US$40,260 per patient cured). There is also moderate evidence from one (+) study that a policy of universal DOT is more costly than a policy of partial DOT (incremental cost of US$24,064 per patient cured).3

There is medium evidence from one (+) cost-effectiveness study7 that a Find and Treat service which combines mobile screening for high-risk populations with enhanced case management support has an incremental cost-effectiveness compared to usual care of £6,400 per QALY (£18,000 per QALY for mobile screening and £4,100 per QALY for enhanced case management).

There is weak evidence from one (−) cost-effectiveness study that a policy of increased outpatient care for TB is less costly than usual care (cost savings of US$10,804 for smear-positive patients, US$9,028 for smear-negative per patient cured), although the addition of DOT and incentives makes little difference to this.

There is weak evidence from one (−) cost-effectiveness study that remote DOT via videophone has an incremental cost-effectiveness of Aus$1.32 per day of observation, compared to in-person DOT.

1 Burman et al., 1997 (+)
2 Moore et al., 1996 (+)
3 Palmer et al., 1998 (+)
4 Weis et al., 1999 (−)
5 Wilton et al., 2001 (−)
6 Snyder and Chin, 1999a (−)
7 Jit et al., 2011 (+)
8 Migliori et al., 1999 (−)
4.4.2 Drug users (N=3)

Three cost-effectiveness studies evaluated directly observed prophylactic therapy for drug users.

Gourevitch and colleagues (1998 (–)) conducted a cost-effectiveness evaluation of a screening and DOPT programme integrated into a methadone maintenance treatment programme in New York City. All clients of the programme were screened at entry and annually for TB by a nurse, and those prescribed chemoprophylaxis were eligible for voluntary DOPT. The model used a programme perspective with a time horizon of 5 years. Most data were drawn from the programme evaluation, with the comparison outcomes (SAT) based on a hypothetical cohort. However, the effectiveness of DOPT appears to have been based purely on assumptions, and no data are cited for this. Adherence or compliance outcomes do not appear to have been considered in the model. The findings were presented in the form of net cost savings, including the costs saved by preventing future cases of TB.

The study found that net cost savings per person treated by SAT ranged from US$1,289 to $3,418 depending on INH efficacy, and under DOPT from $1,380 to $3,590 depending on INH efficacy and DOPT effectiveness. Sensitivity analyses indicated that the programme was cost-saving even under less favourable assumptions (lower population risk). (It should also be noted that the analysis shows that the cost savings per person treated under SAT are actually greater than the additional savings produced by introducing DOPT, although both are cost-saving.)

Perlman and colleagues (2001 (–)) similarly evaluated a screening and DOPT programme for drug users, also in New York City; this programme was based in a needle exchange service. All clients of the service were offered TB screening, with a US$15 incentive for returning to collect the results. Patients prescribed chemoprophylaxis were offered DOPT twice-weekly at the service site, and given transportation tokens to the value of US$5. The model used a healthcare perspective with a horizon of 5 years. Data were drawn from the programme evaluation and from the literature, but treatment effect appears to have based on Gourevitch et al. (1998 (–)), which as discussed above, does not itself appear to have been based on empirical data. The findings were presented in the form of cost per case prevented and net cost savings.

The study found that the costs of the intervention were US$14,213 to $18,951 per case averted, depending on isoniazid efficacy, and the total net cost savings for the programme as a whole were US$46,226 to US$123,081 ($15,407 to $30,770 per case averted). Further analyses indicated that if adherence were hypothetically increased to 100%, the cost would be $10,211 to $23,339 per case averted, and the total net cost savings for the programme $93,416 to $414,856 ($13,345 to $25,928 per case averted).
Snyder and colleagues (1999b (+)) also presents an economic evaluation of a screening and DOPT programme in a methadone maintenance clinic, this one in San Francisco. Clinic clients were offered screening, and those recommended for chemoprophylaxis were educated by clinic staff about the benefits of treatment. A community health worker accompanied them to clinic visits, and transport or tokens and food were provided. A clinic nurse then supported them in developing an adherence plan and observed treatment, and community health workers looked for clients who missed treatment. The model reported in the study used a healthcare perspective with a time horizon of 10 years. Data were mostly drawn from the programme evaluation, which used a retrospective cohort design; however, treatment effect data appear to have been based on a study conducted in Eastern Europe in the 1970s, and the applicability of these results may be limited. The findings were presented in terms of net cost savings per case averted.

The study found that the programme achieved a net cost saving of US$3,724 per TB case prevented. Sensitivity analyses indicated that this finding was sensitive to changes in the rates of treatment completion, with net costs ranging from a cost of $12,677 to a cost saving of $6,674 per case prevented across large changes in the completion rate.

**Evidence statement 8: Cost-effectiveness of screening and DOT for drug users**

There is weak evidence from three (1 +1 and 2 –2,3) cost-effectiveness studies that programmes for drug users which include screening and directly observed prophylactic therapy have lower relative net costs than no intervention, with net cost savings ranging from US$3,724 to US$30,770 per case averted, or from US$1,380 to US$3,590 per person treated1-3.

1 Snyder et al., 1999b (+)
2 Perlman et al, 2001 (–)
3 Gourevitch et al., 1998 (–)

**4.4.3 People with latent TB infection (N=1)**

Holland and colleagues (2009 (–)) conducted a cost-effectiveness study of four regimens for the treatment of latent TB infection (based hypothetically on contacts of TB cases). While the main focus of the study was on drug efficacy, two of the regimens included DOT and two were self-administered, so it meets the criteria for this review: the 9H regimen (daily isoniazid) and the 4R regimen (daily rifampin) were self-administered, while the 9H-DOT (twice-weekly isoniazid) and the 3HP (weekly isoniazid and rifapentine) regimens were directly observed. DOT appears to have been considered to be delivered by an outreach worker in patients’ homes. The model used was a Markov model with some outcomes considered up to a horizon of 9 months, comparing each of the regimens with all the others and with no treatment. Data were drawn from the literature, including some data on treatment effect (although from different studies for the different regimens). The findings are reported.
For our purposes the relevant comparisons are those of the DOT regimens with the SAT regimens and with no treatment. The study found that the 9H-DOT regimen cost US$475.10 per patient treated relative to no treatment, while the 3HP DOT regimen produced a net cost saving of $751.06. Incremental cost-effectiveness ratios in terms of net costs per QALY were: US$48,997 per QALY for 3HP (DOT) compared to 4R (SAT); $25,207 per QALY for 3HP (DOT) compared to 9H (SAT); and $7,879 per QALY for 9H-DOT compared to no treatment. Sensitivity analyses showed that the 4R (SAT) and 3HP (DOT) regimens generally dominated the others under a range of parameter values.

**Evidence statement 9: Cost-effectiveness of DOT for people with latent TB infection**

There is weak evidence from one (−) cost-effectiveness study\(^1\) that weekly isoniazid and rifapentine under DOT is cost saving compared to no intervention, while twice-weekly isoniazid under DOT has an incremental cost-effectiveness ratio of $7,879 per QALY compared to no intervention.

\(^1\) Holland et al., 2009 (−)

**4.4.4 Migrants or new entrants (N=1)**

Porco and colleagues (2006 (++)) conducted a cost-effectiveness study of a programme for new immigrants to the USA. The basic intervention in this study was a programme of new entrant screening and self-administered therapy for LTBI (this alone would not meet the criteria for this review). Over and above this, the study then considered a range of potential interventions to promote uptake and adherence to treatment, including reminder letters and telephone calls, home visiting, and targeted DOPT. The model used was a continuous-time, discrete-event model, with an all-payer perspective and a time horizon of 20 years. Data, including treatment effect data, were drawn from the literature. The presentation of the findings is somewhat different from the other studies in this review. The cost-effectiveness of the basic intervention is presented in terms of net costs and QALY gains. However, the interventions of interest for this review are presented in terms of a decision analysis which sequentially considered a range of interventions to increase uptake or adherence, with the incremental cost and benefit of each considered against the background of the previously implemented interventions.

The main analysis shows the programme as a whole to have made net cost savings of $25,000, and yielded 7.7 net QALYs. (Detailed sensitivity analyses are reported in the study but are not reproduced here, as the intervention considered for this analysis is not strictly within the scope of this review.) The authors report their decision analysis in the form of the following table:
<table>
<thead>
<tr>
<th><strong>Beginning with …</strong></th>
<th><strong>Choose between …</strong></th>
<th><strong>Best choice</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Treat only active cases; detect them only passively</td>
<td>(1) Offer LTBI treatment to TB2s or TB4s, or (2) send letters to improve evaluation</td>
<td>Send letters (2.7 QALYs gained, $10 000 in net savings)</td>
</tr>
<tr>
<td>2. Send letters; treat active cases</td>
<td>(1) Offer LTBI treatment to TB2s, (2) Offer LTBI treatment to TB4s, or (3) make phone calls to improve evaluation rates</td>
<td>Treat TB4s (3.2 QALYs gained, $11 000 in net savings)</td>
</tr>
<tr>
<td>3. Treat active cases and TB4s; improve evaluation by letters</td>
<td>(1) Offer LTBI treatment to TB2s, (2) make phone calls to improve evaluation rates further, (3) improve rates of starting therapy for TB4s, or (4) improve completion rates by DOPT</td>
<td>Improve starting rates (1.3 QALYs saved, $1 800 in net savings)</td>
</tr>
<tr>
<td>4. Treat active cases and TB4s; improve evaluation rates by letters; improve starting rates</td>
<td>(1) send letters to improve evaluation rates further, (2) treat TB2s, or (3) improve completion rates by DOPT</td>
<td>Treat TB2s (0.7 QALYs saved, $3 000 in net cost)</td>
</tr>
<tr>
<td>5. Treat active cases, TB2s, and TB4s; improve evaluation by letters; improve rates of starting therapy</td>
<td>(1) Further improve evaluation rates by phone calls, or (2) improve rates of completing therapy (by targeted DOPT)</td>
<td>Phone calls (0.5 QALYs saved, approximately $1 000 in net savings)</td>
</tr>
<tr>
<td>6. Treat active cases, TB4s, and TB2s; improve evaluation by letters and phone calls</td>
<td>(1) Further improve evaluation rates by home visits, or (2) improve rates of completing therapy by using targeted DOPT</td>
<td>Home visits (0.3 QALYs saved, approximately $1 000 in net cost)</td>
</tr>
<tr>
<td>7. Treat active cases, TB4s, and TB2s; improve evaluation by letters and phone calls</td>
<td>(1) improve rates of completing therapy by using targeted DOPT</td>
<td>$100 000 per QALY saved; no further intervention</td>
</tr>
</tbody>
</table>

**Evidence statement 10: Cost-effectiveness of screening, LTBI treatment and DOPT for new entrants**
There is good evidence from one (++) study\textsuperscript{1} that a screening and LTBI treatment programme for new entrants to the USA is cost saving compared to no intervention, and that reminders by phone, post or home visiting are also cost saving. However, this study finds the incremental cost of DOPT compared to the combination of all these interventions to be over US$100,000 per QALY.

\textsuperscript{1} Porco et al., 2006 (++)

\textbf{4.4.5 Neonates (N=1)}

Berkowitz and colleagues (2006 (–)) present a decision-analytic model to assess the cost-effectiveness of directly observed prophylactic therapy in neonates who had been exposed to an adult with active TB in a hospital nursery, and of parent-administered therapy, compared to no intervention. Very little information was presented on who delivered DOT or in what setting. The model used took into account infection rates, survival rates, and incidence of adverse effects from treatment (hepatotoxicity), with a horizon of 4 years. Many of the data sources were unclear for this study: most of the sources for cost data were not reported; the treatment effect for DOT appears to be assumed; and the treatment effect for parent-administered therapy appears to be drawn from studies of self-administered therapy in adults. Adherence or compliance data were not considered in the model as such. Outcomes were presented in the form of cost per death prevented.

This study found that DOPT had an incremental cost per death prevented of US$21,710,000 relative to no intervention, while parent-administered therapy had an incremental cost per death prevented of US$929,500. Sensitivity analysis indicated that DOPT would dominate no intervention if the probabilities of developing disease were substantially increased and adverse event rates reduced.

\textbf{Evidence statement 11: Cost-effectiveness of DOPT for neonates exposed to TB}

There is weak evidence from one (–) cost-effectiveness study\textsuperscript{1} that directly observed preventive therapy has an incremental cost-effectiveness of US$21,710,000 per death prevented compared to no intervention, substantially greater than parent-administered therapy.

\textsuperscript{1} Berkowitz et al., 2006 (–)

\textbf{4.5 Qualitative evidence}

Two studies presenting qualitative data about interventions were located. One (Wade et al., 2012 (+)) is from the same study as the economic evaluation discussed above. The characteristics of the studies are shown in Table 8.

Table 8. Characteristics of the qualitative studies (N=2)
Craig and colleagues (2008 (−)) conducted a process evaluation of the implementation of a social outreach model of care for socially marginalized people with TB. The main innovation of the service was a case manager or ‘link worker’ role, focusing on supporting patients and facilitating linkages between distinct services. People were referred to the service because of homelessness or housing needs, asylum or immigration issues, substance use or imprisonment. Some had latent TB and others active disease.

Qualitative data were collected from staff in a range of services who were in contact with link workers, such as agencies for refugees or homeless people. Themes included: greater understanding of clinical issues around TB on the part of staff in other agencies; the value of linking together different services; and the value of the emotional support provided by link workers, especially for asylum seekers who may be unable to access many other services. One participant also suggested that people may be more likely to access health services when this can also facilitate accessing other services at the same time.

Wade and colleagues (2012 (+)) conducted a process evaluation of a videophone DOT service, in conjunction with the economic evaluation discussed above. The study included staff involved in delivering the service as well as patients who used the service. Patients' perceptions were generally positive in ten of twelve cases, with two patients expressing more mixed views. They valued the personal relationship with the nurses who delivered DOT, and the improved privacy of the videophone service over the in-clinic DOT service. Staff participants found the videophone service convenient and easy to use, although there were some technical problems in its implementation. Some were concerned that patients found it easier to pretend to swallow pills using the videophone service, but generally had the impression that it improved adherence. The service was also seen to improve communication between staff in the community nursing service and the hospital chest clinic.

**Evidence statement 12: Qualitative evidence on interventions to promote adherence to treatment for TB or LTBI**

There is weak evidence from one (−) UK study¹ that a link worker for marginalized people with TB or LTBI is viewed positively by staff in other agencies. Participants report that the link worker increases understanding of TB among workers in different services, facilitates service users’ access to different services and provides practical and emotional support.

<table>
<thead>
<tr>
<th>Ref.</th>
<th>QA</th>
<th>Country</th>
<th>Population</th>
<th>Intervention</th>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Craig et al., 2008</td>
<td>-</td>
<td>UK</td>
<td>Staff in agencies working with people with TB</td>
<td>Social outreach case management with TB link worker</td>
<td>Interviews; focus groups</td>
</tr>
<tr>
<td>Wade et al., 2012</td>
<td>+</td>
<td>Australia</td>
<td>Clinical and other staff delivering service; patients with TB</td>
<td>Videophone DOT</td>
<td>Interviews</td>
</tr>
</tbody>
</table>
There is medium evidence from one (+) Australian study\(^2\) that a videophone DOT service is viewed positively by staff and patients. The privacy and convenience of the videophone DOT service were especially valued.

1 Craig et al., 2008 (−)
2 Wade et al., 2012 (+)
5 Discussion

5.1 Summary of findings

The interventions discussed in this review can be divided into two types. On the one hand we have directly observed therapy alone, and on the other a range of interventions involving some type of enhanced case management, which include support for individuals undergoing treatment for TB or LTBI, or accessing services, beyond simply observing treatment or providing information or resources.

The evidence on ECM is mixed. On the one hand, three studies show positive findings for some form of CM intervention (Goldberg et al., 2004 (–); Nyamathi et al., 2006 (++); Rüütel et al., 2011 (++)). In addition, one qualitative study shows positive perceptions of a CM service (Craig et al., 2008 (–)), and one cost-effectiveness study finds an ICER of £4,100/QALY for enhanced CM, and £6,400/QALY for a service combining mobile screening and enhanced CM (Jit et al., 2011 (+)).

However, of the CM approaches adopted in the effectiveness studies, two consist mainly of reminders and education or skills training (Nyamathi et al., 2006 (++); Rüütel et al., 2011 (++)). If we focus on ECM in the narrow sense, as an approach which combines interventions to increase adherence with more general social support and facilitating access to services, there are only two studies (Batki et al., 2002 (++); Goldberg et al., 2004 (–)), and of these, the only one to receive a high quality rating (Batki et al., 2002 (++)) finds that this type of ECM is no more effective than DOT and methadone for IDUs.

On DOT alone, the evidence suggests that it is not effective. Two high-quality trials find DOT to be no more effective than SAT (Chaisson et al., 2001 (++; MacIntyre et al., 2003 (++)), and another finds DOT alone to be much less effective than DOT with incentives (Malotte et al., 2001 (++)). These findings are in line with previous reviews of DOT (Volmink and Garner, 2007). Further, one study finds that requiring people to report to a clinic site to collect every dose may have adverse effects on completion (Matteelli et al., 2000 (–)). Those studies which do show a significant benefit for DOT over SAT are either methodologically questionable (Graham et al., 1996 (–)) or else involve different regimens in the DOT and SAT groups, making it impossible to isolate the effect of observation as such (Narita et al., 2002 (+); Sterling et al., 2011 (+)).

The economic evidence on DOT is prima facie more promising, with six studies finding DOT to be cost-saving compared to SAT once the medical costs of treatment for relapses and failures are taken into account (Burman et al., 1997 (+); Moore et al., 1996 (+); Perlman et al., 2001 (–); Snyder and Chin, 1999a (–); Weis et al., 1999 (–); Wilton et al., 2001 (–)), and three showing more mixed findings (Berkowitz et al., 2006 (–); Gourevitch et al., 1998 (–); Holland et al., 2009 (–)). The evidence suggests that DOT is more cost-effective if targeted at high-risk groups than if provided universally (Palmer et al., 1998 (+); Snyder et al., 1999b (+)).
However, on closer examination the economic evidence does not provide strong support for DOT. The finding that DOT is cost-effective generally rests on its being more effective than SAT at preventing treatment failure (i.e., DOT is cost-effective if it is effective). In many of the cost-effectiveness studies, the effectiveness of DOT is simply assumed; where empirical data are cited, they are often of highly questionable reliability and applicability (and none are based on a systematic review of prospective intervention studies). Our effectiveness findings thus cast considerable doubt on the basis of the finding that DOT is cost-effective, and suggest that it may largely be due to overly optimistic assumptions about effectiveness.

It should also be noted that the one study to consider DOT in a broader context than simply the comparison with SAT, and compare it with reminders and other strategies for increasing uptake and adherence, finds that it is not cost-effective (Porco et al., 2006 (++)).

5.2 Limitations

5.2.1 Limitations of the review

This review was carried out using systematic methods, with extensive searching, a priori inclusion criteria, and full quality assessment and data extraction according to the NICE methods manual. However, there may be some limitations.

It is challenging to define the idea of ‘case management’ and operationalize it in a precise way. CM might be considered a way of delivering interventions as much as an intervention in itself. Our search terms may not therefore have picked up all relevant studies, although a broad range of synonyms for elements of CM, as well as for the CM approach, were used. We were reasonably inclusive in defining CM at the screening stage, but we did exclude purely educational or informational interventions (which are covered in a separate review in this work programme) and incentives or enablers alone (which are not covered in either review).

We excluded purely retrospective studies from the effectiveness review, due to their limited reliability in establishing effectiveness. However, we were otherwise inclusive with respect to study design.

We excluded studies of views and barriers, such as qualitative research, which did not relate specifically to an actually implemented intervention programme. This criterion excluded the majority of qualitative research on TB. However, it did mean that the results were more clearly relevant to the effectiveness and cost-effectiveness findings. In addition, two robust (although not absolutely up-to-date) systematic reviews of this qualitative literature already exist (Munro et al., 2007; Noyes and Popay, 2007), and should be consulted for the broader literature on views and barriers.

We were unable to carry out meta-analysis or other quantitative synthesis, and only conducted a narrative synthesis of the evidence.
5.2.2 Limitations of the evidence base

As already noted, the evidence base largely consists of studies of directly observed therapy. As yet, few prospective evaluations or cost-effectiveness studies appear to have been conducted on CM or ECM approaches. Nonetheless, the evidence on DOT is inconclusive, with the economic evidence in particular vitiated by questionable assumptions about treatment effectiveness. Many of the studies also present limited information about who delivered DOT or in what setting.

Most of the cost-effectiveness evidence is analysed in terms of net treatment costs, i.e. by comparing the costs of treatment to the costs of treatment failures and relapses averted, rather than to the impacts of TB on patients and others. Few cost-effectiveness studies are analysed in terms of cost per QALY or other cost-utility measures (as usually recommended by NICE) and still fewer incorporate any measure of the broader social costs of TB. In addition, all the cost-effectiveness studies use static models; none attempt to model transmission dynamics and the likely impacts of this on cost-effectiveness.

Those studies of broader CM approaches which do exist are heterogeneous in terms of the populations and interventions studied. Hence, while the evidence overall is promising, it is hard to draw any conclusions about what types or components of CM are effective for what populations or in what settings.
6 References


Weis, S.E., Foresman, B., Matty, K.J., Brown, A., Blais, F.X., Burgess, G., King, B.,
Cook, P.E., Slocum, P.C., 1999. Treatment costs of directly observed therapy
and traditional therapy for Mycobacterium tuberculosis: a comparative
analysis. *International Journal of Tuberculosis and Lung Disease* 3(11), 976–
984.

treatment for multidrug-resistant tuberculosis: an economic evaluation in the
United States of America and South Africa. *International Journal of
Tuberculosis and Lung Disease* 5(12), 1137–1142.
## Appendix A. Evidence tables

### 7.1 Effectiveness studies

<table>
<thead>
<tr>
<th>Study Details</th>
<th>Population and setting</th>
<th>Method of allocation to intervention/control</th>
<th>Outcomes and methods of analysis</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Authors:</strong> Batki SL, Gruber VA, Bradley JM, Bradley M, Delucci K</td>
<td><strong>Source population/s:</strong> Drug users accessing methadone treatment in San Francisco</td>
<td><strong>Method of allocation:</strong> Concealed randomization</td>
<td><strong>Outcomes:</strong> Treatment completion (defined as ≥80% doses taken, measured by observation in intervention groups and by receipt of medication in usual-care group)</td>
<td><strong>Results for all relevant outcomes:</strong> Completion: Standard MT: N=22 (59.5%; CI 43.6-75.3); Minimal MT: N=27 (77.1%; CI 61.3-91.0); Routine care: N=5 (13.1%; CI 3-23.7) (Notes: Of the n=5 completers in routine care, 2 (40%) admitted to methadone maintenance treatment elsewhere and received daily observed INH outside of the study). Standard MT and Minimal MT significantly higher than routine care (p &lt; 0.0001); no sig diff between Standard MT and Minimal MT. Duration of therapy (retention)</td>
<td><strong>Limitations identified by author:</strong> No arm including DOPT but not methadone, so cannot distinguish effects. Daily dosing regimen used, although less frequent may be possible. HIV+ IDUs excluded and findings may not be generalizable to them.</td>
</tr>
<tr>
<td><strong>Year:</strong> 2002</td>
<td><strong>Eligible population:</strong> Heroin-dependent IDUs that are tuberculin positive entering the 21-day methadone detoxification clinic at San Francisco with negative chest radiograph were recruited by clinic nurse. Percentage agreed to participate: NR. May have more complex needs than general population of IDUs.</td>
<td><strong>Intervention/s description:</strong> Standard MT: received DOPT and daily methadone treatment (no information on context or delivery of DOPT), 7 days per week for 6 months, followed by a 6-week taper off methadone. Twice monthly counselling sessions, weekly random observed urine samples, medical services, psychiatric treatment as needed, and social work referrals. Participants could earn up to two take-home doses of methadone per week as a reward for negative urine drug and breath alcohol tests (but no participants did). Minimal MT: DOPT and methadone as per</td>
<td><strong>Duration of INH preventive therapy:</strong> Standard MT: 5.0 months (CI: 4.5–5.5); Minimal MT: 5.7 months (CI: 5.4–6.0); Routine care 1.6 months (CI: 0.9–2.25) (P&lt; 0.0001).</td>
<td><strong>Follow up periods:</strong> 7 months for completion, 4 years for TB incidence <strong>Method of analysis:</strong> intention-to-treat. Pearson chi-squared. Pearson correlation coefficients for predictors</td>
<td><strong>Limitations identified by review team:</strong> Generally robust. Some minor reporting issues. Population may not be widely generalizable.</td>
</tr>
<tr>
<td><strong>Citation:</strong> A controlled trial of methadone treatment combined with directly observed isoniazid for tuberculosis prevention in injection drug users. Drug and Alcohol Dependence 66(3):283-293. and Country of study: USA</td>
<td><strong>Selected population:</strong> Inclusion criteria: (1) latent TB infection as demonstrated by a positive PPD test (10 mm or greater in duration), a negative chest radiograph, and approval by a TB clinic physician; (2) a DSM-III-R diagnosis of opioid dependence; (3) age between 21 and 59 years; (4) expressed willingness to receive 6 months of INH preventive therapy and</td>
<td><strong>Active TB cases</strong></td>
<td><strong>Evidence gaps and/or recommendations for future research:</strong> Testing DOPT vs methadone, with and without incentives. Different dosing schedules. Cost-effectiveness research.</td>
<td><strong>Aim of study:</strong></td>
<td></td>
</tr>
</tbody>
</table>
To evaluate the effectiveness of methadone, substance abuse counselling, and directly observed preventive treatment in heroin-dependent injecting drug users with latent TB infection

**Study design:** RCT

**Quality Score:** ++

**External validity:** +

<table>
<thead>
<tr>
<th>To evaluate the effectiveness of methadone, substance abuse counselling, and directly observed preventive treatment in heroin-dependent injecting drug users with latent TB infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>methadone treatment.</td>
</tr>
<tr>
<td><strong>Excluded population:</strong> (1) pregnant; (2) HIV positive; (3) had evidence of active liver disease or aspartate transaminase (AST) greater than three times the upper limit of the normal range.</td>
</tr>
<tr>
<td><strong>Sample characteristics:</strong> Participant characteristics - % (n): Gender: Male: Standard MT=54% (20); Minimal MT= 54% (19); Routine= 74% (29); p= 0.114 Female: Standard MT=46% (17); Minimal MT= 46% (16); Routine= 26% (10) Ethnicity: African American: Standard MT=30% (11); Minimal MT= 34% (12); Routine= 27% (10); p= 0.896; X2=1.09 White: Standard MT = 46% (17); Minimal MT = 37% (13); Routine= 40.5% (15) Other: Standard MT=24% (9); Minimal MT= 29% (10); Routine= 32.5% (12) Age (years): Standard MT=40.2 (4.8); Minimal MT= 42.6 (6.2); Routine= 43 (4.8); p= 0.047</td>
</tr>
<tr>
<td>Standard MT group, but no other services, except on an emergency basis or to enforce program rules. Counsellors met with patients approx once per month, for no more than 15 min.</td>
</tr>
<tr>
<td><strong>Control/comparison/s description:</strong> Routine care: Standard referral with self-administered preventive treatment. Methadone not provided, but participants in this group could seek methadone maintenance treatment elsewhere.</td>
</tr>
<tr>
<td><strong>Sample sizes:</strong> Total: N=111 Standard MT: N=37 Minimal MT: N=35 Routine care: N=39</td>
</tr>
<tr>
<td>Baseline comparisons: Usual care group:</td>
</tr>
<tr>
<td>Alcohol abuse/dependence, cocaine abuse/dependence, level of commitment to abstinence, urine test results, ASI psychiatric severity, BDI score, diagnosis of antisocial personality disorder, homelessness, ethnicity, and gender not significantly related to treatment completion results.</td>
</tr>
<tr>
<td>Attrition details: Unclear. Apparently 0 for TB incidence outcome (which was measured by clinic records)</td>
</tr>
</tbody>
</table>

**Source of funding:** National Institute on Drug Abuse
<table>
<thead>
<tr>
<th>Study Details</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Authors</strong></td>
<td>Chaisson RE, Barnes GL, Bakeckman J, et al.</td>
<td><strong>Source population/s:</strong> Injecting drug users in Baltimore</td>
<td><strong>Method of allocation:</strong> Randomisation by computer algorithm.</td>
<td><strong>Outcomes:</strong> Therapy completion Adherence at 80%, 90% and 100% levels (DOPT group observed, other groups self-report validated by pill count)</td>
<td><strong>Limitations identified by author:</strong> NR</td>
</tr>
<tr>
<td><strong>Year:</strong> 2001</td>
<td><strong>Eligible population:</strong> IDUs seeking treatment for TB in the Baltimore City Health Department tuberculosis clinic Patients recruited in clinic. Limited information on recruitment and percentage agreed to participate NR</td>
<td><strong>Intervention/s description:</strong> 1. Supervised group (DOPT): Patients were assigned to an outreach nurse who met with them twice weekly and administered INH 900 mg for 6 months per visit, and observed the patient swallow the medication (and assessed symptoms, provided counselling and encouraged adherence). Arrangements were made for treatment to be given at the clinic or at a mutually convenient community location. 2. Peer group: patients received self-administered therapy in monthly supplies of 300mg/day of INH for 6 months. They were required to return monthly for a refill and a nursing visit/ clinical assessment. Patients also received peer counselling twice during the first month of therapy and once a month</td>
<td><strong>Follow up periods:</strong> 6 months</td>
<td><strong>Results for all relevant outcomes:</strong> Completion: DOPT = 80%; Peer support = 78%; Routine care = 79%. DOPT vs. peer support: p = 0.73; DOPT vs. routine care: p = 0.68; Peer support vs. routine care sig NR</td>
<td><strong>Limitations identified by review team:</strong> Generally robust. Impact of incentives is somewhat unclear. Inconsistent findings with different measures of adherence not explored in depth. Limited information on recruitment; participants had good knowledge of TB and therapy at baseline, which may suggest selection bias.</td>
</tr>
<tr>
<td><strong>Citation:</strong> A randomized, controlled trial of interventions to improve adherence to isoniazid therapy to prevent tuberculosis in injection drug users. American Journal of Medicine, 110(8):610–615.</td>
<td><strong>Selected population:</strong> Patients who were at least 18 years old; used injection drugs (defined as the injection of illegal drugs within the previous 3 months or more remotely if the patient was enrolled in a methadone maintenance program); had a positive TST result; and were candidates for INH preventive therapy.</td>
<td></td>
<td>Took at least 80% of doses: DOPT = 82%; Peer support = 71%; Routine care = 90%. DOPT vs. peer support: p = 0.08; DOPT vs. routine care: p = 0.10; Peer support vs. routine care sig NR</td>
<td></td>
<td><strong>Evidence gaps and/or recommendations for future research:</strong> More research on promoting adherence and cost-effectiveness, especially using short-course regimens</td>
</tr>
<tr>
<td><strong>Country of study:</strong> USA</td>
<td><strong>Excluded population:</strong> Patients who had active TB; a history of serious adverse reactions to INH; previous INH therapy for 6 months or longer; serum alanine aminotransferase level more than 5 times normal; or HIV disease with CD4 &lt;200/mm. <strong>Sample characteristics:</strong></td>
<td></td>
<td>Took at least 90% of doses: DOPT = 80%; Peer support = 51%; Routine care = 77%. DOPT vs. peer support: p &lt; 0.001; DOPT vs. routine care: p-value = 0.63; Peer support vs. routine care sig NR</td>
<td></td>
<td><strong>Source of funding:</strong> National Institute on Drug Abuse; National Institute of Allergy and Infectious Diseases.</td>
</tr>
</tbody>
</table>

Doses taken, as ascertained
to tuberculosis preventive therapy by injection drug users in Baltimore treated at a public tuberculosis clinic.

**Study design:**
RCT

**Quality Score:**
++

**External validity:**
+

<table>
<thead>
<tr>
<th><strong>Age (years, mean SD):</strong></th>
<th><strong>Female sex:</strong></th>
<th><strong>Black race:</strong></th>
<th><strong>HIV seropositive:</strong></th>
<th><strong>Unemployed:</strong></th>
<th><strong>Less than high school education:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Supervised= 41 +/- 7; Peer= 41 +/- 9; Routine= 42 +/- 8</td>
<td>Supervised=27%; Peer= 26%; Routine= 27%</td>
<td>Supervised=88%; Peer= 92%; Routine= 91%</td>
<td>Supervised=18%; Peer= 24%; Routine= 17%</td>
<td>Supervised=85%; Peer= 81%; Routine= 88%</td>
<td>Supervised=42%; Peer= 49%; Routine= 53%</td>
</tr>
</tbody>
</table>

Patients were also asked to attend monthly support group meetings where lunch was provided.

Peers were former IDUs who had completed INH preventive therapy and were trained in counselling patients with TB and HIV about health promotion, prevention, treatment adherence and life-coping strategies.

Isoniazid was provided in bottles equipped with an electronic cap that recorded the time and date the bottle was opened. These patients were also asked to provide urine samples at each monthly visit.

Note: all patients across groups received either an immediate or a deferred $10 stipend for each month they adhered to study procedures such as the routine assessments on adherence and drug toxicity.

**Control/comparison/s description:** Routine care:
Patients received a monthly supply of INH, 300mg/day. Patients had

**Attrition details:** 12.3% (37/300)
an initial counselling session with the nurse, were encouraged to ask questions about their treatment, and were scheduled for a monthly assessment at the clinic where they were asked about adherence.

Isoniazid was provided in bottles equipped with an electronic cap that recorded the time and date the bottle was opened. These patients were also asked to provide urine samples at each monthly visit.

**Sample sizes:**
- **Total:** N=300
- **Supervised (DOPT):** N = 99
- **Peer:** N = 101
- **Routine:** N = 100

**Baseline comparisons:**
There were no statistically significant baseline differences between groups w/r/t age, gender, ethnicity, HIV status, employment or education.

**Study sufficiently powered?** NR
Study Details

Authors: DeMaio J, Schwartz L, Cooley P, Tice A

Year: 2001

Citation: The application of telemedicine technology to a directly observed therapy program for tuberculosis: A pilot project. *Clinical Infectious Diseases* 33(12): 2082-4.

Country of study: USA

Aim of study: To examine the application of telemedicine in a DOT programme

Study design: One-group / crossover

Population and setting

Source population/s: Implicitly, people using TB services

Eligible population: People with active TB under treatment in Pierce County, Washington, USA

Selected population: Candidates for the telemedicine project were selected from active cases of TB treated within the county who had successfully completed at least 4 weeks of standard DOT with >90% adherence.

Excluded population: Patients who did not have a touch-tone phone, did not have a television, or had a previous history of injection drug use.

Sample characteristics: NR

Method of allocation to intervention/control

Method of allocation: Unclear. All participants received some standard DOT and some videophone DOT, and outcomes are compared w/r/t each

Intervention/s description: Videophone units installed in patients’ homes. DOT carried out by videophone (approx 2-5 mins visit, NR by whom).

Control/comparison/s description: ‘Standard DOT’, not further described

Sample sizes: 6

Baseline comparisons: N/A

Study sufficiently powered? NR

Outcomes and methods of analysis:

Outcomes: Adherence (defined as completed visit)

Personnel time

Follow up periods: N/A – outcome is simultaneous with delivery of intervention

Method of analysis: Descriptive and tabulated results

Results

Results for all relevant outcomes:

Standard DOT: 97.5% adherence

Video DOT: 95% adherence

Time for visit: 1h/visit for standard DOT, 3 min/visit for video DOT

Total sample: 6

Attrition details: 0%

Notes

Limitations identified by author: NR

Limitations identified by review team: Generally very limited reporting and methods are highly unclear throughout. Small sample. Limited data to support analysis of time saved.

Evidence gaps and/or recommendations for future research: NR

Source of funding: Tacoma-Pierce County Health Department, Washington
<p>| Quality Score: |
| External validity: |</p>
<table>
<thead>
<tr>
<th>Study Details</th>
<th>Population and setting</th>
<th>Method of allocation to intervention/control</th>
<th>Outcomes and methods of analysis</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Authors: Goldberg SV, Wallace J, Jackson JC, Chaulk CP, Nolan CM</td>
<td>Source population/s: Refugees in King County, WA, USA</td>
<td>Method of allocation: N/A. Pre-test data comes from historical comparison (post 1999-2000, pre 1996-1998)</td>
<td>Outcomes: Treatment start (delivery of initial supply of medication)</td>
<td>Results for all relevant outcomes: Treatment start: pre 73%, post 88% (p=0.001) (Subgroups. Former Soviet pre 57%, post 73% (p=0.007); former Yugoslavia pre 39%, post 99% (p&lt;0.001); Somalia pre 94%, post 92% (p=0.52); other pre 98%, post 91% (p=0.605).) Treatment completion: pre 37%, post 82% (p&lt;0.001) (Subgroups. Former Soviet pre 45%, post 76% (p&lt;0.001); former Yugoslavia pre 60%, post 94% (p&lt;0.001); Somalia pre 34%, post 88% (p&lt;0.001); other pre 31%, post 63% (p=0.001)</td>
<td>Limitations identified by author: Effect might have resulted from broader diffusion in communities, behaviour of other patients and staff. Different individuals pre and post.</td>
</tr>
<tr>
<td>Year: 2004</td>
<td>Eligible population: All refugees newly arriving in King County who presented to Public Health’s Refugee Screening Program, with LTBI</td>
<td>Intervention/s description: Cultural case management (CCM) delivered by case managers of same national origin as target population, known to local community. Case managers trained in CM including TB information, principles of management and information on referrals for social services and primary health care. CM included home readings of tests, tailored TB education, referrals, and general supportive and trusting relationships. Printed educational materials also used.</td>
<td>Method of analysis: chi-square</td>
<td>Limitations identified by review team: Non-comparative design with retrospective pre-test. Recruitment not well defined. Evidence gaps and/or recommendations for future research: Qualitative research on reasons for programme success; cost-effectiveness studies</td>
<td></td>
</tr>
<tr>
<td>Citation: Cultural case management of latent tuberculosis infection. International Journal of Tuberculosis and Lung Disease 8(1): 76-82.</td>
<td>Selected population: Recruitment focused on those from Somalia, former Soviet Union, and former Yugoslavia. Selection of individuals not defined – unclear if any from those groups were excluded; also some participants from other national origins were included</td>
<td>Control/comparison/s description: Standard ‘clinic-centered’ approach to treatment of LTBI. Refugees reported to TB clinic for test readings and other</td>
<td>Follow up periods: 9 months</td>
<td>Source of funding: Federal Refugee Program, Annie E Casey Foundation, Firland Foundation, Nesholm Foundation</td>
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</tr>
<tr>
<td>Country of study: USA</td>
<td>Excluded population: Program had age cut-off of 35; nothing specific to study</td>
<td>National origin: pre test former Soviet N=139, former</td>
<td>Method of analysis:</td>
<td>Attrition details: NR</td>
<td></td>
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<tr>
<td>Aim of study: To evaluate the effectiveness of cultural case management for LTBI in refugee populations</td>
<td>Sample characteristics: Approx 60% male; approx 70% 15-34yo, 12% &gt;34yo, 13%-19% 5-14yo [Note: some inconsistency in age figures, and also don’t appear to line up with incl criteria]</td>
<td>National origin: pre test former Soviet N=139, former</td>
<td>Notes</td>
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</tbody>
</table>
Study design: One-group

Quality Score: –

External validity: –

Yugoslavia N=166, Somalia N=108, other N=349. Post test former Soviet N=128, former Yugoslavia N=109, Somalia N=118, other N=87

treatment if needed. Some education carried out (with interpreter if needed). Persons on treatment either reported to the TB Clinic for a monthly symptom check and medication refill or received a phone call symptom check prior to a monthly refill pickup at a satellite clinic.

Sample sizes:
Total: N=1204
Pre: N=762
Post: N=442

Baseline comparisons:
N/A

Study sufficiently powered?
NR
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Authors:</strong> Graham NMH, Galai N, Nelson KE, et al.</td>
<td><strong>Source population/s:</strong> Injecting drug users, Baltimore, MD, USA</td>
<td><strong>Method of allocation:</strong> N/A</td>
<td><strong>Outcomes:</strong> Incidence of TB and M. avium</td>
<td><strong>Results for all relevant outcomes:</strong> TB incidence. First year (pre) is reference; years 2-3 (unclear if pre or post) RR 2.5(0.5-13.2); years 4-5 (presumably post) RR 0.4(0.04-4.8) M. avium incidence. First year (pre) is reference; years 2-3 (unclear if pre or post) RR 2.7(0.7-10.3); years 4-5 (presumably post) RR 7.3(2.2-24.3)</td>
<td><strong>Attrition details:</strong> NR</td>
</tr>
<tr>
<td><strong>Year:</strong> 1996</td>
<td><strong>Eligible population:</strong> Unclear (recruitment from separate study, not described in detail in report of this study)</td>
<td><strong>Intervention/s description:</strong> Unclear. First year of cohort received SAPT (isoniazid). At some point this changed, there was 'increased access' to chemoprophylaxis, and DOT was implemented (isoniazid, for 6 months, extended to 12 if compliance maintained; no information on context or delivery of DOT). But outcomes relative to timing of intervention are unclear.</td>
<td><strong>Follow up periods:</strong> Approx. 2 years at cohort level; unclear at individual level</td>
<td><strong>Results for all relevant outcomes:</strong> TB incidence. First year (pre) is reference; years 2-3 (unclear if pre or post) RR 2.5(0.5-13.2); years 4-5 (presumably post) RR 0.4(0.04-4.8) M. avium incidence. First year (pre) is reference; years 2-3 (unclear if pre or post) RR 2.7(0.7-10.3); years 4-5 (presumably post) RR 7.3(2.2-24.3)</td>
<td><strong>Attrition details:</strong> NR</td>
</tr>
<tr>
<td><strong>Citation:</strong> Effect of isoniazid chemoprophylaxis on HIV-related mycobacterial disease. Archives of Internal Medicine 156(8): 889.</td>
<td><strong>Selected population:</strong> Recruitment via 'street outreach and word of mouth'. Participants who had reported living in Baltimore City at enrolment and those whose residence was unknown at enrolment, but whose last known residence was Baltimore, were included. Percentage agreed to participate: NR.</td>
<td><strong>Method of analysis:</strong> Relative risks</td>
<td><strong>Evidence gaps and/or recommendations for future research:</strong> NR</td>
<td><strong>Source of funding:</strong> National Institute on Drug Abuse; Centers for Disease Control and Prevention</td>
<td><strong>Source of funding:</strong> National Institute on Drug Abuse; Centers for Disease Control and Prevention</td>
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<td>prophylaxis on tuberculosis incidence</td>
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<tr>
<td>Study design: One-group</td>
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<tr>
<td>Quality Score: –</td>
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<tr>
<td>External validity: –</td>
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<tr>
<td>Study Details</td>
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</tr>
<tr>
<td><strong>Authors:</strong> Jin BW, Kim SC, Mori T, Shimao T</td>
<td><strong>Source population/s:</strong> Unclear – apparently general population</td>
<td><strong>Method of allocation:</strong> Randomisation at level of the subcentres within health centres (methods of randomisation not stated); only post test data reported</td>
<td><strong>Outcomes:</strong> Number of patient examinations</td>
<td><strong>Results for all relevant outcomes:</strong> Patient examinations: X-rays I 98.0%, C 80.2%; sputum smear and culture I 97.6%, C 70.2% (significance NR)</td>
<td><strong>Limitations identified by author:</strong> NR</td>
</tr>
<tr>
<td><strong>Year:</strong> 1993</td>
<td><strong>Eligible population:</strong> A total of 7 health centre areas, 3 urban and 4 rural, were selected as the project areas. 2 subcentres under each health centre were selected and each of them was randomly allocated to either the ‘intensive’ or the ‘routine’ service group.</td>
<td><strong>Drug collection rates</strong></td>
<td><strong>Drug collection rates; I 87.9%, C 77.1% (p&lt;0.01)</strong></td>
<td><strong>Limitations identified by review team:</strong> Details of the methods of study allocation, randomisation and blinding are not described. Contamination may have occurred because randomisation was at the level of the subcentre within the health centre and so staff may have had contact with each other</td>
<td></td>
</tr>
<tr>
<td><strong>Citation:</strong> The impact of intensified supervisory activities on tuberculosis treatment. <em>Tubercle and Lung Disease</em> 74:267-272</td>
<td><strong>Selected population:</strong> Patients newly registered at these health centers or subcentres during the year following April 1980 were taken into the study. The study aimed to recruit equal numbers of bacteriologically positive (including patients positive for both smear and culture and those positive only for culture) and negative patients in each treatment group.</td>
<td><strong>Delayed drug collection</strong></td>
<td><strong>Drug collection delayed by 7 days or more: I 4.7%, C 12.2% (p&lt;0.01)</strong></td>
<td><strong>Evidence gaps and/or recommendations for future research:</strong> NR</td>
<td></td>
</tr>
<tr>
<td><strong>Country of study:</strong> South Korea</td>
<td><strong>Excluded population:</strong> NR</td>
<td><strong>Treatment completion</strong></td>
<td><strong>Treatment completion:</strong> I 78.8%, C 65.2% (p&lt;0.01)</td>
<td><strong>Source of funding:</strong> Partly funded by the World Health Organization. Western Pacific Regional Office, Manila.</td>
<td></td>
</tr>
<tr>
<td><strong>Aim of study:</strong> to determine the importance of the motivation of the tuberculosis personnel in improving the results of a treatment programme.</td>
<td><strong>Sample characteristics:</strong> Urban 49.8% Initial positive bacteriology 46% Male 68.8% Age &lt;29 years 31.7%, 30-39</td>
<td><strong>Treatment success (conversion rates)</strong></td>
<td><strong>Treatment success (bacteriological conversion):</strong> I 75.2%, C 45.8% (p&lt;0.01)</td>
<td></td>
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<tr>
<td><strong>Study design:</strong></td>
<td><strong>Control/comparison/s description:</strong> Staff were instructed to follow the usual case</td>
<td><strong>Follow up periods:</strong> NR</td>
<td><strong>Inequalities:</strong> For patient examination, greater effect in rural than urban areas; for completion, greater in urban than rural. No significant difference by sex or age.</td>
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<td><strong>Attrition details:</strong> N/A – only post test reported</td>
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<tr>
<td>Randomised controlled trial (cluster randomised)</td>
<td>years 16.2%, 40-49 years 16.8%, 50-59 years 14.5%, 60 years or more 20.7% Previous treatment 17.5% [Characteristics of health centre staff (who were the group initially targeted by the intervention) NR]</td>
<td>motivation procedure as described in their service manual. Their performance was periodically supervised by the health centre director and the supervisory medical officer of the provincial government. Sample sizes: 1300 total = 651 in the intervention group and 649 in the control group [patients] Baseline comparisons: There were slightly more cases with a past history of tuberculosis in ‘intensive’ areas than in ‘routine’ areas. Other factors were equally distributed between groups. Study sufficiently powered? NR</td>
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<tr>
<td>Study Details</td>
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<tr>
<td>Authors: MacIntyre CR, Goebl K, Brown GV, Skill S, Starr M, Fullinfaw RO</td>
<td>Source population/s: People under treatment for TB in Victoria, Australia</td>
<td>Method of allocation: Alternating (i.e. quasi-random)</td>
<td>Outcomes: Completion of treatment (measured by drug collection)</td>
<td>Results for all relevant outcomes:</td>
<td>Limitations identified by author: FDOT not suitable for many patients because no suitable family member; study not adequately powered; urine testing may not accurately measure compliance (because INH persists up to 24 hours in urine).</td>
</tr>
<tr>
<td>Year: 2003</td>
<td>Eligible population: All new TB patients in two clinics in North-Western Health Care Network. Recruited by physicians, with information supplied by study nurse. Recruitment of sites NR (these clinics serve 30% of all TB patients in the city).</td>
<td>Intervention/s description: FDOT (family-based directly observed treatment): A suitable family member, nominated by the patient, was educated and trained to watch the patient swallow the anti-tuberculosis drugs (daily treatment. Patients received normal monthly clinic follow-up and telephone support from nurse.</td>
<td>Compliance with treatment (measured by (i) urine testing, with compliance defined as all six urinary INH levels greater than zero (ii) electronic pill bottles in random subsample (N=10)</td>
<td>Non-completion: I 3.4%, C 9.3% (p=0.11)</td>
<td>Limitations identified by review team: Generally robust other than limitations noted by authors. Differences in baseline NR. Not true random allocation.</td>
</tr>
<tr>
<td>Citation: A randomised controlled clinical trial of the efficacy of family-based direct observation of anti-tuberculosis treatment in an urban, developed-country setting. International Journal of Tuberculosis and Lung Disease 7(9), 848-854.</td>
<td>Selected population: All consenting TB patients in two clinics in the North-Western Health Care Network, commencing treatment from 30 January 1998 to 11 July 2000 were selected. Urban/industrialised area.</td>
<td>Control/comparison/s description: Standard treatment: Patients supervised at monthly clinic visits, but does not include DOT as standard. Patients received education and filled out their own pill sheets and handed their pill sheets to the study nurse at clinic visits.</td>
<td>Follow up periods: Minimum of 6 months or until treatment was completed</td>
<td>Non-compliance with treatment on urine testing ITT analysis: I 25.3%, C 22.1% (RR 1.04, 95%CI 0.88–1.23). Comparing those who actually received FDOT to all others (i.e. per-protocol analysis): RR 0.96, 95%CI 0.75–1.23</td>
<td>Evidence gaps and/or recommendations for future research: Evaluate intervention in high-incidence countries and in cultural settings where extended family units are the norm.</td>
</tr>
<tr>
<td>Country of study: Australia</td>
<td>Excluded population: Patients with MDR-TB; HIV co-infection; non-TB mycobacterial infections</td>
<td>Method of analysis: Intention-to-treat (but per-protocol also reported)</td>
<td>Trend analysis over 6 months on this outcome shows significantly better compliance in I than C (appears to be ITT, but not totally clear): chi-square for trend 11.12, p&lt;0.05).</td>
<td>Non-compliance by electronic pill bottles: 13% of doses missed, not analysed by group</td>
<td>Source of funding: NR</td>
</tr>
<tr>
<td>Aim of study: To assess the</td>
<td>Sample characteristics: Mean age: 41 years (median 38 years, range 14–83); Sex: 51% male (n=89/73); Countries of birth: Vietnam (29%).</td>
<td></td>
<td></td>
<td>Non-compliance by electronic pill bottles: 13% of doses missed, not analysed by group</td>
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<td>Sample sizes: Total N=173</td>
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</table>
The effectiveness of a family-based program of DOT for tuberculosis (FDOT), in comparison to non-observed, supervised treatment (ST) as is currently practised in Victoria.

**Study design:** quasi-RCT

**Quality Score:** ++

**External validity:** +

- Somalia (10.4%), Australia (10.4%), China (5.2%), Ethiopia (3.5%); English as first language: 18.5% (32/173); Required interpreter: 36% (62/173).

- At the time of diagnosis, 26% (45/173) in paid employment; 24% (41/173) were home carers and 30% (52/173) were students.

- Pulmonary TB: 57% (98/173). Symptomatic TB: 81.5% (141/173). Over half (92/173, 53%) had treatment initiated in hospital, with the remainder treated entirely on an outpatient basis. No study patients were placed on nurse-administered DOT.

**Control N=86**

**Baseline comparisons:** NR

**Study sufficiently powered?** Not sufficiently powered: A sample size of 224 patients (112 in each arm) was required for 95% confidence and 80% power for detecting a difference in non-compliance, ranging from 25% in the ST arm to 10% in the FDOT arm.

**Attrition details:** Unclear

significantly predict compliance.
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Authors:</strong> Malotte CK, Hollingshead JR, Larro M</td>
<td><strong>Source population/s:</strong> Active drug users (injecting or crack cocaine) with LTBI in Long Beach, California, USA</td>
<td><strong>Method of allocation:</strong> Concealed random allocation in blocks of 18</td>
<td><strong>Outcomes:</strong> Treatment completion (participants were counted as non-completers if lost to follow-up) Percentage of medication taken on time</td>
<td><strong>Results for all relevant outcomes:</strong> Treatment completion c1 52.8%; c2 3.6%; c3 60%. C1 vs c2 p&lt;0.0001; c3 vs c2 p&lt;0.0001 ORs for completion w/r/t c2: c1 29.7 (56.5–134.5), c3 39.7 (58.7–134.5) Medication taken on time c1 72%, c2 12%, c3 69% [authors report p&lt;0.001, but unclear what comparison this refers to] No binge drinking and earlier recruited participants associated with increased completion.</td>
<td><strong>Limitations identified by author:</strong> NR <strong>Limitations identified by review team:</strong> Generally robust study. Sampling not well-defined in this report. <strong>Evidence gaps and/or recommendations for future research:</strong> NR <strong>Source of funding:</strong> National Institute of Drug Abuse.</td>
</tr>
<tr>
<td><strong>Year:</strong> 2001</td>
<td><strong>Eligible population:</strong> Unclear - recruitment via another study. Setting was a 'storefront facility' conducting research and risk-reduction programmes for drug users.</td>
<td><strong>Intervention/s description:</strong> Condition 1: Twice weekly DOT by outreach worker at a location chosen by the participant (active outreach); and $5 monetary incentive per visit. Condition 2: DOT as in condition 1, but no monetary incentive</td>
<td><strong>Follow up periods:</strong> 8-12 months</td>
<td><strong>Control/comparison/s description:</strong> As above <strong>Method of analysis:</strong> ANOVA, chi-square; intention-to-treat</td>
<td></td>
</tr>
<tr>
<td><strong>Citation:</strong> Incentives vs outreach workers for latent tuberculosis treatment in drug users. American Journal of Preventive Medicine, 20(2):103-107.</td>
<td><strong>Selected population:</strong> Participation rate 169/202 (84%). Included those with a positive tuberculin skin test (10mm indurations for HIB negative; 5 mm for HIV positive or unknown status) and no evidence of active disease or major contraindications to isoniazid.</td>
<td><strong>Condition 3:</strong> Twice weekly DOT at the study community site; and $5 monetary incentive if they appeared for the prescribed doses.</td>
<td><strong>Baseline comparisons:</strong> Total: N=163; condition 1 N=53, condition 2 N=55, condition 3 N=55</td>
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</tr>
<tr>
<td><strong>Country of study:</strong> USA</td>
<td><strong>Excluded population:</strong> Participants with active disease or medical contraindications.</td>
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<tr>
<td><strong>Aim of study:</strong> To compare the independent and combined effects of monetary incentives and outreach worker</td>
<td><strong>Sample characteristics:</strong> Mean age: 42 years (range 23 to 69 years). Male: 82% African American: 71% Hispanic: 92.2% White: 13.5% Other race/ethnicity: 6.7%</td>
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</table>
provision of DOT (for LTBI) treatment in a sample of active drug users.

**Study design:**
RCT

**Quality Score:**
++

**External validity:**
+

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<table>
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<tbody>
<tr>
<td>No statistically significant differences at baseline in demographic or drug use variables</td>
<td>Study sufficiently powered? NR</td>
</tr>
<tr>
<td>Study Details</td>
<td>Population and setting</td>
</tr>
<tr>
<td>---------------</td>
<td>------------------------</td>
</tr>
<tr>
<td><strong>Authors:</strong> Matteelli A, Casalini C, Raviglione MC, et al.</td>
<td><strong>Source population/s:</strong> Recruitment sites: one health care unit for immigrants in Brescia and one clinic in Turin that serves as a TB screening site for contacts and people applying to enter dormitories/housing (Northern Italy--Brescia and Turin).</td>
</tr>
<tr>
<td><strong>Year:</strong> 2000</td>
<td><strong>Eligible population:</strong> Unclear. No details on recruitment or percentage agreed to participate</td>
</tr>
<tr>
<td><strong>Country of study:</strong> Italy</td>
<td><strong>Selected population:</strong> Eligible for the preventive therapy trial if subjects came from countries with an estimated tuberculosis incidence of 50/100,000 or more, history of immigration of less than 5 yr, and development of a skin induration &gt;10 mm 72 h after intradermal injection of 5 international units of PPD.</td>
</tr>
<tr>
<td><strong>Aim of study:</strong> To conduct a comparative prospective study to assess adherence to one supervised,</td>
<td><strong>Excluded population:</strong> Exclusion criteria included pregnancy, age older than 35 yr, and liver enzymes (AST, ALT) five times or more than the upper normal values..</td>
</tr>
<tr>
<td></td>
<td><strong>Sample characteristics:</strong> Male</td>
</tr>
<tr>
<td></td>
<td><strong>Sample sizes:</strong> Total N=208 Regimen A: n=82 patients Regimen B: n=73 patients Regimen C: n=53 patients</td>
</tr>
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</tr>
<tr>
<td>Study design:</td>
<td>RCT</td>
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<tr>
<td>Quality Score:</td>
<td>–</td>
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<tr>
<td>External validity:</td>
<td>–</td>
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<table>
<thead>
<tr>
<th>sex-</th>
<th>Regimen A: 48 (58.5%); Regimen B: 48 (65.7%); Regimen C: 32 (60.3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 15-24yr-</td>
<td>Regimen A: 26 (31.7%); Regimen B: 22 (30.2%); Regimen C: 16 (30.2%)</td>
</tr>
<tr>
<td>Age 25-35yr-</td>
<td>Regimen A: 56 (68.3%); Regimen B: 51 (69.8%); Regimen C: 37 (69.8%)</td>
</tr>
<tr>
<td>Country of Origin – Africa-</td>
<td>Regimen A: 60 (73.2%); Regimen B: 50 (68.5%); Regimen C: 37 (69.8%)</td>
</tr>
<tr>
<td>Country of Origin – Other-</td>
<td>Regimen A: 22 (26.8%); Regimen B: 23 (31.5%); Regimen C: 17 (32%)</td>
</tr>
</tbody>
</table>

- no statistically significant differences w/r/t gender, age, country of origin, marital status, religion, employment, alcohol/drug abuse
- **Study sufficiently powered?**
  - Not sufficiently powered: 411 evaluable subjects needed to show a 15% difference in adherence between arms A and C. However, the trial was terminated early because of a larger than expected difference in adherence within the treatment arms.
<table>
<thead>
<tr>
<th>Study Details</th>
<th>Population and setting</th>
<th>Method of allocation to intervention/control</th>
<th>Outcomes and methods of analysis</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Authors:</strong> Narita M, Kellman M, Franchini DL, McMillian ME, Hollender ES, Ashkin D</td>
<td><strong>Source population/s:</strong> HIV infected patients in Broward County, Florida community HIV clinics&lt;br&gt;<strong>Eligible population:</strong> All HIV-infected patients seen by healthcare providers from February 1, 1999, to March 31, 2001. These patients were evaluated for LTBI and active tuberculosis disease. Percentage agreed to participate: NR.&lt;br&gt;<strong>Selected population:</strong> TST-positive patients with the following characteristics: (1) the patient was a close contact to an infectious tuberculosis disease case, or (2) the patient had a current or previously documented positive TST result with no history of adequate treatment for LTBI.&lt;br&gt;<strong>Excluded population:</strong> NR&lt;br&gt;<strong>Sample characteristics:</strong> Mean age pre 38, post 42 Male 57% pre, 67% post Black 90% pre, 83% post</td>
<td><strong>Method of allocation:</strong> N/A. Pre-test data come from retrospective cohort&lt;br&gt;<strong>Intervention/s description:</strong> Pre: self-administered therapy (isoniazid). Post: twice-weekly DOT observed by clinic staff (rifamycin and pyrazinamide)&lt;br&gt;<strong>Control/comparison/s description:</strong> N/A</td>
<td><strong>Outcomes:</strong> Treatment completion&lt;br&gt;<strong>Follow up periods:</strong> 24 months at individual level</td>
<td><strong>Results for all relevant outcomes:</strong> Treatment completion pre 61%, post 93% (p&lt;0.001)&lt;br&gt;<strong>Attrition details:</strong> Pre 5%; post 17% at 12 months, 53% at 24 months (individual level; N/A at cohort level)</td>
<td><strong>Limitations identified by author:</strong> Choice of specific regimen within DOT group not randomized. Historical comparison group. Pre group received longer treatment (and completion outcome measured at longer scale) than current guidelines indicate.&lt;br&gt;<strong>Limitations identified by review team:</strong> Non-comparative design. Main focus of study is not on DOT and there is limited information on it.&lt;br&gt;<strong>Evidence gaps and/or recommendations for future research:</strong> NR&lt;br&gt;<strong>Source of funding:</strong> NR</td>
</tr>
</tbody>
</table>
| **Aim of study:**  
To evaluate short-course rifamycin and pyrazinamide treatment of (LTBI) in HIV-infected patients |
| **Study design:**  
Before-after |
| **Quality Score:**  
+ |
| **External validity:**  
+ |
<table>
<thead>
<tr>
<th>Study Details</th>
<th>Population and setting</th>
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<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Authors:</strong> Nyamathi AM, Christiani A, Nahid P, Gregerson P, Leake B.</td>
<td><strong>Source population/s:</strong> homeless adults residing in the Skid Row region of Los Angeles, US from 1998 to 2003</td>
<td><strong>Method of allocation:</strong> Random allocation (details NR) by site, stratified by type, stability of population, and size</td>
<td><strong>Outcomes:</strong> Treatment completion (directly observed)</td>
<td><strong>Results for all relevant outcomes:</strong> Treatment completion: I 61.5%, C 39.3% (p&lt;0.01) TB knowledge improvement: I 3.8±3.5, C 2.0±4.2 (p&lt;0.01) Logistic regression model controlling for confounders shows odds ratio of 3.01 (2.15-4.20) in favour of intervention group wrt treatment completion outcome (p&lt;0.001) Compared to non-completers, completers were more likely to be Black, were older, were more often recruited from emergency rather than drug recovery shelters, and were more likely to be highly motivated to adhere Failure to complete treatment was positively associated with lifetime IDU, recent daily substance use and recent hospitalization Taken from Nyamathi 2008 (write up of same study focusing on subgroups)</td>
<td><strong>Limitations identified by author:</strong> Cannot identify precise contributions of different intervention components; may be bias in self-report outcomes <strong>Limitations identified by review team:</strong> Generally robust. Some minor limitations in methods; cluster randomisation not taken into account in analysis; some unclarity on recruitment of sites <strong>Evidence gaps and/or recommendations for future research:</strong> Additional studies are needed to assess cost effectiveness, program portability, and the feasibility of using lay personnel. <strong>Source of funding:</strong> The National Institute on Drug Abuse</td>
</tr>
<tr>
<td><strong>Year:</strong> 2006</td>
<td><strong>Eligible population:</strong> People attending homeless emergency and residential recovery shelters; recruited by flyers at intervention sites</td>
<td><strong>Intervention/s description:</strong> Nurse case-managed with incentives (NCMI) programme: The NCMI programme was based on the comprehensive health seeking and coping paradigm. Delivered by a research nurse and a trained outreach worker. Participants received eight one-hour TB education sessions, which included visual coping scenarios over the 24 weeks of treatment. The intervention components focused on 1) self esteem and attitudinal readiness for change; 2) TB and HIV risk reduction education; 3) coping, self management, and communication skills; 4) cognitive problem solving to implement behavior change; and 5) positive relationships and social networks to maintain behavior change.</td>
<td><strong>Follow up periods:</strong> 6 months</td>
<td><strong>Method of analysis:</strong> Wilcoxon two-sample test; chi-square; t-test; logistic regression for modelling predictors</td>
<td></td>
</tr>
<tr>
<td><strong>Country of study:</strong> Los Angeles, US</td>
<td><strong>Selected population:</strong> participants were homeless adults aged 18–55, or those aged over 55 with reported risk activation factors for TB, who had slept in one of the study shelters the previous night and who reported no previous LTBI treatment; and who were TST-positive</td>
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<td><strong>Excluded population:</strong> None</td>
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<td></td>
<td><strong>Sample characteristics:</strong> Mean age 41.5 Male 79.6% Black 81% High school graduate 72.5% No insurance 75.4% Median (range) of years homeless 1 (0.003–24) Lifetime intravenous drug use 20% Recent intravenous drug use</td>
<td></td>
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</tbody>
</table>
Aim of study:
To compare the effectiveness of an intervention programme employing nurse case management and incentives (NCMI) vs. a control programme with standard care and incentives on completion of LTBI treatment; and tuberculosis knowledge among participants.

Study design:
cluster RCT

Quality Score:
++

External validity: +

11.4%
Prior drug treatment 23.9%
Recent self help programme 63.5%

Over 80% indicated that they wanted to take INH and intended to adhere

Intervention group participants were provided with community resources and were escorted to their medical and social service appointments. Unlike control group participants, NCMI participants were tracked when they missed a DOT dose. Tracking was performed by the outreach worker with a locator guide using contact data and pre-approved photos collected from all participants at baseline.

Control/comparison/s description:
Standard with incentives (SI) program: The SI control group was staffed by a separate team consisting of a trained nurse and outreach worker. This control group received a 20-minute basic lecture on TB and the importance of treatment adherence along with a local community resource guide. All participants had a 10-minute period to discuss questions with their nurse when they presented for each INH dose over the 6-month study period.

All participants received $5 US for each DOT dose.

intervention completers n (%) / control completers n (%)
Males
I: 149 (61) C: 71 (37)
RR 1.46 95% CI 1.21, 1.77
Females
I: 22 (65) C: 24 (33)
RR 1.94 95% CI: 1.26, 2.98
African Americans
I: 148 (64) C: 84 (44)
RR 1.45 95% CI: 1.22, 1.74
Non-African Americans
I: 24 (50) C: 11(22)
RR 2.32 95% CI 1.32, 4.06
Homeless shelter recruits I: 253 (91) C: 161 (66.5)
RR 1.57 95% CI 1.29, 1.90
Veteran
I: 17 (68) C: 9 (43)
RR 1.50 95% CI 0.93, 2.71
Lifetime IDU
I: 21 (55) C: 23 (35)
RR 1.59 95% CI 1.01, 2.48

Attrition details:
11 in each group were lost to follow up. 57 in the intervention and 97 in the control group dropped out of intervention but completed the 6 month questionnaire.
Both treatment groups.

**Sample sizes at baseline:**
- Total N=520
- Intervention N=279
- Control N=241

**Baseline comparisons:**
- I more male; more from emergency shelters rather than recovery shelters; less lifetime IDU. No differences in age, ethnicity, education, alcohol/drug use, mental health, physical health

**Study sufficiently powered?** Calculated for difference of 15% with power of 0.80 – but calculated wrt individual participants (as per analysis), not wrt site (as per allocation)
<table>
<thead>
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</tr>
</thead>
<tbody>
<tr>
<td>Authors:</td>
<td>Rüütel K, Loit HM, Sepp T, Kliiman K, McNutt LA, Uusküla A</td>
<td>Source population/s: Drug users in Estonia</td>
<td>Outcomes: Attendance at TB services</td>
<td>Results for all relevant outcomes: Attendance: I 57.1%, C 30.4% (p = 0.004). None of the following were significantly associated with outcomes: age, gender, education, employment, drug injection history, prison, TB contacts, Mantoux results, HIV status</td>
<td>Limits identified by author: Small sample recruited from one centre, and low response rate, may limit generalizability</td>
</tr>
<tr>
<td>Year:</td>
<td>2011</td>
<td>Eligible population: Recruited from community-based methadone substitution treatment centre in Jõhvi (small town in north-eastern Estonia). All clients using centre on selected dates were approached by centre nurses. Participation rate 59%; refusals not different from participants w/r/t age or gender.</td>
<td>Follow up periods: 2 months</td>
<td></td>
<td>Limits identified by review team: None to add to authors’</td>
</tr>
<tr>
<td>Citation:</td>
<td>Enhanced tuberculosis case detection among substitution treatment patients: a randomized controlled trial. <em>BMC Research Notes</em> 4(1), 192.</td>
<td>Selected population: (1) participation in substitution treatment program; (2) age 18 years or more; (3) able to read and write in Estonian or Russian; (3) able to provide informed consent.</td>
<td>Method of analysis: Wilcoxon rank-sum test or Fisher exact test; univariate and multivariable logistic regressions.</td>
<td></td>
<td>Evidence gaps and/or recommendations for future research: Methods for screening among IDUs not in contact with harm reduction services.</td>
</tr>
<tr>
<td>Aim of study:</td>
<td>To evaluate a case management intervention aimed at increasing tuberculosis screening and treatment entry among injecting drug users.</td>
<td>Intervention/s description: Active case management. Study personnel scheduled the appointment and reminded to keep it, transportation was organized when needed. Participants were expected to attend TB services within the two months after the initial randomization. For those who returned to skin test reading on time an incentive was given (food voucher, value €6.40).</td>
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<tr>
<td>Source population/s: Drug users in Estonia</td>
<td>Sample characteristics: 64.9% male, mean age 26.2 (83.9% &lt;30), 9.8% Estonian ethnicity</td>
<td>Control/comparison/s description: Passive referral. Instructed to schedule an appointment with TB services themselves.</td>
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</tr>
<tr>
<td>Sample sizes: Total N=112</td>
<td>Method of allocation: Randomization conducted by study nurses</td>
<td>Sample sizes: Total N=112</td>
<td>Baseline comparisons: No sig differences w/r/t</td>
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<tr>
<td>Intervention N=56</td>
<td></td>
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<tr>
<td>Control N=56</td>
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drug users referred from a methadone drug treatment program.

**Study design:** RCT

**Quality Score:** ++

**External validity:** +

<table>
<thead>
<tr>
<th>gender, age, ethnicity, education, employment, TB exposure, or risk factors</th>
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**Study sufficiently powered?** NR
<table>
<thead>
<tr>
<th>Study Details</th>
<th>Population and setting</th>
<th>Method of allocation to intervention/control</th>
<th>Outcomes and methods of analysis:</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Authors: Sterling TR, Villarino ME, Borisov AS, et al.</td>
<td>Source population/s: People at high risk of TB in USA, Canada, Brazil and Spain</td>
<td>Method of allocation: Simple randomization (by household for those recruited and treated by household, individually for others)</td>
<td>Outcomes: Treatment completion</td>
<td>Results for all relevant outcomes: Treatment completion: I 82.1%, C 69.0% (p=0.001)</td>
<td>Limitations identified by author: Cannot distinguish effects of regimen from effects of observation. Control group had higher completion rates than usually observed in clinical practice. HIV+ rate lower in sample than in practice.</td>
</tr>
<tr>
<td>Year: 2011.</td>
<td>Eligible population: Limited information on sampling or recruitment (and likely that this differed between countries). Percentage agreed to participate: Unclear. Of 7,452 assessed for eligibility in the later recruitment phase, 1,756 (23.6%) declined to participate (and 1,469 (19.7%) did not meet criteria, and a further 359 (4.8%) did not participate for 'other reasons'). But these data are unavailable for the 4,185 who enrolled in the earlier recruitment phase.</td>
<td>Intervention/s description: DOT using combination therapy (rifapentine and isoniazid once weekly). No information on context or delivery of DOT.</td>
<td>Incidence of TB</td>
<td>Incidence of TB: ITT analysis: I 0.19 cumulative rate per person-year aggregated over study period, C 0.43 (NS); per-protocol: I 0.13, C 0.32 (NS)</td>
<td>Limitations identified by review team: Sampling and recruitment unclear. Study authors conceptualize the comparison as between two drug regimens rather than between DOT and SAT.</td>
</tr>
<tr>
<td>Citation: Three months of rifapentine and isoniazid for latent tuberculosis infection. New England Journal of Medicine 365(23):2155-2166.</td>
<td>Country of study: USA, Canada, Brazil, Spain</td>
<td>Control/comparison/s description: Self-administered treatment using isoniazid only (daily).</td>
<td>Death</td>
<td>After adjustment for factors independently associated with TB risk (viz. smoking, HIV status and BMI), I patients were at significantly lower risk than C (adjusted hazard ratio, 0.38; 95% CI, 0.15 to 0.99; p=0.05)</td>
<td>Evidence gaps and/or recommendations for future research: NR</td>
</tr>
<tr>
<td>Aim of study: To evaluate rifapentine plus isoniazid compared to isoniazid alone</td>
<td>Selected population: 12 years or older (expanded to 2 years or older midway through study): contact of TB patient within previous 2 years or positive TST</td>
<td>Sample sizes: Total N=7,731 Intervention N=3,986 Control N=3,745</td>
<td>Follow up periods: 33 months</td>
<td>Death: C 0.8%, I 1.0% (p=0.22)</td>
<td>Source of funding: Centers for Disease Control and Prevention (CDC)</td>
</tr>
<tr>
<td>Study design: Randomised controlled trial</td>
<td>Excluded population: Confirmed or suspected tuberculosis, resistance to isoniazid or rifampin in the source case, treatment with rifamycin or isoniazid during the previous 2 years, previous completion of treatment for</td>
<td>Baseline comparisons: Significantly higher % American Indian and homeless in intervention group. Otherwise no sig differences by indication, age, ethnicity, HIV status, BMI or risk factors</td>
<td>Method of analysis: Chi-square. Both intention-to-treat and per-protocol analyses conducted.</td>
<td>Attrition details: Somewhat unclear. Paper reports 33-month follow-up rate as 88% for combination therapy and 86% for isoniazid-only. But flow diagram in the appendix shows that 1065/3745 (28%) of the isoniazid group and 623/3986 (16%) of the combination group did not complete regimen per protocol, most of which is dropouts.</td>
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</table>
tuberculosis or M. tuberculosis infection in HIV seronegative persons, sensitivity or intolerance to isoniazid or rifamycin, a serum aspartate aminotransferase level that was five times the upper limit of the normal range, pregnancy or lactation, HIV therapy within 90 days after enrolment, or a weight of less than 10.0 kg

Sample characteristics: Median age I 35, C 36. Male I 53.5%, C 55.4%. White I 57.5%, C 57.6%; Black I 25.3%, C 24.5%; Asian or Pacific Islander I 13.1%, C 12.4%; North American Indian: I 0.9%, C 2.1%; Multiracial (in Brazil) I 3.1%, C 3.4%

size of 3200 subjects per study group would provide a power of more than 80% to show the noninferiority of combination therapy. To allow for 20% loss to follow-up and to account for clustering, 4000 subjects were targeted for enrolment in each study group.
## 7.2 Cost-effectiveness studies

<table>
<thead>
<tr>
<th>Study Details</th>
<th>Population and setting</th>
<th>Intervention/ comparator description</th>
<th>Outcomes and methods of analysis:</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Authors:</strong> Berkowitz FE, Severens JL, Blumberg HM</td>
<td><strong>Source population/s:</strong> [NB this is a pure modelling study rather than an economic evaluation – the intervention, population and setting are hypothetical.] Neonates</td>
<td><strong>Intervention/s description:</strong> Isoniazid administered by directly observed therapy for 5 days/week for 3 months, plus additional prophylaxis administered daily by parents to children with positive TST results</td>
<td><strong>Outcomes:</strong> Cost per death prevented</td>
<td><strong>Primary analysis:</strong> Incremental cost-effectiveness of DOT wrt no prophylaxis: $21,710,000 per death prevented Incremental cost-effectiveness of non-DOT (parent-administered prophylaxis) wrt no prophylaxis: $929,500 per death prevented</td>
<td><strong>Limitations identified by author:</strong> Only survival and death taken into account, not e.g. impairment as a result of tuberculous meningitis, or costs of litigation [sic].</td>
</tr>
<tr>
<td><strong>Year:</strong> 2006</td>
<td><strong>Setting:</strong> Hospital nursery</td>
<td><strong>Comparator/control/s description:</strong> Isoniazid administered by parents 7 days/week</td>
<td><strong>Time horizon:</strong> 4 years</td>
<td><strong>Secondary analysis:</strong> Sensitivity analysis compare DO prophylaxis to no prophylaxis. “One-way sensitivity analysis of the probability of survival showed that the DO prophylaxis strategy was dominant under the following circumstances: (1) the probability of developing infection was greater than 0.0002, (2) the probability of developing disease in the absence of prophylaxis was greater than 0.12, (3) the probability of dying of tuberculosis was greater than 0.025, (4) the probability of hepatotoxicity was less than 0.004, and (5) the probability of dying of hepatic toxicity”</td>
<td><strong>Limitations identified by review team:</strong> Static model; transmission not taken into account. Efficacy of DOT is simply assumed and not based on literature or evaluation data at all, and applicability of sources cited for efficacy of parent-administered prophylaxis is questionable. Derivation of many parameters unclear. No QALY analysis. Short time horizon and high discount rate. Population may be of limited relevance to this review.</td>
</tr>
<tr>
<td><strong>Citation:</strong> Exposure to tuberculosis among newborns in a nursery: decision analysis for initiation of prophylaxis. <em>Infection Control and Hospital Epidemiology</em>, 27(6): 604-611</td>
<td><strong>Data sources:</strong> All from the literature</td>
<td><strong>Sample characteristics:</strong> NR</td>
<td><strong>Discount rates:</strong> 5%</td>
<td><strong>Evidence gaps and/or recommendations for future research:</strong> Data on probability of infection, of hepatotoxicity</td>
<td></td>
</tr>
</tbody>
</table>
infection.” (p604)

**Type of economic analysis:**
Cost-effectiveness analysis

**Economic perspective:**
Healthcare system

**Quality score:** –

**Applicability:** +

| Onset of hepatotoxicity | Survival of hepatotoxicity | hepatotoxicity was less than 0.04.”
|-------------------------|---------------------------|---------------------------------|

Also 2-way sensitivity analysis presented graphically for outcomes above (full data not extracted here)

**Source of funding:** NR
<table>
<thead>
<tr>
<th>Study Details</th>
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<th>Outcomes and methods of analysis:</th>
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<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Authors:</strong></td>
<td>Burman WJ, Dalton CB, Cohn DL, Butler JRG, Reves RR</td>
<td><strong>Source population/s:</strong></td>
<td><strong>Outcomes:</strong></td>
<td><strong>Primary analysis:</strong></td>
<td><strong>Limitations identified by author:</strong></td>
</tr>
<tr>
<td><strong>Year:</strong></td>
<td>1997</td>
<td>A hypothetical cohort of 100 patients with active tuberculosis</td>
<td><strong>Average net cost</strong></td>
<td>Programme perspective: DOT net costs US$1,405, SAT $2,314 per patient treated (=relative cost saving from DOT of $909)</td>
<td>Did not include other outcomes of treatment that are likely to make DOT more cost-effective than SAT. Did not include an analysis of the costs of a fatal relapse of TB. Did not include any costs that result from transmission.</td>
</tr>
<tr>
<td><strong>Citation:</strong></td>
<td>A cost-effectiveness analysis of directly observed therapy vs self-administered therapy for treatment of tuberculosis. <em>Chest</em> 112(1):63-70.</td>
<td><strong>Setting:</strong> Health service</td>
<td><strong>Time horizon:</strong> None for model itself; 6-24 months considered for some probabilities</td>
<td>Healthcare perspective (excluding patient time cost but including hospitalisation costs for treatment failures): DOT net costs $2,785, SAT $10,529 per patient treated (=relative cost saving of $7,744)</td>
<td></td>
</tr>
<tr>
<td><strong>Aim of study:</strong></td>
<td>To compare the costs and effectiveness of directly observed therapy (DOT) vs self-administered therapy (SAT) for the treatment of active tuberculosis</td>
<td><strong>Data sources:</strong> Retrospective data from Denver Metro Tuberculosis Clinic, unpublished data from Denver General Hospital, Medical Consumer Price Index, literature</td>
<td><strong>Discount rates:</strong> 0%, 5% and 8% considered</td>
<td>Healthcare perspective (including patient time cost): DOT net cost $2,117, SAT $1,339 per patient treated (=relative cost of $778); including patient time costs of treatment failures DOT net cost $3,999, SAT $12,167, per patient treated (=relative cost saving of $8,168).</td>
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</tr>
<tr>
<td><strong>Type of economic analysis:</strong></td>
<td>cost-effectiveness</td>
<td><strong>Comparator/control/s description:</strong> The SAT arm uses the currently recommended regimen for self-administered short-course therapy: daily isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months followed by daily isoniazid and rifampin for 4 months. SAT estimated to require 8 clinic visits over 6 months.</td>
<td><strong>Perspective:</strong> programme and healthcare system</td>
<td><strong>Secondary analysis:</strong> Threshold analysis calculate values required for SAT to overturn DOT’s advantage.</td>
<td><strong>Limitations identified by review team:</strong> Model is very simplified. Effect and baseline data from programme only.</td>
</tr>
<tr>
<td><strong>Sample sizes:</strong></td>
<td>Total 100</td>
<td><strong>Sample characteristics:</strong> NR</td>
<td><strong>Measures of uncertainty:</strong> One-way threshold analysis of a number of parameters</td>
<td><strong>Source of funding:</strong> NR</td>
<td>Evidence gaps and/or recommendations for future research: Effectiveness and cost-effectiveness of DOT in developing countries</td>
</tr>
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<td></td>
<td>Intervention 100</td>
<td></td>
<td><strong>Modelling method:</strong> Decision tree</td>
<td>Cost of medications used for</td>
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<td></td>
<td>Control N/A</td>
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<tr>
<td>Economic perspective: programme and healthcare system</td>
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<td>Quality score: +</td>
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<tr>
<td>Applicability: +</td>
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<p>|  | initial treatment using DOT ($): model value=193, TB program perspective=1102, healthcare perspective=7937  |
|  | Cost of medications used for initial treatment using SAT ($): model value=584, TB program=not found, healthcare=not found (DOT advantage remains)  |
|  | Nursing time to administer one DOT dose (h): model=0.25, TBp=1.25, hc=8.75  |
|  | Cost of hospitalization for a drug-susceptible treatment failure ($): model=7662, TBp=not found, hc=not found  |
|  | Cost of hospitalization for a MDR treatment failure ($): model=15740, TBp=not found, hc=not found  |
|  | Failure rate of initial therapy using DOT: model=0.55, TBp=0.306, hc=0.325  |
|  | Proportion of DOT treatment failures acquiring MDR: model=0.16, TBp=not found, hc=not found  |
|  | Failure rate of initial therapy using SAT: model=0.21, TBp=0.035, hc=0.035  |
| Proportion of SAT treatment failures acquiring MDR: model=0.29, TBp=not found, hc=not found |
| Hourly cost of a patient's time ($) : model=11.75, TBp=n/a, hc=not found |</p>
<table>
<thead>
<tr>
<th>Study Details</th>
<th>Population and setting</th>
<th>Intervention/ comparator description</th>
<th>Outcomes and methods of analysis:</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Authors:</strong> Gourevitch MN, Alcabes P, Wasserman WC, Arno PS</td>
<td><strong>Source population/s:</strong> Drug users enrolled in a methadone maintenance treatment program in the Bronx, New York</td>
<td>Screening by X-ray and smear and sputum culture. Chemoprophylaxis for eligible patients given on-site and observed by clinical staff when patients receive dose of methadone (or given for off-site consumption when patients do not receive methadone at clinic). Programme of DOPT is voluntary and can be refused (but rarely is). Regimen is INH 300mg and pyroxidine 50mg daily for 6 months (HIV-) or 12 months (HIV+).</td>
<td><strong>Outcomes:</strong> Net cost savings per patient receiving chemoprophylaxis</td>
<td><strong>Primary analysis:</strong> Net cost savings of programme per patient receiving chemoprophylaxis: under SAT range from US$1,289 to $3,418 depending on INH efficacy, and under DOT from $1,380 to $3,590 depending on INH efficacy and DOT effectiveness. (Note: authors interpret this as showing that DOT is cost-effective, even though in some cases the cost savings from DOT are less than those from SAT.)</td>
<td><strong>Limitations identified by author:</strong> Did not model the impact of chemoprophylaxis beyond 5 years of follow-up. Model did not take into account of multi-drug resistance, multiple hospitalizations per case of TB, out-patient costs of TB care, and the costs of treating secondary infections and cases that could have been averted by chemoprophylaxis. Model is based on analysis of the population attending a single methadone maintenance treatment program in the Bronx.</td>
</tr>
<tr>
<td><strong>Year:</strong> 1998</td>
<td><strong>Setting:</strong> Drug treatment programme which provides comprehensive medical services</td>
<td>Comparator/control/programme: Implicitly, self-administered therapy</td>
<td><strong>Time horizon:</strong> 5 years</td>
<td></td>
<td><strong>Limitations identified by review team:</strong> Appears to be some biased reporting of outcomes and discrepancies between figures and write-up of findings. Treatment effect of DOT appears to be pure assumption, not based on any data. Data sources elsewhere are also unclear.</td>
</tr>
<tr>
<td><strong>Citation:</strong> Cost-effectiveness of directly observed chemoprophylaxis of tuberculosis among drug users at high risk for tuberculosis. International Journal of Tuberculosis and Lung Disease 2(7):531–540</td>
<td><strong>Data sources:</strong> Literature, clinic records</td>
<td>Sample sizes: Total N=507 (screening); N=151 (chemoprophylaxis)</td>
<td><strong>Discount rates:</strong> 3%</td>
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<tr>
<td>economic analysis:</td>
<td>15%, White 19%, Other race 1%; PPD+ve 29%; anergic 6%; PPD-ve (non-anergic) 66%.</td>
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<tr>
<td>Economic perspective:</td>
<td>compartmental model than baseline)</td>
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<tr>
<td>Quality score:</td>
<td>Lower prevalence of HIV infection (drop from 31% to 5%): $117096/4=$29274 (lower than baseline)</td>
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<tr>
<td>Applicability:</td>
<td>No TB in HIV-seropositive anergic: $244584/7=$34941 (lower than baseline)</td>
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<tr>
<td></td>
<td>Include out-patient costs ($3009.90): $431395/11=$39218</td>
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<td></td>
<td>Include multi-drug resistance costs (13 cases at a cost of $100000 per case): $498370/11=$45306.36</td>
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<tr>
<td>recommendations for future research:</td>
<td>Applicability of model to other settings; effect of diminishing TB incidence on outcomes; cost-effectiveness of prevention compared with case finding and treatment</td>
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<tr>
<td>Source of funding:</td>
<td>National Institute of Drug Abuse, NY State AIDS Institute, and New York City Department of Health</td>
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<tr>
<td>Study Details</td>
<td>Population and setting</td>
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<td>Outcomes and methods of analysis:</td>
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<tr>
<td><strong>Authors:</strong> Holland DP, Sanders GD, Hamilton CD, Stout JE</td>
<td><strong>Source population/s:</strong> hypothetical cohort, no information on source</td>
<td><strong>Intervention/s description:</strong> (1) Isoniazid 300 mg given as daily self-administered therapy for 9 months (9H); (2) Isoniazid 900 mg given twice weekly by DOT for 9 months (9H-DOT); (3) Isoniazid 900 mg 1 rifapentine 900 mg given once weekly by DOT for 12 weeks (3HP); (4) Rifampin 600 mg given as daily self-administered therapy for 4 months (4R). I.e. (2) and (3) = DOT, (1) and (4) = SAT. DOT administered by outreach worker, apparently in patients’ homes</td>
<td><strong>Outcomes:</strong> Net costs; cost per QALY</td>
<td><strong>Primary analysis:</strong> 9H-DOT net cost of US$475.10 relative to no treatment (NT) per patient. Others all net cost saving: 9H (SAT) -$847.81, 4R (SAT) -$1,032.12, 3HP (DOT) -$751.06</td>
<td><strong>Limitations identified by author:</strong> Limited data on efficacy and adherence for 3HP.</td>
</tr>
<tr>
<td><strong>Year:</strong> 2009</td>
<td><strong>Setting:</strong> NR</td>
<td><strong>Time horizon:</strong> None for model itself; some outcomes considered up to 9 months</td>
<td><strong>ICERs:</strong> 3HP (DOT) vs 4R (SAT): US$48,997/QALY; 3HP (DOT) vs 9H (SAT): $25,207/QALY. 9H-DOT vs no treatment [calculated, not given in study report]: $7,879/QALY</td>
<td><strong>Limitations identified by review team:</strong> Model does not consider transmission. Presentation of findings is rather unclear, particularly for sensitivity analyses. Effect of direct observation not clearly distinguished from drug efficacy. DOT and SAT treatment effect estimates come from different studies with different populations. Data source for 9H-DOT effectiveness unclear (study quotes ref (24), but this appears to be an error).</td>
<td></td>
</tr>
<tr>
<td><strong>Citation:</strong> Costs and Cost-effectiveness of Four Treatment Regimens for Latent Tuberculosis Infection. American Journal of Respiratory and Critical Care Medicine 179:1055–1060</td>
<td><strong>Data sources:</strong> Most from literature, some from other programme records</td>
<td><strong>Discount rates:</strong> 3%</td>
<td><strong>Secondary analysis:</strong> [Detailed quantitative data not provided for sensitivity analyses, mostly reported verbally]</td>
<td><strong>Evidence gaps and/or recommendations for future research:</strong> NR</td>
<td></td>
</tr>
<tr>
<td><strong>Aim of study:</strong> To evaluate the costs and cost-effectiveness of regimens for the treatment of LTBI</td>
<td><strong>Sample characteristics:</strong> Recent contacts of infectious TB cases; average age 39 years</td>
<td><strong>Perspective:</strong> Not explicitly stated, appears to be healthcare perspective</td>
<td></td>
<td><strong>Source of funding:</strong> NR</td>
<td></td>
</tr>
<tr>
<td><strong>Type of economic analysis:</strong> Cost-effectiveness</td>
<td><strong>Comparator/control/s description:</strong> No treatment</td>
<td><strong>Measures of uncertainty:</strong> One-way sensitivity analyses on Risk of TB, Adherence, Efficacy, Toxicity and Costs</td>
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<tr>
<td>Economic perspective:</td>
<td>(DOT) if completion &gt;54% for 4R; 3HP (DOT) if both SAT regimens have low compliance (&lt;34% for 9H, &lt;37% for 4R)</td>
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<tr>
<td>Quality score: –</td>
<td>Efficacy: [only SAT regimens considered]</td>
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<tr>
<td>Applicability: +</td>
<td>Toxicity: not sensitive to changes in toxicity rates</td>
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<td></td>
<td>Costs: if DOT &lt;$1.00/dose, 3HP (DOT) dominates 4R (SAT). [Analysis on drug costs not considered here.]</td>
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</table>

Not explicitly stated, appears to be healthcare perspective.
<table>
<thead>
<tr>
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<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Authors:</strong> Jit M, Stagg HR, Aldridge RW, White PJ, Abubakar I, for the Find and Treat Evaluation Team</td>
<td>Individuals with active pulmonary tuberculosis screened or managed by the service with record dates between September 2007 and September 2010</td>
<td>Find and Treat service including (1) mobile radiography unit which visits drug treatment centres, homeless shelters etc., and provides voluntary screening (2) enhanced case management service to support treatment completion (including home visits and accompanying clients to services, and links with other services e.g. drug support, criminal justice), and awareness raising</td>
<td>Cost per QALY</td>
<td><strong>Primary analysis:</strong> £6,400 per QALY (net cost of £1.4 million and gains 220 QALYs). Mobile screening unit £18,000/QALY; case management component £4,100/QALY</td>
<td>Limitations identified by author: Absence of a trial randomising TB cases to be either managed or not managed by the F&amp;T service. Methods used for modelling do not fully capture the benefits of the F&amp;T service (because transmission not taken into account). Did not measure the effect of the F&amp;T service on reducing the likelihood of patients developing and transmitting acquired drug resistance (as a result of poor treatment adherence)</td>
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<tr>
<td><strong>Year:</strong> 2011</td>
<td>Source population/s: Health services</td>
<td>Comparator/control/s description:</td>
<td><strong>Time horizon:</strong> 5 years</td>
<td><strong>Secondary analysis:</strong> Increased mobile screening unit costs: F&amp;T=£6,700/QALY, mobile screening=£20,000, case management=£4,100; Increased treatment costs: F&amp;T=£7,600, mobile screening=£18,000, case management=£5,600; Improved QoL for untreated TB and poor QoL for treated TB: F&amp;T=£6,500, mobile screening=£19,000, case management=£4,200; Asymptomatic mobile screening unit cases do not always progress to symptomatic disease: F&amp;T=£6,500, mobile screening=£22,000, case management=£4,100; Cases referred to F&amp;T for enhanced cases management have lower rate of loss to follow-up than those not referred: F&amp;T=£7,100, mobile</td>
<td>Limitations identified by review team: None to add to authors’. (NB unlike other cost-effectiveness studies in this review, averted treatment costs are not taken into account in assessing benefits.)</td>
</tr>
<tr>
<td><strong>Citation:</strong> Dedicated outreach service for hard to reach patients with tuberculosis in London: observational study and economic evaluation. BMJ 343:d5376</td>
<td>Data sources: Retrospective data from Find and Treat database/records; HPA enhanced tuberculosis surveillance system; hospital and community health services pay and prices index; literature</td>
<td><strong>Discount rates:</strong> 3.5%</td>
<td><strong>Perspective:</strong> “healthcare taxpayer”</td>
<td><strong>Evidence gaps and/or recommendations for future research:</strong> Point of care testing within</td>
<td></td>
</tr>
<tr>
<td><strong>Aim of study:</strong> To evaluate the cost-effectiveness of the Find and Treat service from September 2007 to July 2010 in London</td>
<td><strong>Sample sizes:</strong> Total: 668</td>
<td><strong>Measures of uncertainty:</strong> One-way sensitivity analyses on a range of conditions that are unfavourable to Find and Treat, including increased costs for mobile screening unit (£530024 to £600000); increased cost of TB treatment (drug sensitive and MDR-TB rise from £5522 and £31329, to £8300 and £75000 respectively); improved quality of life for untreated TB (0.68 to 0.76), and poor quality of life for</td>
<td><strong>Primary analysis:</strong> £6,400 per QALY (net cost of £1.4 million and gains 220 QALYs). Mobile screening unit £18,000/QALY; case management component £4,100/QALY</td>
<td><strong>Secondary analysis:</strong> Increased mobile screening unit costs: F&amp;T=£6,700/QALY, mobile screening=£20,000, case management=£4,100; Increased treatment costs: F&amp;T=£7,600, mobile screening=£18,000, case management=£5,600; Improved QoL for untreated TB and poor QoL for treated TB: F&amp;T=£6,500, mobile screening=£19,000, case management=£4,200; Asymptomatic mobile screening unit cases do not always progress to symptomatic disease: F&amp;T=£6,500, mobile screening=£22,000, case management=£4,100; Cases referred to F&amp;T for enhanced cases management have lower rate of loss to follow-up than those not referred: F&amp;T=£7,100, mobile</td>
<td><strong>Limitations identified by review team:</strong> None to add to authors’. (NB unlike other cost-effectiveness studies in this review, averted treatment costs are not taken into account in assessing benefits.)</td>
</tr>
<tr>
<td><strong>Type of economic analysis:</strong> Cost-effectiveness</td>
<td><strong>Intervention:</strong> N=416 (including N=48 identified by mobile screening unit, N=188 referred to Find and Treat for case management support, N=180 referred to Find and Treat for loss to follow-up)</td>
<td><strong>Comparative:</strong></td>
<td><strong>Perspective:</strong> “healthcare taxpayer”</td>
<td><strong>Evidence gaps and/or recommendations for future research:</strong> Point of care testing within</td>
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<tr>
<td>Economic perspective:</td>
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<td>“healthcare taxpayer”</td>
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<td>Quality score: +</td>
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<td>Applicability: ++</td>
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<td>suspected tuberculosis; cases merely receiving prophylaxis (and hence unlikely to have active tuberculosis); cases for which the diagnostic delay could not be calculated; and cases younger than 16 years. Other than that no info.</td>
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<tr>
<td>TB cases on treatment (0.79 to 0.76); asymptomatic cases detected by mobile screening unit do not always progress to symptomatic disease (50% of original); cases referred to Find and Treat service for enhanced case management have a reduced loss to follow-up rate in the absence of the service (34.7% to 17.2%); cases referred to Find and Treat service for loss to follow-up could still passively re-engage with treatment (51%)</td>
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<tr>
<td>Modelling method: discrete, multiple age cohort, compartmental model</td>
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<tr>
<td>screening=£18,000, case management=£4,600; Case referred to F&amp;T service for loss to follow-up could passively re-engage with treatment: F&amp;T=£7,500, mobile screening=£18,000, case management=£4,700. Combination of all most unfavourable components: F&amp;T £10,000/QALY, mobile screening £26,000, case management £6,800</td>
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<td>community outreach settings; community-based delivery of treatment; randomised trial of F&amp;T service</td>
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<tr>
<td>Source of funding: English Department of Health, MRC, NIHR</td>
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<tr>
<td>Study Details</td>
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<tr>
<td><strong>Authors:</strong> Migliori, GB, Ambrosetti M, Besozzi G, et al.</td>
<td><strong>Source population/s:</strong> 41 TB-reporting units in Italy; no further information</td>
<td><strong>Intervention/s description:</strong> Scenario 1: Current policy of managing TB patients in Italy. Smear-positive patients admitted for 2 months, smear-negative and extrapulmonary patients admitted for 1.5 months, total treatment duration 6.5 months, standardised treatment regimen for 88% of patients. No DOT outside of hospital admission.</td>
<td><strong>Outcomes:</strong> Cost per case cured</td>
<td><strong>Primary analysis:</strong> Assuming a success rate of 77.3% (smear positive) and 86.3% (smear negative) as observed in Italy (new and retreatment cases) smear positive/negative Scenario 1: 1 (no DOT). US$16,494 / 11,230 2 (DOT). $16,703 / 11,438 3. (DOT + addnl staff) $17,105 / 11,838 4. (DOT + incentives) $17,576 / 12,308 5. (DOT + addnl staff + incentives) $17,978 / 12,708 Scenario 2: 1 (no DOT). $5690 / 2202 2. (DOT). $5946 / 2448 3. (DOT + addnl staff) $6437 / 2920 4. (DOT + incentives) $7014 / 3474 5. (DOT + addnl staff + incentives) $7505 / 3946 [These are apparently health perspective results, but this is unclear.]</td>
<td><strong>Limitations identified by author:</strong> Methodology to estimate indirect costs, as they aggregated possible individual losses of income into a lost production for the society as a whole. The treatment effectiveness for the scenario 2 is not known.</td>
</tr>
<tr>
<td><strong>Year:</strong> 1999</td>
<td><strong>Setting:</strong> 17 outpatient units, 10 inpatient units, 14 in- and outpatient units.</td>
<td><strong>Comparator/control/s description:</strong> Scenario 2: Hypothetical policy orientated to outpatient care. 50% smear positive, 10% smear negative and extrapulmonary cases admitted for 1 month, treatment duration 6 months. Standardised regimens for all patients.</td>
<td><strong>Time horizon:</strong> 1 year</td>
<td><strong>Secondary analysis:</strong> Test Positive, scenario 1: For no DOT the range was</td>
<td><strong>Limitations identified by review team:</strong> Source data for effects not clearly described. Modelling method not described. The results from the broader perspective are only reported in a summary form and the assumptions not clearly described.</td>
</tr>
<tr>
<td><strong>Citation:</strong> Cost-comparison of different management for tuberculosis patients in Italy. <em>Bulletin of the World Health Organization</em> 77(6): 467–476</td>
<td><strong>Data sources:</strong> Questionnaires collected from the units</td>
<td><strong>Discount rates:</strong> None</td>
<td><strong>Perspective:</strong> Health; social</td>
<td><strong>Evidence gaps and/or recommendations for future research:</strong> NR</td>
<td><strong>Source of funding:</strong> Istituto Superiore di Sanità, Rome</td>
</tr>
<tr>
<td><strong>Aim of study:</strong> To perform an economic analysis of changes to TB management policies in Italy</td>
<td><strong>Sample characteristics:</strong> not described. 15 centres were in the North, 13 in the Centre and 13 in the South and the Islands</td>
<td><strong>Measures of uncertainty:</strong> No exhaustive list of parameters tested is given. Sensitivity analysis was conducted on the variable when a result was uncertain to test the robustness of the student results. In particular all fixed and variable costs in determining the costs per case treated successfully in scenario 2 were progressively increased until a similar cost-effectiveness was obtained at different</td>
<td><strong>Discount rates:</strong> None</td>
<td></td>
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<tr>
<td><strong>Type of economic analysis:</strong> Cost-comparison</td>
<td><strong>Data sources:</strong> Questionnaires collected from the units</td>
<td><strong>Perspective:</strong> Health; social</td>
<td><strong>Discount rates:</strong> None</td>
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<tr>
<td><strong>Economic perspective:</strong> Two perspectives used: social perspective and health perspective</td>
<td><strong>Sample characteristics:</strong> not described. 15 centres were in the North, 13 in the Centre and 13 in the South and the Islands</td>
<td><strong>Measures of uncertainty:</strong> No exhaustive list of parameters tested is given. Sensitivity analysis was conducted on the variable when a result was uncertain to test the robustness of the student results. In particular all fixed and variable costs in determining the costs per case treated successfully in scenario 2 were progressively increased until a similar cost-effectiveness was obtained at different</td>
<td><strong>Discount rates:</strong> None</td>
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<tr>
<td><strong>Data sources:</strong> Questionnaires collected from the units</td>
<td><strong>Sample characteristics:</strong> not described. 15 centres were in the North, 13 in the Centre and 13 in the South and the Islands</td>
<td><strong>Measures of uncertainty:</strong> No exhaustive list of parameters tested is given. Sensitivity analysis was conducted on the variable when a result was uncertain to test the robustness of the student results. In particular all fixed and variable costs in determining the costs per case treated successfully in scenario 2 were progressively increased until a similar cost-effectiveness was obtained at different</td>
<td><strong>Discount rates:</strong> None</td>
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<tr>
<td><strong>Data sources:</strong> Questionnaires collected from the units</td>
<td><strong>Sample characteristics:</strong> not described. 15 centres were in the North, 13 in the Centre and 13 in the South and the Islands</td>
<td><strong>Measures of uncertainty:</strong> No exhaustive list of parameters tested is given. Sensitivity analysis was conducted on the variable when a result was uncertain to test the robustness of the student results. In particular all fixed and variable costs in determining the costs per case treated successfully in scenario 2 were progressively increased until a similar cost-effectiveness was obtained at different</td>
<td><strong>Discount rates:</strong> None</td>
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</tbody>
</table>
staff and incentives. Incentives were the provision of a meal and 5 US dollars.

Smear positive and smear negative were also analysed separately. And different % of success rate 50%, 70%, 77.3% 80% and 90% assumed.

Sample sizes: N=682 for treatment effect data, N=992 for cost data (although appear to be the same sample)

levels of success rate

Modelling method: NR

25,503 (50%) to 14,181 (90%)
For DOT the range was
25,827 (50%) to 14,362 (90%)
For DOT + staff
26,448 (50%) to 14707 (90%)
For DOT + incentives
27,177 (50%) to 15,112 (90%)
For DOT + staff + incentives
27,798 (50%) to 15,458 (90%)

Test positive scenario 2:
For no DOT the range was
8799 (50%) to 4893 (90%)
For DOT the range was
9195 (50%) to 5113 (90%)
For DOT + staff
9954 (50%) to 5535 (90%)
For DOT + incentives
10,845 (50%) to 6030 (90%)
For DOT + staff + incentives
11,604 (50%) to 6452 (90%)

Test negative, scenario 1:
For no DOT the range was
19,374 (50%) to 10,752 (90%)
For DOT the range was
19,734 (50%) to 10,952 (90%)
For DOT + staff
20,424 (50%) to 11,335 (90%)
For DOT + incentives
21,234 (50%) to 11,785 (90%)
For DOT + staff + incentives
21,924 (50%) to 12,168 (90%)

Test negative scenario 2:
For no DOT the range was
3799 (50%) to 2108 (90%)
For DOT the range was
4224 (50%) to 2344 (90%)  
For DOT + staff  
5038 (50%) to 2796 (90%)  
For DOT + incentives  
5994 (50%) to 3327 (90%)  
For DOT + staff + incentives  
6809 (50%) to 3779 (90%)  
[Note: these are understood to be health perspective results; the costs from a broader perspective are summarised only and it is unclear what the assumed success rate is: "$4159 for smear positive and $2792.20 for smear negative in scenario 1 … $2079.90 for smear positive and $1864.10 for smear negative in scenario 2"]
<table>
<thead>
<tr>
<th>Study Details</th>
<th>Population and setting</th>
<th>Intervention/ comparator</th>
<th>Outcomes and methods of analysis:</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Authors:</strong> Moore RD, Chaulk P, Griffiths R, Cavalcante S, Chaisson RE</td>
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<tr>
<td><strong>Year:</strong> 1996</td>
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<tr>
<td><strong>Citation:</strong> Cost-effectiveness of directly observed versus self-administered therapy for tuberculosis. American Journal of Respiratory and Critical Care Medicine 154(4 Part 1):1013-9</td>
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</tr>
<tr>
<td><strong>Aim of study:</strong> To compare 3 alternative strategies for a 6 month course of treatment for tuberculosis; DOT, self administered fixed-dose combination drug therapy and self-administered conventional individual drug therapy.</td>
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<tr>
<td><strong>Source population/s:</strong> (hypothetical cohort) No information on population; cost data taken from population under TB treatment in Baltimore</td>
<td><strong>Intervention/s description:</strong> DOT included one on-site visit and 50 subsequent patient outreach visits (drug regimen was rifampin, ethambutol, pyrazinamide). Observed by nurse, for 6 months</td>
<td><strong>Outcomes:</strong> Cost per relapse averted and Cost per life saved</td>
<td><strong>Primary analysis:</strong> Cost per relapse averted $17,305 for conventional $15,446 for fixed dose $14,378 for DOT</td>
<td><strong>Limitations identified by author:</strong> Rate of completion of fixed dose combination therapy not well known, but analysis described as not sensitive to this parameter. Relapse rates for DOT abstracted from foreign treatment studies. Lack of trial data to inform rate of relapse rate for drug resistant TB for fixed dose combination.</td>
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<tr>
<td><strong>Setting:</strong> NR; costs include an assumption of one on-site TB clinic visit and 50 subsequent outreach visits</td>
<td><strong>Comparator/control/s description:</strong> Self administered individual conventional = isoniazid, rifampin, ethambutol, pyrazinamide – 6 months Self administed fixed dose combination = rifater, rifamate, ethambutol, isoniazid – 6 months</td>
<td><strong>Time horizon:</strong> Unclear (relapse rates assume 2-year window) <strong>Discount rates:</strong> 4% <strong>Perspective:</strong> ‘urban public health’</td>
<td><strong>Secondary analysis:</strong> Cost effectiveness of the 3 regimens was not found to be sensitive to variability in cost of managing resistant or non resistant TB in patients who relapsed Per relapse averted DOT is more cost effective than fixed dose combination therapy until the direct cost of DOT exceeds $14,500 an increase in of $1000 over the baseline direct cost. An increase in the cost of DOT of only $100 would result in comparable cost-effectiveness per life saved for DOT and fixed dose combination therapy. Results were also sensitivity to estimates of the effectiveness of the interventions DOT and</td>
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<tr>
<td><strong>Data sources:</strong> Resource use is from a time and motion study of the programme in Baltimore. Hospitalisation costs taken from State data. Effects are taken from published literature. Baseline probabilities mostly assumed.</td>
<td><strong>Sample characteristics:</strong> NR</td>
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<tr>
<td><strong>Sample sizes:</strong> NR</td>
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<tr>
<td><strong>Measures of uncertainty:</strong> Sensitivity analyses completed for completion rates for fixed dose combination therapy, the drug-resistant TB rate for fixed dose combination therapy, and cure rate for DOT when therapy is not completed. Costs of relapse with resistant TB, relapse with non resistant TB, the direct of DOT were also adjusted</td>
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<tr>
<td><strong>Limits of the study:</strong></td>
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</table>

- **Evidence gaps and/or recommendations for future research:** NR
| **Type of economic analysis:** Cost effectiveness |
| **Economic perspective:** ‘urban public health department’ |
| **Quality score:** + |
| **Applicability:** + |
| **Modelling method:** Decision tree |
| **Source of funding:** Supported in part by Marion Merrell Dow, Inc |

**Sensitivity analyses (abstracted from figures and not fully reported in text, so all numbers approximate):**

- **Cost of DOT:** marginal cost per life saved of DOT $0 to $1,350, and marginal cost per relapse averted $0 to $450, as cost of DOT ranges from $13,600 to $15,000.
- **Probability that incomplete DOT leads to relapse:** marginal cost per life saved of DOT $0 to $43 as probability ranges 0.27-0.30.
- **Probability of relapse with resistant TB for fixed-dose combination therapy:** marginal cost per life saved of DOT $170 to $0 as probability ranges 0.001-0.0016.
<table>
<thead>
<tr>
<th>Study Details</th>
<th>Population and setting</th>
<th>Intervention/ comparator description: DOT observed either in clinic or in other site, by a health professional (100%)</th>
<th>Outcomes and methods of analysis:</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Authors:</strong> Palmer CS, Miller B, Halpern MT, Geiter LJ</td>
<td><strong>Source population/s:</strong> Hypothetical cohort of 25,000 TB patients using data taken from 178 patient records</td>
<td><strong>Comparator/control/s description:</strong> Partial DOT (15%) No DOT (all 'patient responsible' i.e. self-administered therapy).</td>
<td><strong>Outcomes:</strong> Cost per TB case cured</td>
<td><strong>Primary analysis:</strong> Direct cost per TB case cured: US$16,846 for partial DOT $20,106 for No DOT $17,323 for 100% DOT Incremental cost of 100% DOT vs partial DOT = $24,064 per cure</td>
<td><strong>Limitations identified by author:</strong> Mortality rate was held constant at 9% across treatment delivery strategies, but in the data patients who received DOT had a higher mortality rate. Data were in some cases from a comparatively small number of patient records from a small number of clinics. The model did not include direct costs of all TB activities relate to treatment failure. The model did not include indirect costs associated with decreased productivity or intangible costs associated with impaired quality of life. It was assumed that all lost patients returned to treatment within 2 years and that lost patients placed on patient responsible therapy switched to DOT. All patients in the model initially had drug susceptible TB. Immunosuppressed</td>
</tr>
<tr>
<td><strong>Year:</strong> 1998</td>
<td><strong>Setting:</strong> Outpatient</td>
<td><strong>Details of DOT or patient responsible therapy not described. The following is noted about the sources of the patient records:</strong> In Newark patient began on patient responsible therapy and switched to DOT if treatment failed, in San Francisco certain patients were selected for DOT a priori based on clinical characteristics (not described), in Los Angeles patients received DOT depending on the clinic they attended, in Mississippi all patients received DOT.</td>
<td><strong>Time horizon:</strong> 10 years</td>
<td><strong>Secondary analysis:</strong> Sensitivity analyses only presented for incremental cost of 100% DOT vs partial DOT not against not DOT. Discount rate 6% = $24,441 5% increase in default rate = $24,092 15% increase in infection rate following default $23,453 5% increase in development of drug resistant TB following default = $22,810 Increase in drug resistant TB mortality rate of 20% = $24,031 Decrease in immunosuppression among patient with drug resistant TB to 50% = $24,735 Mean hospital stay increased to 30 days = $23,735 60% hospitalised = $22,519</td>
<td></td>
</tr>
<tr>
<td><strong>Citation:</strong> A model of the cost effectiveness of directly observed therapy for treatment of tuberculosis. Journal of Public Health Management Practice 4(3):1-13</td>
<td><strong>Data sources:</strong> TB clinical records from 4 outpatient TB control programmes (11 clinics) in US (see below), national surveillance data, CDC reports, published literature, authors’ estimates in the absence of published data.</td>
<td><strong>Discount rates:</strong> 3%</td>
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<tr>
<td><strong>Aim of study:</strong> To compare universal DOT with partial DOT (15%) and no DOT (100% patient responsible therapy)</td>
<td><strong>Sample characteristics:</strong> Outpatient data from Newark (n=35), San Francisco (N=86), Los Angeles (n=36), Mississippi (n=21). Males = 73%, White = 32%, US born 58%, mean age 44. Noted to be somewhat</td>
<td><strong>Perspective:</strong> Health</td>
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<tr>
<td><strong>Type of economic analysis:</strong> Cost-effectiveness</td>
<td><strong>Sample sizes:</strong> Total: 178</td>
<td><strong>Measures of uncertainty:</strong> 1. Discount rates 3% vs 6% 2. Default rate 3. Infection rate following default 4. Rate of development of drug resistant TB following default 5. Death rate for drug resistant TB 6. Rate of immunosuppression among patients 7. Length of hospital stay 8. Proportion hospitalised 9. Outpatient costs</td>
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<tr>
<td><strong>Economic perspective:</strong> Health (direct costs of curative and preventative TB treatment)</td>
<td><strong>Modelling method:</strong></td>
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</table>
| Quality score: + | younger than US national estimates (49 years) | **Intervention:** 70 patients received DOT  
**Control:** 91 patients received patient responsible therapy only, 17 switched from patient responsible therapy to DOT. | Decision tree  
20% hospitalised = $24,991  
outpatient costs decreased by 20% = $18,184  
Outpatient costs increased by 20% $29,944 | patients with drug resistant TB died within the year they began treatment |
| Limitations identified by review team:  
The authors’ list of limitations appears comprehensive. The data is for a cost year 1992 and therefore may not be accurate for the current context.  
**Evidence gaps and/or recommendations for future research:** NR  
**Source of funding:** Center for Disease Control (CDC) |
<table>
<thead>
<tr>
<th>Study Details</th>
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<th>Outcomes and methods of analysis:</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Authors:</strong> Perlman DC, Gourevitch MN, Trihn C, Salomon N, Horn L, Des Jarlais DC</td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Year:</strong> 2001</td>
<td></td>
<td></td>
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<tr>
<td><strong>Citation:</strong> Cost-effectiveness of tuberculosis screening and observed preventative therapy for active drug injectors at a syringe-exchange programme. <em>Journal of Urban Health</em> 78(3): 550-67</td>
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<tr>
<td><strong>Aim of study:</strong> To examine the cost-effectiveness of a screening and DOPT programme, and of incentives to increase adherence</td>
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<tr>
<td><strong>Type of economic analysis:</strong> Cost-effectiveness</td>
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<tr>
<td><strong>Source population/s:</strong> hypothetical cohort of 1000 patients, based on the characteristics of people visiting a needle exchange programme in New York City, USA.</td>
<td><strong>Intervention/s description:</strong> TB screening offered to all needle exchange clients (cash and transport token incentive offered, total $15) DOPT: Twice weekly visits to received INH 900mg and pyridoxine 50mg for 6 months (HIV+ 9 months). Patients could be dosed on any two non consecutive days of the week. Four transportation tokens were provided for transportation to and from DOPT visits. Patients were monitored monthly for isoniazid toxicity.</td>
<td><strong>Outcomes:</strong> Cost per case of TB averted; net cost savings <strong>Time horizon:</strong> 3 years, 5 years <strong>Discount rates:</strong> None</td>
<td><strong>Primary analysis:</strong> Baseline model (31% CXR completion rate and no monetary incentives). INH effectiveness is assumed (from the literature) across a range of 65% to 90%. 3 year follow up, INH 65% effective: 3 TB cases prevented, US$103,078 TB costs prevented Costs of programme per case of TB averted $18,951 Net savings $46,226 5 year follow up INH 65% effective: same results as for 3 years 3 year follow up INH 90% effective: 3 TB cases prevented, $141,506 TB costs prevented, cost of programme per case of TB averted $14,213, Net savings $84,654 5 year follow up, INH 90% effective: 4 TB cases prevented, $179,934 TB costs prevented, cost of programme per case of TB averted $14,213, Net</td>
<td><strong>Limitations identified by author:</strong> Uncertainties in input data; otherwise NR</td>
<td><strong>Limitations identified by review team:</strong> Limited description of model (although some of this is reported in Gourevitch et al. 1998). Data sources for inputs unclear (some assumed, some from literature and some from programme evaluation data). Unclear how patient characteristics incorporated into modelling process. Difficult to reach conclusions on different components of intervention (screening, incentives, DOPT)</td>
</tr>
</tbody>
</table>
Economic perspective: Healthcare

Quality score: –

Applicability: +

Median age 33, White (not hispanic) 47%, US Born 88%, ever in drug treatment 72%, drug use in past 6 months any heroin 65%, any cocaine 58%, HIV+ 18%, previously known PPD result negative 67%.

Note: how these characteristics relate to the baseline characteristics of the cohort in the model is unclear, only 175 of the patients are suitable to receive DOPT

Scenario ascribed to HIV infected anergic patients had a moderate risk of developing TB and received DOPT

Modelling method: Updated version of the model in Gourevitch 1998 (also included in this review, see the DE for that study). Described in this paper only as ‘analysed in a relational database’ (Paradox, Borland).

Secondary analysis: The cost per TB case averted is reported in the data extraction. The authoris report than all these scenarios resulted in cost savings ranging from $45,000 to $500,000

Hypothetical: If the CXR adherence rate was increased to 50% with a $25 incentive the cost of programme per case of TB averted for 3 year follow up was $21,684 (65% effective) and $17,347 (90% effective). For 5 year follow up the results were $17,347 and $12,391 respectively

If the $25 incentive increased adherence to 100% the cost of programme per case of TB averted was $23,339 (65% effective) and $14,852 (90% effective). For 5 year follow up the results were $13,614 and $10,211 respectively

Scenario 1 with no anergy The cost of programme per case of TB averted was $16,661 (65% effective) and $12,496 (90% effective). For 5 year follow up the results were
$16,661 and $9,997 respectively
Scenario 2 with anergy no DOPT
The cost of programme per case of TB averted was $17,914 (65% effective) and $13,435 (90% effective). For 5 year follow up the results were $17,914 and $10,748 respectively

Scenario 3 with anergy and DOPT: The cost of programme per case of TB averted was $18,951 (65% effective) and $14,213 (90% effective). For 5 year follow up the results were $18,951 and $14,213 respectively
<table>
<thead>
<tr>
<th>Study Details</th>
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<th>Outcomes and methods of analysis:</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Authors:</strong> Porco TC, Lewis B, Marseille E, Grinsdale J, Flood JM, Royce SE</td>
<td><strong>Source population/s:</strong> [NB hypothetical cohort rather than evaluation data.] Immigrants to California with LTBI (‘TB4’) or inactive TB (‘TB2’)</td>
<td><strong>Intervention/s description:</strong> First analysis considers screening programme in general; further analysis incorporates active recruitment of immigrants using letters, phone calls and home visits; screening; directly observed preventive therapy for those eligible (setting and intervention delivery unclear)</td>
<td><strong>Outcomes:</strong> Cost/QALY</td>
<td><strong>Primary analysis:</strong> Screening programme yields net cost saving of US$25,000, and yielded 7.7 net QALYs</td>
<td><strong>Limitations identified by author:</strong> Accurate cost data hard to find. Life years not adjusted for quality in some cases. HIV+ people not included in model (because generally barred from immigration). Findings not disaggregated by age. Considerable uncertainty on many parameters.</td>
</tr>
<tr>
<td><strong>Year:</strong> 2006</td>
<td><strong>Setting:</strong> Health services</td>
<td><strong>Comparator/control/s Description:</strong> None as such, but a range of different programme components considered – see Table 9</td>
<td><strong>Time horizon:</strong> 20 years</td>
<td><strong>Secondary analysis:</strong> Full three-way analysis on</td>
<td><strong>Limitations identified by review team:</strong> Generally highly robust study. Most inputs based on single studies, not systematic reviews. Unclear how reliable reimbursement standards are as guides to costs. Presentation of cost-effectiveness findings not the most perspicuous for this review.</td>
</tr>
<tr>
<td><strong>Citation:</strong> Cost-effectiveness of tuberculosis evaluation and treatment of newly-arrived immigrants. <em>BMC Public Health</em> 6:157</td>
<td><strong>Data sources:</strong> Most from the literature; cost data from Medi-Cal reimbursement standards</td>
<td><strong>Sample characteristics:</strong> No info, other than clinical characteristics</td>
<td><strong>Discount rates:</strong> 3% (5% considered in sensitivity analysis)</td>
<td><strong>Evidence gaps and/or recommendations for future research:</strong> NR</td>
<td><strong>Source of funding:</strong> Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td><strong>Aim of study:</strong> To evaluate the cost-effectiveness of domestic follow-up of suspected LTBI cases among new immigrants to California</td>
<td><strong>Sample sizes N/A:</strong> hypothetical cohort N=1000</td>
<td><strong>Perspective:</strong> ‘Domestic all-payer’</td>
<td><strong>Perspective:</strong> ‘Domestic all-payer’</td>
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</table>
(i.e. societal but without lost productivity / wage costs)

**Quality score:** ++

**Applicability:** ++

| Severe hepatitis, disutility of hospitalization, disutility of hepatitis, disutility of INH side-effects, QALY loss from INH, disutility multipliers of hospitalization and outpatient treatment, and discount rate | Evaluation rate, starting rate and completion rate presented in Table 4 – not extracted completely here. Evaluation rate sensitivity analysis: 45% 1.9 QALYs, saving $11,000; 65% 2.9 QALYs, saving $16,000; 85% 3.9 QALYs, saving $22,000 Passive treatment delay 100 days (reference 74): 10 QALYs, save $22,000 Screening delay 14 days (reference 0): 8.1 QALYs, save $25,000 % active cases 6% (reference 3%): 12 QALYs, save $290,000 Transmission rate 16 (reference 8): 8.3 QALYs, save $33,000 Hospitalisation rates: not fully extracted here Reactivation rates of people with inactive TB 430 (reference 600): 7.1 QALYs, save $12,000 Hospitalisation cost multiplier 20% more: 7.8 QALYs, save $83,000 Other cost multiplier 20% more: 7.7 QALYs, cost $14,000 Nurse refill visit cost $8.40 (reference $16.80): 7.5 QALYs, save $43,000 DOT visit cost $25.00 (reference $19.23): 7.8 |

**Modelling method:** Continuous time, discrete event model
<table>
<thead>
<tr>
<th>QALYs, save $24,000</th>
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</thead>
<tbody>
<tr>
<td>TST specificity 0.875 (reference 0.99): 7.6 QALYs, save $21,000</td>
</tr>
<tr>
<td>Fraction INH resistant 0.2 (reference 0.13): 6.7 QALYs, save $16,000</td>
</tr>
<tr>
<td>Risk multiplier for severe hepatitis 3x more: 7.6 QALYs, save $17,000</td>
</tr>
<tr>
<td>Disutility for hepatitis hospitalization 0.9 (reference 0.4): 8.0 QALYs, save $23,000</td>
</tr>
<tr>
<td>Disutility for outpatient hepatitis 0.5 (reference 0.265): 8.0 QALYs, save $24,000</td>
</tr>
<tr>
<td>Disutility for other INH side-effects 0.2 (reference 0.1): 7.4 QALYs, save $22,000</td>
</tr>
<tr>
<td>Disutility for untreated TB 0.2 (reference 0.1): 9.0 QALYs, save $22,000</td>
</tr>
<tr>
<td>QALY loss from one month INH 0.01 (reference 0): lose 16 QALYs, save $22,000</td>
</tr>
<tr>
<td>Disutility multiplier for TB hospitalization 0.5 (reference 1): 7.9 QALYs, save $24,000</td>
</tr>
<tr>
<td>Disutility multiplier for outpatient TB 0.5 (reference 1): 8.3 QALYs, save $21,000</td>
</tr>
<tr>
<td>Discount rate 5% (reference 3%): 5.9 QALYs, save $16,000</td>
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</tbody>
</table>

Threshold analysis: net cost saving when fraction of active cases >2.7%; cost effective at WTP threshold of $50k/QALY
when fraction of active cases >0.4%
<table>
<thead>
<tr>
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<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Authors:</strong> Snyder DC, Chin DP</td>
<td>Source population/s: Patients in California defined as at low risk for default, i.e. at least 15 yr of age; no history of HIV infection; disease without documented resistance to isoniazid, rifampin, and pyrazinamide; antituberculosis treatment was entirely self-administered; no history of injection-drug use, non-injection-drug use, homelessness, and incarceration. All these patients received self-administered treatment</td>
<td>Intervention/s description: Directly observed therapy daily for 2wk followed by twice-weekly for 22wk, including incentives to the value of US$25/week. No details on setting or intervention delivery</td>
<td>Outcomes: Cost per patient treated, per patient cured</td>
<td>Primary analysis: DOT has total incremental cost wrt SAT of US$1,332 per patient treated; net incremental cost of US$919 per patient treated; net incremental cost of US$40,620 per patient cured (or $51,656 from programme perspective, i.e. not counting hospitalisation costs)</td>
<td>Limitations identified by author: Benefits of DOT not fully measured</td>
</tr>
<tr>
<td><strong>Year:</strong> 1999</td>
<td>Comparator/control/s description: Self-administered therapy daily for 24wk</td>
<td></td>
<td>Time horizon: Effects estimated with reference to 2-year horizon (time horizon of model itself unclear)</td>
<td>Secondary analysis: SAT probability of default 0%, incremental net cost $51,234 per cure; 40%, net cost saving of $2,160 per cure</td>
<td>Limitations identified by review team: Only includes healthcare costs. Model is simple. Cost data are from reimbursement regulations, not estimates of actual cost. Only outcome reported is cost per cure; implications of this are unclear</td>
</tr>
<tr>
<td><strong>Citation:</strong> Cost-effectiveness analysis of directly observed therapy for patients with tuberculosis at low risk of treatment default. American Journal of Respiratory and Critical Care Medicine 160: 582-6</td>
<td>Sample sizes: Total N=1,377</td>
<td></td>
<td>Discount rates: 4%</td>
<td>Evidence gaps and/or recommendations for future research: Further analyses with more complete measurement of benefits of DOT; comparison of DOT with other TB control activities</td>
<td></td>
</tr>
<tr>
<td><strong>Aim of study:</strong> To determine the cost-effectiveness of DOT for people at low risk of default, to inform the decision to extend DOT to this group (i.e. to change from selective to universal DOT)</td>
<td>Setting: TB services</td>
<td></td>
<td>Perspective: Programme / healthcare system</td>
<td>Source of funding: NR</td>
<td></td>
</tr>
<tr>
<td><strong>Type of economic analysis:</strong> Cost-effectiveness</td>
<td>Data sources: Retrospective cohort study for population data; previous cost-effectiveness analysis for treatment effect</td>
<td></td>
<td>Measures of uncertainty: Sensitivity analysis according to: default rate on SAT; DOT effectiveness wrt default rates; relapse rate on SAT; contacts with active disease; hospitalization rate; cost of hospitalization</td>
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<tr>
<td>Economic perspective: Programme / healthcare system</td>
<td>and other transition probabilities; cost data mainly from Medi-Cal reimbursement rates</td>
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<tr>
<td>Quality score: –</td>
<td>Sample characteristics: None reported beyond inclusion criteria</td>
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<tr>
<td>Applicability: +</td>
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<tr>
<td>Study Details</td>
<td>Population and setting</td>
<td>Intervention/ comparator</td>
<td>Outcomes and methods of analysis:</td>
<td>Results</td>
<td>Notes</td>
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<tr>
<td><strong>Authors:</strong> Snyder DC, Paz EA, Mohle-Boetani JC, Fallstad R, Black RL, Chin DP</td>
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<td></td>
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<tr>
<td><strong>Year:</strong> 1999</td>
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<tr>
<td><strong>Citation:</strong> Tuberculosis prevention in methadone maintenance clinics: effectiveness and cost-effectiveness. <em>American Journal of Respiratory and Critical Care Medicine</em> 160: 178-185</td>
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<tr>
<td><strong>Aim of study:</strong> To evaluate the effectiveness of a DOT programme implemented in a methadone clinic</td>
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<tr>
<td><strong>Type of economic analysis:</strong> Cost-effectiveness</td>
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<tr>
<td><strong>Economic Source population/s:</strong> People attending methadone maintenance clinic in San Francisco</td>
<td><strong>Intervention/s description:</strong> All clients of methadone clinic tested for TB. Those recommended for preventive therapy received 6/12 mo (depending on HIV status) of isoniazid and pyridoxine, observed by nurse; education by methadone clinic staff; clients accompanied by community health worker who facilitated registration; transport and food provided; reminders; clients encouraged to produce individual adherence plan</td>
<td><strong>Outcomes:</strong> Net cost saving (i.e. cost of DOT programme minus costs of treatment and contact tracing averted)</td>
<td><strong>Primary analysis:</strong> Net savings US$104,660 (programme cost US$771,569 and averted costs of US$876,229); mean cost saving per case averted US$3,724</td>
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<tr>
<td><strong>Setting:</strong> Methadone clinic</td>
<td><strong>Comparator/control/s description:</strong> N/A</td>
<td><strong>Time horizon:</strong> 10 years</td>
<td><strong>Secondary analysis:</strong> 60% of patients have TB-related hospitalization (reference 81%): net cost per case $2,702. Completion rate 95% (reference 75.4%): net cost saving $6,674. Completion rate 30%: net cost $12,677 75% return for test result (reference unclear): net cost saving $6,674 75% begin preventive therapy (reference 91%): net cost $822 75% receive medical evaluation (reference 96%): net cost $1,776</td>
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<tr>
<td><strong>Data sources:</strong> Retrospective cohort data from project evaluation; data from literature for treatment effect and transition probabilities; cost data from California Dept of Health and unpublished evaluation data</td>
<td><strong>Sample sizes:</strong> Total N=2689 (total seen by programme); N=417 (commenced preventive therapy)</td>
<td><strong>Discount rates:</strong> 3%</td>
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<tr>
<td><strong>Sample characteristics:</strong> 59% M; 58% non-Hispanic white, 27% African-American, 12% Latino, 2% Asian/Pacific Islander, 1% other; median age 40 (range</td>
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<td><strong>Perspective:</strong> Healthcare system</td>
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<td><strong>Measures of uncertainty:</strong> Sensitivity analysis on: rates of hospitalization; completion rates; rates of return for test reading; rates of uptake of preventive therapy; receipt of medical evaluation</td>
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<td><strong>Modelling method:</strong> Markov model; 1-year cycles; 4 states (remain well, develop TB and survive, develop TB and die,</td>
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<tr>
<td><strong>Limitations identified by author:</strong> Data for model inputs derived from other (i.e. non-IDU) populations</td>
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<tr>
<td><strong>Limitations identified by review team:</strong> Health states not valued in model. No comparison group. Model structure is simple</td>
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<tr>
<td><strong>Evidence gaps and/or recommendations for future research:</strong> NR</td>
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<tr>
<td><strong>Source of funding:</strong> NR</td>
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<tr>
<td>perspective: Healthcare system</td>
<td>18-77); 63% HIV–, 18% HIV+, 19% unknown HIV status</td>
<td>die of other causes</td>
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<tr>
<td>Study Details</td>
<td>Population and setting</td>
<td>Intervention/ comparator</td>
<td>Outcomes and methods of analysis</td>
<td>Results</td>
<td>Notes</td>
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</tr>
<tr>
<td><strong>Authors:</strong> Wade VA, Karnon J, Elliott JA, Hiller JE</td>
<td><strong>Source population/s:</strong> TB cases commencing treatment at Royal Adelaide Hospital Chest Clinic</td>
<td><strong>Intervention/s description:</strong> Telehealth system for medication management. Desktop videophones and broadband connections installed in patients' homes. Daily video calls made by nurses to patients at agreed times. (This arm includes patients who were deemed unsuitable for videophone treatment and continue to receive the 'residual' in-person service.)</td>
<td><strong>Outcomes:</strong> Cost per successful observation</td>
<td><strong>Primary analysis:</strong> Videophone service: cost per complete care episode A$2,654 In-person service: cost per complete care episode A$2,589 ICER A$1.32 (95% CI 0.51–2.26) per additional successful day of observation</td>
<td><strong>Limitations identified by author:</strong> Retrospective cohort data cannot rule out confounding; referral service changed criteria, leading to demographic difference between groups; client record search may not have been complete; clinical outcomes not measured (study not powered to measure them); no group who received therapy at clinic; no access to confidential financial data to establish cost figures; model may be a simplification wrt practice.</td>
</tr>
<tr>
<td><strong>Year:</strong> 2012</td>
<td><strong>Setting:</strong> Hospital specialist TB service</td>
<td><strong>Comparator/control/s description:</strong> In-person 'drive-around' directly observed therapy service delivered by nurses (site unclear, but presumably patients' homes)</td>
<td><strong>Time horizon:</strong> N/A</td>
<td><strong>Secondary analysis:</strong> Only reported qualitatively. Number of patients: reduced number makes video service more costly but still favours video; increased number favours video</td>
<td></td>
</tr>
<tr>
<td><strong>Citation:</strong> Home videophones improve direct observation in tuberculosis treatment: a mixed methods evaluation. PLoS ONE 7(11): e50155</td>
<td><strong>Data sources:</strong> Retrospective cohort study based on clinical records</td>
<td><strong>Discount rates:</strong> N/A</td>
<td><strong>Type of patients:</strong> if noncompliance reduced from 25% to 10%, ICER unchanged; if increased to 40%, favours in-person</td>
<td></td>
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</tr>
<tr>
<td><strong>Aim of study:</strong> &quot;to compare the effectiveness of in-person versus home videophone direct observation as measured by the proportion of missed observations in each group; to determine the cost-effectiveness of home videophone observations under a range of condition; to determine the acceptability,</td>
<td><strong>Sample characteristics:</strong> Video group: 55% M, 45% F; 41% &lt;30 years; 12% African origin, 2% Australian, 3% European, 16% E Asian, 31% SE Asian, 36% S Asian; 69% proficient in English In-person group: 66% M, 34% F; 34% &lt;30 years; 17% African origin, 16% Australian, 9% European, 7% E Asian, 31% SE Asian, 36% S Asian; 69% proficient in English</td>
<td><strong>Driving time:</strong> Cost of technology: Staff salaries; Weekend service; Length of service</td>
<td><strong>Modelling method:</strong> Decision tree analysis</td>
<td><strong>Evidence gaps and/or recommendations for future research:</strong> Large-scale RCT of video observation; research on use of mobile technologies</td>
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<td></td>
<td><strong>Sample sizes:</strong> Total N=128</td>
<td><strong>Measures of uncertainty:</strong> Deterministic sensitivity analyses conducted with respect to: Number of patients; Type of patients (% noncompliant); Driving time; Cost of technology; Staff salaries; Weekend service; Length of service</td>
<td></td>
<td><strong>Perspective:</strong> Healthcare system</td>
<td></td>
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</tbody>
</table>
usability and sustainability of the home videophone service by interviewing patients and providers"

**Type of economic analysis:** Cost-effectiveness analysis

**Economic perspective:** Healthcare system

**Quality score:** –

**Applicability:** +

<table>
<thead>
<tr>
<th>Source of funding:</th>
<th>Royal District Nursing Service of South Australia; Australian Government (postgraduate award)</th>
</tr>
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<tbody>
<tr>
<td>Length of service:</td>
<td>If in-person service increased to same length of time as video service, video becomes dominant</td>
</tr>
<tr>
<td>20% S Asian; 56% proficient in English</td>
<td>person, increasing favours video</td>
</tr>
</tbody>
</table>

20% S Asian; 56% proficient in English
<table>
<thead>
<tr>
<th>Study Details</th>
<th>Population and setting</th>
<th>Intervention/ comparator</th>
<th>Outcomes and methods of analysis:</th>
<th>Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Authors:</strong> Weis SE, Foresman B, Matty KJ, et al.</td>
<td><strong>Source population/s:</strong> All TB cases reported in Tarrant County, Texas, between 1980-1985 (traditional therapy) and 1987-1994 (DOT)</td>
<td><strong>Intervention/s description:</strong> Directly observed therapy with isoniazid and rifampin, carried out in the clinic, the patient’s home or workplace or some other location. Duration of treatment 6-9 months at minimum, extended for several groups (HIV+, non-adherence etc.)</td>
<td><strong>Outcomes:</strong> Net costs</td>
<td><strong>Primary analysis:</strong> Total net cost per patient US$11,260 in DOT group, US$27,630 in ‘traditional’ group</td>
<td><strong>Limitations identified by author:</strong> Comparison is between two time periods and may be confounded by other factors. Short-course therapy was more widely used in the later (DOT) period.</td>
</tr>
<tr>
<td><strong>Year:</strong> 1999</td>
<td><strong>Setting:</strong> TB care services</td>
<td><strong>Comparator/control/s description:</strong> Limited information; self-administered therapy</td>
<td><strong>Time horizon:</strong> N/A (retrospective study)</td>
<td><strong>Secondary analysis:</strong> None</td>
<td><strong>Limitations identified by review team:</strong> Purely descriptive analysis; health states are not valued, or projected into the future using modelling</td>
</tr>
<tr>
<td><strong>Citation:</strong> Treatment costs of directly observed therapy and traditional therapy for Mycobacterium tuberculosis: a comparative analysis. International Journal of Tuberculosis and Lung Disease 3(11): 978-984</td>
<td><strong>Data sources:</strong> All based on a retrospective cohort study; data drawn from patient charts and hospital records</td>
<td><strong>Discount rates:</strong> N/A (retrospective study)</td>
<td><strong>Perspective:</strong> Healthcare system</td>
<td><strong>Evidence gaps and/or recommendations for future research:</strong> NR</td>
<td><strong>Source of funding:</strong> NR</td>
</tr>
<tr>
<td><strong>Aim of study:</strong> To compare costs of DOT and ‘traditional’ (self-administered) therapy</td>
<td><strong>Sample characteristics:</strong> Non-DOT group: 24% aged &lt;30; 38% white, 30% black, 24% Hispanic, 8% Asian; 70% male; 23% foreign-born; 24% history of alcohol abuse; 4% history of drug abuse; 0% HIV+ DOT group: 23% aged &lt;30; 30% white, 41% black, 19%</td>
<td><strong>Sample sizes:</strong> Total N=659 Intervention N=402 Control N=257</td>
<td><strong>Measures of uncertainty:</strong> None</td>
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<tr>
<td><strong>Type of economic analysis:</strong> Cost-comparison</td>
<td></td>
<td></td>
<td><strong>Modelling method:</strong> None – analysis is based purely on descriptive data about service use in the two periods</td>
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<tr>
<td>Quality score: –</td>
<td>Hispanic, 10% Asian; 64% male; 22% foreign-born; 22% history of alcohol abuse; 29% history of drug abuse; 10% HIV+</td>
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<tr>
<td>Authors: Wilton P, Smith RD, Coast J, Millar M, Karcher A</td>
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<td></td>
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<tr>
<td>Year: 2001</td>
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<tr>
<td>Citation: Directly observed treatment for multidrug-resistant tuberculosis: an economic evaluation in the United States of America and South Africa. International Journal of Tuberculosis and Lung Disease 5(12): 1137-42</td>
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**Aim of study:** To develop an economic model of DOT for MDR-TB

**Type of economic analysis:** Cost-effectiveness analysis

**Economic perspective:**

<table>
<thead>
<tr>
<th>Population and setting</th>
<th>Intervention/ comparator methods of analysis:</th>
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</thead>
<tbody>
<tr>
<td><strong>Source population/s:</strong> Hypothetical cohort and intervention. Not clearly defined; USA and South Africa (only USA data considered here)</td>
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<tr>
<td><strong>Setting:</strong> Not clearly defined</td>
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<tr>
<td><strong>Data sources:</strong> All from literature</td>
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<tr>
<td><strong>Sample characteristics:</strong> NR</td>
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| Intervention/s description: DOT, not further defined |
| Comparator/control/s description: ‘Conventional therapy’, not further defined |

**Sample sizes:** N/A

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<tr>
<th>Outcomes and methods of analysis:</th>
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<tr>
<td><strong>Outcomes:</strong> Cost savings based on costs of healthcare per patient treated</td>
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<tr>
<td><strong>Time horizon:</strong> Unclear</td>
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<tr>
<td><strong>Discount rates:</strong> None</td>
</tr>
<tr>
<td><strong>Perspective:</strong> Healthcare system</td>
</tr>
<tr>
<td><strong>Measures of uncertainty:</strong> Second-line drug costs</td>
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<tr>
<td><strong>Modelling method:</strong> Monte Carlo model incorporating cure rates, death rates and probability of progressing to more severe forms of drug-resistance</td>
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<tr>
<th>Results</th>
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<tr>
<td><strong>Primary analysis:</strong> DOT total mean cost US$18,932 (SD $2,329) ‘Conventional therapy’ total mean cost US$20,720 (SD $2,070)</td>
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<td><strong>Secondary analysis:</strong> DOT remains more cost-effective when protocol regarding resistance to second-line drugs is altered</td>
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<th>Notes</th>
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<tbody>
<tr>
<td><strong>Limitations identified by author:</strong> Model is simplistic and does not take account of all factors affecting spread of resistance, or of ‘feedback loops’ regarding defaulters. Original data could not be located, so analysis is based on previous economic analyses.</td>
</tr>
<tr>
<td><strong>Limitations identified by review team:</strong> Some concerns regarding reliability and applicability of input data. Very little information on intervention content, esp. comparator.</td>
</tr>
<tr>
<td><strong>Evidence gaps and/or recommendations for future research:</strong> Use of Markov modelling to encompass more complex impacts; application of model to other countries</td>
</tr>
<tr>
<td><strong>Source of funding:</strong> Global Forum for Health Research, Geneva</td>
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<tr>
<td>Healthcare system</td>
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<tr>
<td>Quality score: –</td>
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<tr>
<td>Applicability: +</td>
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### 7.3 Views studies

<table>
<thead>
<tr>
<th>Study details</th>
<th>Research parameters</th>
<th>Population and sample selection</th>
<th>Outcomes and methods of analysis</th>
<th>Notes by review team</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Authors:</strong> Craig GM, Booth H, Hall J, et al.</td>
<td><strong>Report the research questions:</strong> Process evaluation of a social outreach model of care including a link worker to develop collaborative care pathways.</td>
<td><strong>Report population were the sample recruited from:</strong> Stakeholders with experience of collaborative working from agencies “representative of the type of referrals made by the [link worker] and patients’ presenting problems” (p415)</td>
<td><strong>Brief description of methods and process of analysis:</strong> Analysed “in relation to the questions in the interview schedule” using N*Vivo</td>
<td><strong>Limitations identified by author:</strong> NR for qualitative aspect of the study</td>
</tr>
<tr>
<td><strong>Year:</strong> 2008</td>
<td><strong>Report theoretical approach:</strong> NR</td>
<td><strong>Report how many participants were recruited:</strong> N=8 individual i/vs (44% response rate), N=1 group i/v (exact total N NR)</td>
<td><strong>Key themes relevant to this review:</strong> Other workers have better understanding of TB patients’ needs: “Once the client was diagnosed with TB he was quite unmotivated, missing appointments, and we worked jointly to help him re-motivate himself with the understanding he would feel weak, have a temperature and he wasn’t just being lazy. Now we understand the symptoms and can be flexible around that.” (homeless hostel worker) “It’s been good for frontline staff to understand where TB links in, and get support accessing services.” (homeless organisation) Link workers help to link together services: “The TBLW’s done what the job implies: Link the community, person and health service with a consistency of service you wouldn’t otherwise get. With limited resources it’s helped us to make appropriate criteria links, by accessing the medical to those most in need.” (social worker) Link workers offered emotional and practical support, and a trusting relationship with patients, and could communicate patients’ needs to other agencies. This was especially important for asylum seekers who may be excluded from other services. Referral documents helped to reassure other agencies, e.g. housing, about potential health risks.</td>
<td><strong>Limitations identified by review team:</strong> Qualitative component is only one aspect of total evaluation. Limited information on methods or sample. Unclear if negative findings would be adequately represented in analysis. <strong>Evidence gaps and/or recommendations for future research:</strong> NR</td>
</tr>
<tr>
<td><strong>Citation:</strong> Establishing a new service role in tuberculosis care: the tuberculosis link worker. <em>Journal of Advanced Nursing</em> 61(4): 413-424.</td>
<td><strong>State how the data were collected:</strong> What method(s): Group discussions and interviews, face-to-face or by telephone (for stakeholders; NB patient data is quantitative, so not considered here).</td>
<td><strong>State specific inclusion criteria:</strong> NR</td>
<td><strong>Source of funding:</strong> King's Fund, The Henry Smith's Charity, The Sir Halley Stewart Trust, The Kirby Laing Foundation, The Adint Charitable Trust.</td>
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</tr>
<tr>
<td><strong>Quality score:</strong> –</td>
<td><strong>By whom:</strong> NR</td>
<td><strong>State specific exclusion criteria:</strong> NR</td>
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<tr>
<td>Improved communication with hospital clinicians was important, especially in relation to service discharge. Provision of other services acts as an incentive for patients to access services: “They will have loads of other issues apart from their health and are more likely to turn up to the services if other issues can be addressed. It’s like a day centre – get tea, see nurses, get help with housing and other issues.” (homeless case worker)</td>
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### Study details

<table>
<thead>
<tr>
<th>Research parameters</th>
<th>Population and sample selection</th>
<th>Outcomes and methods of analysis</th>
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<tbody>
<tr>
<td><strong>Report the research questions:</strong> To investigate the implementation of a videophone DOT intervention, and identify reasons for successful uptake</td>
<td>Report population were the sample recruited from: Clinicians and other staff involved in delivering the service; patients</td>
<td>Brief description of methods and process of analysis: Used NVivo for analysis. “Realist” thematic analysis method. Staff reviewed transcripts.</td>
</tr>
<tr>
<td>Report theoretical approach: NR</td>
<td>Report how they recruited: Patients recruited by service staff and then contacted by researcher; staff recruited by email or direct contact</td>
<td>Key themes relevant to this review: Staff see services as more convenient for patients, especially those who are working long hours and short of time. Patients can request call at specific times which are convenient for them, and change time at the last minute, so service is more flexible. 10/12 patients [sic – elsewhere N=11 total] wholly positive about service, 2/12 express more mixed feelings. Patients value relationship with nurses: “you sort of develop this friendship with the nurses … there are two nurses that I was first introduced to when I was taking my medication, “cause when I started mine I was isolated at home, so I was always there for a solid three weeks … they are very caring people.” Patients say videophone improves privacy, although some would prefer to go to clinic so their families did not know they had TB. Technology seen as easy to use. Staff find videophone service more efficient than in-person DOT. Easier to finish visits as patients do not try to prolong interactions out of politeness. Technical difficulties with service created considerable problems, particularly for patients who did not speak fluent English. Video service may make it easier for patients who struggle to physically swallow pills.</td>
</tr>
<tr>
<td><strong>State how the data were collected:</strong> What method(s): Semi-structured interviews; some information also from case notes By whom: Lead researcher What setting(s): NR When: NR (quantitative component of study runs 2003-2010)</td>
<td>State specific inclusion criteria: Staff: any delivering or associated with the service. Patients: had been receiving service at least 1 month</td>
<td><strong>Limitations identified by author:</strong> Only patients receiving intervention included, not comparison group (in-person DOT). Interpreters not used for patients who did not speak fluent English. <strong>Limitations identified by review team:</strong> Reporting of qualitative component is fairly brief, both methods and data. Limited information on sampling. Unclear if negative perceptions would have been reflected in analysis. <strong>Evidence gaps and/or recommendations for future research:</strong> Larger RCT of intervention; investigate this approach in low-income countries <strong>Source of funding:</strong> Royal District Nursing Service of South Australia; Australian Government (postgraduate award)</td>
</tr>
</tbody>
</table>

### Notes by review team

**Limitations identified by review team:** Reporting of qualitative component is fairly brief, both methods and data. Limited information on sampling. Unclear if negative perceptions would have been reflected in analysis. **Evidence gaps and/or recommendations for future research:** Larger RCT of intervention; investigate this approach in low-income countries **Source of funding:** Royal District Nursing Service of South Australia; Australian Government (postgraduate award)
Patients may find it easier to 'cheat' by pretending to take tablets with videophone. Service improved communication between staff in community nursing service and Chest Clinic. Chest Clinic encouraged other hospitals to refer to the service. Staff impression that the service was increasing adherence.
Appendix B: Search annex

<table>
<thead>
<tr>
<th>Database</th>
<th>Hits</th>
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</thead>
<tbody>
<tr>
<td>MEDLINE</td>
<td>2189</td>
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<tr>
<td>MEDLINE In Process</td>
<td>173</td>
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<tr>
<td>EMBASE</td>
<td>2886</td>
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<td>ASSIA</td>
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<td>BL Ethos</td>
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<td>British Nursing Index</td>
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Search Annex

**Database**: MEDLINE  
**Host**: OVID  
**Data Parameters**: 1946 to October Week 1 2013  
**Date Searched**: 14/10/2013  
**Hits**: 2189

**Search Strategy**:

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<th>#</th>
<th>Searches</th>
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<td>157772</td>
</tr>
<tr>
<td>3</td>
<td>1 or 2</td>
<td>195113</td>
</tr>
<tr>
<td>4</td>
<td>*Directly Observed Therapy/</td>
<td>700</td>
</tr>
<tr>
<td>5</td>
<td>(DOT$ or (directly observ$ adj3 (therap$ or treat$))).ti,ab,kw.</td>
<td>33781</td>
</tr>
<tr>
<td>6</td>
<td>(short$ course$ adj3 (therap$ or treat$)).ti,ab,kw.</td>
<td>2162</td>
</tr>
</tbody>
</table>
((observ$ or supervis$ or watch$ or witness$ or see$ or monitor$ or check$) adj3 (therap$ or treat$)).ti,ab,kw.

((record$ or report$) adj3 (therap$ or treat$)).ti,ab,kw.

or/4-8

Case Management/

((case or care or treatment) adj3 manage$).ti,ab,kw.

((manag$ or support$ or plan$) adj3 care).ti,ab,kw.

Managed Care Programs/

("patient centered" or "patient centred").ti,ab,kw. or Patient-Centered Care/

((Tuberculosis or TB) adj5 (nurs$ or staff or team$ or multidisciplinary or outreach or centre$1 or center$1 or clinic$1)).ti,ab,kw.

((case or link) adj3 worker$1).ti,ab,kw.

("treatment partner" or "treatment supporter").ti,ab,kw.

"Continuity of Patient Care"/

or/10-18

9 or 19

(uptake or up-take or (up adj1 tak$) or takeup or take-up).ti,ab,kw.

(Adher$ or nonadheren$ or (non adj1 adheren$) or access or refus$ or compliance or comply$ or compli$ or concordan$ or default$ or dropout$1 or dropout$1 or interrupt$ or complet$ or finish$ or (follow$ adj1 up$1) or (miss$ adj2 appointment$1)).ti,ab,kw.

*Medsication Adherence/ 4269

*Patient Compliance/ 19401

*PATIENT DROPOUTS/ 2374

*TREATMENT REFUSAL/ 5293

or/21-26

3 and 20 and 27

limit 28 to yr="1993 -Current"

limit 29 to english language

exp animals/ not humans.sh.

30 not 31

(cow or cows or cattle or bovine or calves or badger or badgers or hedgehog or hedgehogs or mice or mouse or rat or rats).mp.

32 not 33

33

34 2189
Notes: this search was run whilst the American government was in partial shut-down. The NLM (PubMed) records might be out of date.

File Name: Medline2189.txt

Database: MEDLINE In Process
Host: OVID
Data Parameters: October 01, 2013
Date Searched: 14/10/2013
Hits: 173

Search Strategy:

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<td>exp Tuberculosis/</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1 or 2</td>
<td>9499</td>
</tr>
<tr>
<td>4</td>
<td>*Directly Observed Therapy/</td>
<td>0</td>
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<td>5</td>
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<td>6461</td>
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<tr>
<td>6</td>
<td>(short$ course$ adj3 (therap$ or treat$)).ti,ab,kw.</td>
<td>128</td>
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<tr>
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<td>6621</td>
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<td>3317</td>
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<tr>
<td>9</td>
<td>or/4-8</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Case Management/</td>
<td></td>
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<tr>
<td>11</td>
<td>((case or care or treatment) adj3 manage$).ti,ab,kw.</td>
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<tr>
<td>12</td>
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<td>13</td>
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<td>14</td>
<td>(&quot;patient centered&quot; or &quot;patient centred&quot;).ti,ab,kw. or Patient-Centered Care/</td>
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<tr>
<td>17</td>
<td>(&quot;treatment partner&quot; or &quot;treatment supporter&quot;).ti,ab,kw.</td>
<td>4</td>
</tr>
<tr>
<td>18</td>
<td>&quot;Continuity of Patient Care&quot;/</td>
<td>0</td>
</tr>
<tr>
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<td>or/10-18</td>
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</tr>
<tr>
<td>20</td>
<td>9 or 19</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>(uptake or up-take or (up adj1 tak$) or uptake or take-up).ti,ab,kw.</td>
<td>14072</td>
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<td>2</td>
<td>exp tuberculosis/</td>
<td>192490</td>
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<td>3</td>
<td>1 or 2</td>
<td>236380</td>
</tr>
<tr>
<td>4</td>
<td>*directly observed therapy/</td>
<td>364</td>
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<td>(DOT$ or (directly observ$ adj3 (therap$ or treat$))).ti,ab,kw.</td>
<td>43277</td>
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<td>6</td>
<td>(short$ course$ adj3 (therap$ or treat$)).ti,ab,kw.</td>
<td>2814</td>
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<td>(observ$ or supervis$ or watch$ or witness$ or see$ or monitor$ or check$ adj3 (therap$ or treat$)).ti,ab,kw.</td>
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<td>((record$ or report$) adj3 (therap$ or treat$)).ti,ab,kw.</td>
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<td>or/4-8</td>
<td>253687</td>
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<tr>
<td>10</td>
<td>case management/</td>
<td>7291</td>
</tr>
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</table>

**Notes:** this search was run whilst the American government was in partial shut-down. The NLM (PubMed) records might be out of date.

**File Name:** MedlineInProcess173.txt

**Database:** EMBASE  
**Host:** OVID  
**Data Parameters:** 1974 to 2013 Week 41  
**Date Searched:** 15/10/2013  
**Hits:** 2886  
**Search Strategy:**

11  ((case or care or treatment) adj3 manage$).ti,ab,kw.  73646
12  ((manag$ or support$ or plan$) adj3 care).ti,ab,kw.  80309
13  *patient care/  45104
14  ("patient centered" or "patient centred").ti,ab,kw.  9953
15  ((Tuberculosis or TB) adj5 (nurs$ or staff or team$ or multidisciplinary or outreach or centre$1 or center$1 or clinic$1)).ti,ab,kw.  3445
16  ((case or link) adj3 worker$1).ti,ab,kw.  853
17  ("treatment partner" or "treatment supporter").ti,ab,kw.  52
18  or/10-17  168254
19  9 or 18  418219
20  (uptake or up-take or (up adj1 tak$) or takeup or take-up).ti,ab,kw.  328356
21  (Adher$ or nonadheren$ or (non adj1 adheren$) or access or refus$ or compliance or comply$ or compli$ or concordan$ or default$ or dropout$1 or drop out$1 or interrupt$ or complet$ or finish$ or (follow$ adj1 up$1) or (miss$ adj2 appointment$1)).ti,ab,kw.  3253976
22  *medication compliance/  360
23  *patient compliance/  18476
24  *treatment refusal/  3566
25  or/20-24  3546960
26  3 and 19 and 25  3697
27  limit 26 to yr="1993 -Current"  3414
28  limit 27 to english language  2922
29  exp animals/ not exp humans/  4345750
30  28 not 29  2900
31  (cow or cows or cattle or bovine or calves or badger or badgers or hedgehog or hedgehogs or mice or mouse or rat or rats).mp.  3348026
32  30 not 31  2886

Notes: Some MeSH did not map to Emtree. Accordingly lines such as managed care programmes were not used here.

File Name: EMBASE2886.txt

Database: ASSIA
Host: ProQuest
Data Parameters: 1987 - current
Date Searched: 14/10/2013
Hits: 124
Search Strategy:

Set#: S1
Searched for: (Tuberculosis or TB)
Databases: Applied Social Sciences Index and Abstracts (ASSIA)
Results: 999°

Set#: S2
Searched for: SU.EXACT("Tuberculosis")
Databases: Applied Social Sciences Index and Abstracts (ASSIA)
Results: 671°

Set#: S3
Searched for: s1 or s2
Databases: Applied Social Sciences Index and Abstracts (ASSIA)
Results: 999°

Set#: S4
Searched for: (DOT* or (directly observ* NEAR/3 (therap* or treat*)))
Databases: Applied Social Sciences Index and Abstracts (ASSIA)
Results: 557°

Set#: S5
Searched for: SU.EXACT("Directly observed therapy")
Databases: Applied Social Sciences Index and Abstracts (ASSIA)
Results: 44°

Set#: S6
Searched for: (short* course* NEAR/3 (therap* or treat*))
Databases: Applied Social Sciences Index and Abstracts (ASSIA)
Results: 96°

Set#: S7
Searched for: ((observ* or supervis* or watch* or witness* or see* or monitor* or check*)
NEAR/3 (therap* or treat*))
Databases: Applied Social Sciences Index and Abstracts (ASSIA)
Results: 3885°

Set#: S8
Searched for: ((record* or report*) NEAR/3 (therap* or treat*))
Databases: Applied Social Sciences Index and Abstracts (ASSIA)
Results: 2138°

Set#: S9
Searched for: s4 or s5 or s6 or s7 or s8
Databases: Applied Social Sciences Index and Abstracts (ASSIA)
Results: 6349*

Set#: S10
Searched for: SU.EXACT("Case management")
Databases: Applied Social Sciences Index and Abstracts (ASSIA)
Results: 580°

Set#: S11
Searched for: ((case or care or treatment) NEAR/3 manage*)
Databases: Applied Social Sciences Index and Abstracts (ASSIA)
Results: 7632*

Set#: S12
Searched for: ((manag* or support* or plan*) NEAR/3 care)
Databases: Applied Social Sciences Index and Abstracts (ASSIA)
Results: 9214*

Set#: S13
Searched for: ("patient centered" or "patient centred")
Databases: Applied Social Sciences Index and Abstracts (ASSIA)
Results: 1050°

Set#: S14
Searched for: ((Tuberculosis or TB) NEAR/5 (nurs* or staff or team* or multidisciplinary or outreach or centre*1 or center*1 or clinic*1))
Databases: Applied Social Sciences Index and Abstracts (ASSIA)
Results: 143°

Set#: S15
Searched for: ((case or link) NEAR/3 worker*1)
Databases: Applied Social Sciences Index and Abstracts (ASSIA)
Results: 331°

Set#: S16
Searched for: ("treatment partner" or "treatment supporter")
Databases: Applied Social Sciences Index and Abstracts (ASSIA)
Results: 5°

Set#: S17
Searched for: s10 or s11 or s12 or s13 or s14 or s15 or s16
Databases: Applied Social Sciences Index and Abstracts (ASSIA)
Results: 12970*
Set#: S18
Searched for: s9 or s17
Databases: Applied Social Sciences Index and Abstracts (ASSIA)
Results: 19048*

Set#: S19
Searched for: (uptake or up-take or (up NEAR/1 tak*) or takeover or take-up)
Databases: Applied Social Sciences Index and Abstracts (ASSIA)
Results: 2489°

Set#: S20
Searched for: (Adher* or nonadheren* or (non NEAR/1 adheren*) or access or refus* or compliance or comply* or compli* or concordan* or default* or dropout*1 or drop out*1 or interrupt* or complet* or finish* or (follow* NEAR/1 up*1) or (miss* NEAR/2 appointment*))
Databases: Applied Social Sciences Index and Abstracts (ASSIA)
Results: 72855*

Set#: S21
Searched for: SU.EXACT("Adherence")
Databases: Applied Social Sciences Index and Abstracts (ASSIA)
Results: 1473°

Set#: S22
Searched for: s19 or s20 or s21
Databases: Applied Social Sciences Index and Abstracts (ASSIA)
Results: 74715*

Set#: S23
Searched for: s3 and s18 and s22
Databases: Applied Social Sciences Index and Abstracts (ASSIA)
Results: 129°

Set#: S24
Searched for: (s3 and s18 and s22) AND yr(1994-2013)
Databases: Applied Social Sciences Index and Abstracts (ASSIA)
Results: 124°

* Duplicates are removed from your search, but included in your result count.
° Duplicates are removed from your search and from your result count.

Notes: The year limit 1993-Current was applied by the earliest record returned by the search was from 1994. Hence the application of the date limit at line 24.

File Name: ASSIA124.txt
**Database:** BL Ethos  
**Host:** [http://ethos.bl.uk/Home.do](http://ethos.bl.uk/Home.do)  
**Data Parameters:** Not Specified  
**Date Searched:** 15/10/2013  
**Hits:** 8  
**Search Strategy:**

- 
  - 
  - 

**Notes:** 1 hit was a duplicate. This was manually removed.  
**File Name:** BLETHOS7.txt

**Database:** British Nursing Index (BNI)  
**Host:** ProQuest  
**Data Parameters:** 1994-Current  
**Date Searched:** 15/10/2013  
**Hits:** 191  
**Search Strategy:**

- **Set#:** S1  
  - Searched for: ti((Tuberculosis or TB)) OR ab((Tuberculosis or TB))  
    - Databases: British Nursing Index with Full Text  
    - Results: 3821°

- **Set#:** S2  
  - Searched for: SU.EXACT("Tuberculosis")  
    - Databases: British Nursing Index with Full Text  
    - Results: 2621°

- **Set#:** S3  
  - Searched for: s1 or s2  
    - Databases: British Nursing Index with Full Text  
    - Results: 4257°

- **Set#:** S4  
  - Searched for: ti((DOT* or (directly observ* NEAR/3 (therap* or treat*))))) OR ab((DOT* or (directly observ* NEAR/3 (therap* or treat*)))))  
    - Databases: British Nursing Index with Full Text  
    - Results: 468°

- **Set#:** S5
Searched for: ti((short* course* NEAR/3 (therap* or treat*))) OR ab((short* course* NEAR/3 (therap* or treat*)))
Databases: British Nursing Index with Full Text
Results: 163°

Set#: S6
Searched for: ti(((observ* or supervis* or watch* or witness* or see* or monitor* or check*) NEAR/3 (therap* or treat*))) OR ab(((observ* or supervis* or watch* or witness* or see* or monitor* or check*) NEAR/3 (therap* or treat*)))
Databases: British Nursing Index with Full Text
Results: 2931°

Set#: S7
Searched for: ti(((record* or report*) NEAR/3 (therap* or treat*))) OR ab(((record* or report*) NEAR/3 (therap* or treat*)))
Databases: British Nursing Index with Full Text
Results: 1326°

Set#: S8
Searched for: S4 or S5 or S6 or S7
Databases: British Nursing Index with Full Text
Results: 4617°

Set#: S9
Searched for: SU.EXACT("Care Plans and Planning")
Databases: British Nursing Index with Full Text
Results: 2758°

Set#: S10
Searched for: ti(((case or care or treatment) NEAR/3 manage*)) OR ab(((case or care or treatment) NEAR/3 manage*))
Databases: British Nursing Index with Full Text
Results: 8762°

Set#: S11
Searched for: ti(((manag* or support* or plan*) NEAR/3 care)) OR ab(((manag* or support* or plan*) NEAR/3 care))
Databases: British Nursing Index with Full Text
Results: 12929°

Set#: S12
Searched for: ti("patient centered" or "patient centred") OR ab("patient centered" or "patient centred")
Databases: British Nursing Index with Full Text
Set#: S13
Searched for: ti(((Tuberculosis or TB) NEAR/5 (nurs* or staff or team* or multidisciplinary or outreach or centre*1 or center*1 or clinic*1))) OR ab(((Tuberculosis or TB) NEAR/5 (nurs* or staff or team* or multidisciplinary or outreach or centre*1 or center*1 or clinic*1)))
Databases: British Nursing Index with Full Text
Results: 244°

Set#: S14
Searched for: ti(((case or link) NEAR/3 worker*1)) OR ab(((case or link) NEAR/3 worker*1))
Databases: British Nursing Index with Full Text
Results: 199°

Set#: S15
Searched for: ti(“treatment partner” or “treatment supporter”) OR ab(“treatment partner” or “treatment supporter”)
Databases: British Nursing Index with Full Text
Results: 1°

Set#: S16
Searched for: s9 or s10 or s11 or s12 or s13 or s14 or s15
Databases: British Nursing Index with Full Text
Results: 19005*

Set#: S17
Searched for: s8 or s16
Databases: British Nursing Index with Full Text
Results: 23386*

Set#: S18
Searched for: ti((uptake or up-take or (up NEAR/1 tak*) or takeup or take-up)) OR ab((uptake or up-take or (up NEAR/1 tak*) or takeup or take-up))
Databases: British Nursing Index with Full Text
Results: 3144°

Set#: S19
Searched for: ti((Adher* or nonadheren* or (non NEAR/1 adheren*) or access or refus* or compliance or comply* or compli* or concordan* or default* or dropout*1 or drop out*1 or interrupt* or complet* or finish* or (follow* NEAR/1 up*1) or (miss* NEAR/2 appointment*1))) OR ab((Adher* or nonadheren* or (non NEAR/1 adheren*) or access or refus* or compliance or comply* or compli* or concordan* or default* or dropout*1 or drop out*1 or interrupt* or complet* or finish* or (follow* NEAR/1 up*1) or (miss* NEAR/2 appointment*1)))
Databases: British Nursing Index with Full Text
Results: 3144°
Results: 69693*

Set#: S20
Search for: s18 or s19
Databases: British Nursing Index with Full Text
Results: 72209*

Set#: S21
Search for: s3 and s17 and s20
Databases: British Nursing Index with Full Text
Results: 203°

Set#: S22
Search for: (s3 and s17 and s20) AND pd(19930101-20131015)
Databases: British Nursing Index with Full Text
Results: 191°

* Duplicates are removed from your search, but included in your result count.
° Duplicates are removed from your search and from your result count.

----------------------------------------------------------
Notes: N/A
File Name: BNI191.txt

Database: CINAHL
Host: Ebsco HOST
Data Parameters: 1937-Current
Date Searched: 15/10/2013
Hits: 396
Search Strategy:

S1. (Tuberculosis or TB)
S2. (MH "Tuberculosis+")
S3. S1 or S2
S4. (MM "Directly Observed Therapy")
S5. (DOT* or (directly observ* N3 (therap* or treat*)))
S6. (short* course* N3 (therap* or treat*))
S7. ( observ* or supervis* or watch* or witnes* or see* or monitor* or check* ) N3
( therap* or treat* )
S8. (record* or report* ) N3 (therap* or treat*)
S9. S4 or S5 or S6 or S7 or S8
S10. (MM "Case Management")
S11. ((case or care or treatment) N3 manage*)
S12. ((manag* or support* or plan*) N3 care)
S13. (MM "Managed Care Programs")
S14. ("patient centered" or "patient centred")
#13 MeSH descriptor: [Managed Care Programs] this term only 290
#14 ("patient centered" or "patient centred") 826
#15 MeSH descriptor: [Patient-Centered Care] this term only 248
#16 ((Tuberculosis or TB) near/5 (nurs* or staff or team* or multidisciplinary or outreach or centre*1 or center*1 or clinic*1)) 48
#17 ((case or link) near/3 worker*1 0
#18 ("treatment partner" or "treatment supporter") 15
#19 MeSH descriptor: [Continuity of Patient Care] this term only 469
#20 ((manag* or support* or plan*) near/3 care) 7052
#21 #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 10760
#22 #9 or #21 37559
#23 (uptake or up-take or (up near/1 tak*)) or takeover or take-up 10368
#24 (Adher* or nonadheren* or (non near/1 adheren*) or access or refus* or compliance or compli* or compli* or concordan* or default* or dropout*1 or drop out*1 or interrupt* or complet* or finish* or (follow* near/1 up*1) or (miss* near/2 appointment*1)) 178971
#25 MeSH descriptor: [Medication Adherence] this term only 655
#26 MeSH descriptor: [Patient Compliance] this term only 7224
#27 MeSH descriptor: [Patient Dropouts] this term only 1418
#28 MeSH descriptor: [Treatment Refusal] this term only 251
#29 #23 or #24 or #25 or #26 or #27 or #28 186430
#30 #3 and #22 and #29 from 1993 to 2013 204

Notes: N/A
File Name: Cochrane204.txt

Database: TRoPHI
Host: http://eppi.ioe.ac.uk/webdatabases/Intro.aspx?ID=5
Data Parameters: not specified
Date Searched: 15/10/2013
Hits: 0
Search Strategy:

<table>
<thead>
<tr>
<th>Select</th>
<th>Search #</th>
<th>Search No</th>
</tr>
</thead>
<tbody>
<tr>
<td>of hits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Freetext: &quot;((Tuberculosis or TB) and (DOT)) &quot;</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Freetext: &quot;((Tuberculosis or TB) and (directly observed therapy)) &quot;</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Freetext: &quot;((Tuberculosis or TB) and (case management)) &quot;</td>
<td>0</td>
</tr>
</tbody>
</table>

Notes: N/A
File Name: N/A
Set#: S1
Searched for: ti((Tuberculosis or TB)) OR ab((Tuberculosis or TB))
Databases: ERIC
Results: 1953°

Set#: S2
Searched for: ti((DOT* or (directly observ* NEAR/3 (therap* or treat*)))) OR ab((DOT* or (directly observ* NEAR/3 (therap* or treat*))))
Databases: ERIC
Results: 1026°

Set#: S3
Searched for: ti((short* course* NEAR/3 (therap* or treat*))) OR ab((short* course* NEAR/3 (therap* or treat*)))
Databases: ERIC
Results: 19°

Set#: S4
Searched for: ti(((observ* or supervis* or watch* or witness* or see* or monitor* or check*) NEAR/3 (therap* or treat*))) OR ab(((observ* or supervis* or watch* or witness* or see* or monitor* or check*) NEAR/3 (therap* or treat*)))
Databases: ERIC
Results: 1655°

Set#: S5
Searched for: ti(((record* or report*) NEAR/3 (therap* or treat*))) OR ab(((record* or report*) NEAR/3 (therap* or treat*)))
Databases: ERIC
Results: 1207°

Set#: S6
Searched for: s2 or s3 or s4 or s5
Databases: ERIC
Results: 3852°

Set#: S7
Searched for: ti(((case or care or treatment) NEAR/3 manage*)) OR ab(((case or care or treatment) NEAR/3 manage*))
Databases: ERIC
Results: 3211°

Set#: S8
Searched for: ti(((manag* or support* or plan*) NEAR/3 care)) OR ab(((manag* or support* or plan*) NEAR/3 care))
Databases: ERIC
Results: 3527°

Set#: S9
Searched for: ti("patient centered" or "patient centred") OR ab("patient centered" or "patient centred")
Databases: ERIC
Results: 93°

Set#: S10
Searched for: ti(((Tuberculosis or TB) NEAR/5 (nurs* or staff or team* or multidisciplinary or outreach or centre*1 or center*1 or clinic*1))) OR ab(((Tuberculosis or TB) NEAR/5 (nurs* or staff or team* or multidisciplinary or outreach or centre*1 or center*1 or clinic*1)))
Databases: ERIC
Results: 23°

Set#: S11
Searched for: ti(((case or link) NEAR/3 worker*1)) OR ab(((case or link) NEAR/3 worker*1))
Databases: ERIC
Results: 279°

Set#: S12
Searched for: ti("treatment partner" or "treatment supporter") OR ab("treatment partner" or "treatment supporter")
Databases: ERIC
Results: 0°

Set#: S13
Searched for: s7 or s8 or s9 or s10 or s11 or s12
Databases: ERIC
Results: 5934*

Set#: S14
Searched for: s6 or s13
Databases: ERIC
Results: 9714*
Set#: S15
Searched for: ti((uptake or up-take or (up NEAR/1 tak*) or takeup or take-up)) OR ab((uptake or up-take or (up NEAR/1 tak*) or takeup or take-up))
Databases: ERIC
Results: 2410°

Set#: S16
Searched for: ti((Adher* or nonadheren* or (non NEAR/1 adheren*) or access or refus* or compliance or comply* or compli* or concordan* or default* or dropout*1 or drop out*1 or interrupt* or complet* or finish* or (follow* NEAR/1 up*1) or (miss* NEAR/2 appointment*1))) OR ab((Adher* or nonadheren* or (non NEAR/1 adheren*) or access or refus* or compliance or comply* or compli* or concordan* or default* or dropout*1 or drop out*1 or interrupt* or complet* or finish* or (follow* NEAR/1 up*1) or (miss* NEAR/2 appointment*1)))
Databases: ERIC
Results: 163968*

Set#: S17
Searched for: s15 or s16
Databases: ERIC
Results: 165987*

Set#: S18
Searched for: s1 and s14 and s17
Databases: ERIC
Results: 8°

Set#: S19
Searched for: (s1 and s14 and s17) AND pd(19930101-20131015)
Databases: ERIC
Results: 6°

* Duplicates are removed from your search, but included in your result count.
° Duplicates are removed from your search and from your result count.

Notes: N/A
File Name: ERIC6.txt

Database: HMIC Health Management Information Consortium
Host: OVID
Data Parameters: 1979 to March 2013
Date Searched: 14/10/2013
Hits: 47
## Search Strategy:

<table>
<thead>
<tr>
<th>#</th>
<th>Searches</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(Tuberculosis or TB).ti,ab.</td>
<td>776</td>
</tr>
<tr>
<td>2</td>
<td>Tuberculosis.mp.</td>
<td>886</td>
</tr>
<tr>
<td>3</td>
<td>1 or 2</td>
<td>905</td>
</tr>
<tr>
<td>4</td>
<td>Directly Observed Therap*.mp.</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>(DOTS or (directly observ$ adj3 (therap$ or treat$))).ti,ab.</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>(short$ course$ adj3 (therap$ or treat$)).ti,ab.</td>
<td>16</td>
</tr>
<tr>
<td>7</td>
<td>(((observ$ or supervis$ or watch$ or witness$ or see$ or monitor$ or check$) adj3 (therap$ or treat$))).ti,ab.</td>
<td>817</td>
</tr>
<tr>
<td>8</td>
<td>((record$ or report$) adj3 (therap$ or treat$)).ti,ab.</td>
<td>524</td>
</tr>
<tr>
<td>9</td>
<td>4 or 5 or 6 or 7 or 8</td>
<td>1375</td>
</tr>
<tr>
<td>10</td>
<td>Case Management.mp.</td>
<td>842</td>
</tr>
<tr>
<td>11</td>
<td>((case or care or treatment) adj3 manage$).ti,ab.</td>
<td>5194</td>
</tr>
<tr>
<td>12</td>
<td>((manag$ or support$ or plan$) adj3 care).ti,ab.</td>
<td>8534</td>
</tr>
<tr>
<td>13</td>
<td>Managed Care Programs.mp.</td>
<td>3</td>
</tr>
<tr>
<td>14</td>
<td>(&quot;patient centered&quot; or &quot;patient centred&quot;).ti,ab. or Patient-Centered Care.mp.</td>
<td>1037</td>
</tr>
<tr>
<td>15</td>
<td>((Tuberculosis or TB) adj5 (nurs$ or staff or team$ or multidisciplinary or outreach or centre$1 or center$1 or clinic$1)).ti,ab.</td>
<td>38</td>
</tr>
<tr>
<td>16</td>
<td>((case or link) adj3 worker$1).ti,ab.</td>
<td>138</td>
</tr>
<tr>
<td>17</td>
<td>(&quot;treatment partner&quot; or &quot;treatment supporter&quot;).ti,ab.</td>
<td>1</td>
</tr>
<tr>
<td>18</td>
<td>Continuity of Patient Care.mp.</td>
<td>333</td>
</tr>
<tr>
<td>19</td>
<td>10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18</td>
<td>11045</td>
</tr>
<tr>
<td>20</td>
<td>9 or 19</td>
<td>12336</td>
</tr>
<tr>
<td>21</td>
<td>(uptake or up-take or (up adj1 tak$) or takeup or take-up).ti,ab.</td>
<td>2587</td>
</tr>
<tr>
<td>22</td>
<td>(Adher$ or nonadheren$ or (non adj1 adheren$) or access or refus$ or compliance or comply$ or compli$ or concordan$ or default$ or dropout$1 or drop out$1 or interrupt$ or complet$ or finish$ or (follow$ adj1 up$1) or (miss$ adj2 appointment$1)).ti,ab.</td>
<td>34162</td>
</tr>
<tr>
<td>23</td>
<td>Medication Adherence.mp.</td>
<td>80</td>
</tr>
<tr>
<td>24</td>
<td>Patient Compliance.mp.</td>
<td>476</td>
</tr>
<tr>
<td>25</td>
<td>PATIENT DROPOUTS.mp.</td>
<td>1</td>
</tr>
<tr>
<td>26</td>
<td>TREATMENT REFUSAL.mp.</td>
<td>9</td>
</tr>
<tr>
<td>27</td>
<td>21 or 22 or 23 or 24 or 25 or 26</td>
<td>36130</td>
</tr>
<tr>
<td>28</td>
<td>3 and 20 and 27</td>
<td>50</td>
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<td></td>
<td>Searches</td>
<td>Results</td>
</tr>
<tr>
<td>---</td>
<td>--------------------------------------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>29</td>
<td>limit 28 to yr=&quot;1993 -Current&quot;</td>
<td>47</td>
</tr>
<tr>
<td>30</td>
<td>limit 29 to english</td>
<td>47</td>
</tr>
<tr>
<td>31</td>
<td>(cow or cows or cattle or bovine or calves or badger or badgers or hedgehog or hedgehogs or mice or mouse or rat or rats).mp.</td>
<td>1015</td>
</tr>
<tr>
<td>32</td>
<td>30 not 31</td>
<td>47</td>
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</tbody>
</table>

**Notes:** N/A

**File Name:** HMIC47.txt

**Database:** OpenGrey

**Host:** [http://ethos.bl.uk/Home.do](http://ethos.bl.uk/Home.do)

**Data Parameters:** not specified

**Date Searched:** 15/10/2013

**Hits:** 1

**Search Strategy:**

- ((Tuberculosis or TB) and (DOT)) n=0
- ((Tuberculosis or TB) and (directly observed therapy)) n=0
- ((Tuberculosis or TB) and (case management)) n=1

**Notes:** N/A

**File Name:** OG1.txt

**Database:** Social Policy and Practice (SPP)

**Host:** OVID

**Data Parameters:** 201307

**Date Searched:** 17/10/2013

**Hits:** 2

**Search Strategy:**

<table>
<thead>
<tr>
<th>#</th>
<th>Searches</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(Tuberculosis or TB).ti,ab.</td>
<td>139</td>
</tr>
<tr>
<td>2</td>
<td>Tuberculosis.mp.</td>
<td>169</td>
</tr>
<tr>
<td>3</td>
<td>1 or 2</td>
<td>180</td>
</tr>
<tr>
<td>4</td>
<td>Directly Observed Therap*.mp.</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>(DOT$ or (directly observ$ adj3 (therap$ or treat$))).ti,ab.</td>
<td>76</td>
</tr>
<tr>
<td>6</td>
<td>(short$ course$ adj3 (therap$ or treat$)).ti,ab.</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>((observ$ or supervis$ or watch$ or witness$ or see$ or monitor$ or check$) adj3 (therap$ or treat$)).ti,ab.</td>
<td>728</td>
</tr>
<tr>
<td>8</td>
<td>((record$ or report$) adj3 (therap$ or treat$)).ti,ab.</td>
<td>580</td>
</tr>
<tr>
<td></td>
<td>Description</td>
<td>Hits</td>
</tr>
<tr>
<td>---</td>
<td>-----------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>9</td>
<td>4 or 5 or 6 or 7 or 8</td>
<td>1354</td>
</tr>
<tr>
<td>10</td>
<td>Case Management.mp.</td>
<td>1390</td>
</tr>
<tr>
<td>11</td>
<td>(case or care or treatment) adj3 manage$.ti,ab.</td>
<td>4541</td>
</tr>
<tr>
<td>12</td>
<td>((manag$ or support$ or plan$) adj3 care).ti,ab.</td>
<td>9413</td>
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<tr>
<td>13</td>
<td>Managed Care Programs.mp.</td>
<td>1</td>
</tr>
<tr>
<td>14</td>
<td>(&quot;patient centered&quot; or &quot;patient centred&quot;).ti,ab. or Patient-Centered Care.mp.</td>
<td>179</td>
</tr>
<tr>
<td>15</td>
<td>((Tuberculosis or TB) adj5 (nurs$ or staff or team$ or multidisciplinary or outreach or centre$1 or center$1 or clinic$1)).ti,ab.</td>
<td>4</td>
</tr>
<tr>
<td>16</td>
<td>((case or link) adj3 worker$1).ti,ab.</td>
<td>266</td>
</tr>
<tr>
<td>17</td>
<td>(&quot;treatment partner&quot; or &quot;treatment supporter&quot;).ti,ab.</td>
<td>0</td>
</tr>
<tr>
<td>18</td>
<td>Continuity of Patient Care.mp.</td>
<td>2</td>
</tr>
<tr>
<td>19</td>
<td>10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18</td>
<td>11418</td>
</tr>
<tr>
<td>20</td>
<td>9 or 19</td>
<td>12728</td>
</tr>
<tr>
<td>21</td>
<td>(uptake or up-take or (up adj1 tak$) or takeup or take-up).ti,ab.</td>
<td>2343</td>
</tr>
<tr>
<td>22</td>
<td>(Adher$ or nonadheren$ or (non adj1 adheren$) or access or refus$ or compliance or comply$ or compli$ or concordan$ or default$ or dropout$1 or drop out$1 or interrupt$ or complet$ or finish$ or (follow$ adj1 up$1) or (miss$ adj2 appointment$1)).ti,ab.</td>
<td>41154</td>
</tr>
<tr>
<td>23</td>
<td>Medication Adherence.mp.</td>
<td>84</td>
</tr>
<tr>
<td>24</td>
<td>Patient Compliance.mp.</td>
<td>10</td>
</tr>
<tr>
<td>25</td>
<td>PATIENT DROOUTS.mp.</td>
<td>0</td>
</tr>
<tr>
<td>26</td>
<td>TREATMENT REFUSAL.mp.</td>
<td>8</td>
</tr>
<tr>
<td>27</td>
<td>21 or 22 or 23 or 24 or 25 or 26</td>
<td>43046</td>
</tr>
<tr>
<td>28</td>
<td>3 and 20 and 27</td>
<td>2</td>
</tr>
</tbody>
</table>

**Notes:** N/A

**File Name:** spp2

**Database:** Sociological Abstracts

**Host:** ProQuest

**Data Parameters:** 1952 - current

**Date Searched:** 14/10/2013

**Hits:** 27

**Search Strategy:**

- **Set#:** S1
- **Search for:** (Tuberculosis or TB)
- **Databases:** Sociological Abstracts
- **Results:** 652°
Set#: S2
Searched for: SU.EXACT("Tuberculosis")
Databases: Sociological Abstracts
Results: 234°

Set#: S3
Searched for: s1 or s2
Databases: Sociological Abstracts
Results: 652°

Set#: S4
Searched for: (DOT* or (directly observ* NEAR/3 (therap* or treat*)))
Databases: Sociological Abstracts
Results: 741°

Set#: S5
Searched for: (short* course* NEAR/3 (therap* or treat*))
Databases: Sociological Abstracts
Results: 9°

Set#: S6
Searched for: ((observ* or supervis* or watch* or witness* or see* or monitor* or check*) NEAR/3 (therap* or treat*))
Databases: Sociological Abstracts
Results: 1683°

Set#: S7
Searched for: ((record* or report*) NEAR/3 (therap* or treat*))
Databases: Sociological Abstracts
Results: 575°

Set#: S8
Searched for: s4 or s5 or s6 or s7
Databases: Sociological Abstracts
Results: 2940°

Set#: S9
Searched for: SU.EXACT("Case Management")
Databases: Sociological Abstracts
Results: 143°

Set#: S10
Searched for: ((case or care or treatment) NEAR/3 manage*)
Databases: Sociological Abstracts
Results: 2581°

Set#: S11
Searched for: ((manag* or support* or plan*) NEAR/3 care)
Databases: Sociological Abstracts
Results: 3528°

Set#: S12
Searched for: ("patient centered" or "patient centred")
Databases: Sociological Abstracts
Results: 154°

Set#: S13
Searched for: ((Tuberculosis or TB) NEAR/5 (nurs* or staff or team* or multidisciplinary or outreach or centre*1 or center*1 or clinic*1))
Databases: Sociological Abstracts
Results: 39°

Set#: S14
Searched for: ((case or link) NEAR/3 worker*1)
Databases: Sociological Abstracts
Results: 1033°

Set#: S15
Searched for: ("treatment partner" or "treatment supporter")
Databases: Sociological Abstracts
Results: 5°

Set#: S16
Searched for: s9 or s10 or s11 or s12 or s13 or s14 or s15
Databases: Sociological Abstracts
Results: 5999*

Set#: S17
Searched for: s8 or s16
Databases: Sociological Abstracts
Results: 8861*

Set#: S18
Searched for: (uptake or up-take or (up NEAR/1 tak*) or takeup or take-up)
Databases: Sociological Abstracts
Results: 2847°
Set#: S19
Searched for: (Adher* or nonadheren* or (non NEAR/1 adheren*) or access or refus* or compliance or comply* or compli* or concordan* or default* or dropout*1 or drop out*1 or interrupt* or complet* or finish* or (follow* NEAR/1 up*1) or (miss* NEAR/2 appointment*1))
Databases: Sociological Abstracts
Results: 82463*

Set#: S20
Searched for: s18 or s19
Databases: Sociological Abstracts
Results: 84891*

Set#: S21
Searched for: s3 and s17 and s20
Databases: Sociological Abstracts
Results: 27°

* Duplicates are removed from your search, but included in your result count.
° Duplicates are removed from your search and from your result count.

Notes: N/A
File Name: SOCABS27.txt

Database: Web of Science (SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH)
Host: ISI
Data Parameters: ((SCI-EXPANDED) --1900-present; (SSCI) --1956-present; (CPCI-S) -- 1990-present; (CPCI-SSH) --1990-present)
Date Searched: 15/10/2013
Hits: 1654
Search Strategy:

# 1
98,619
Topic=(Tuberculosis or TB)
Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=1993-2013

# 2
257,029
Topic=((DOT*))
Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=1993-2013

# 3
1,360
Topic=(("directly observ*" NEAR/3 (therap* or treat*)))
Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=1993-2013

# 4
1,643
Topic=(("short* course*" near/3 (therap* or treat*)))
Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=1993-2013

# 5
32,096
Topic=(((observ* or supervis* or watch* or witness* or see* or monitor* or check*) near/3 (therap*)))
Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=1993-2013

# 6
95,675
Topic=(((observ* or supervis* or watch* or witness* or see* or monitor* or check*) near/3 (treat*)))
Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=1993-2013

# 7
14,261
Topic=(((record* or report*) near/3 (therap*)))
Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=1993-2013

# 8
36,208
Topic=(((record* or report*) near/3 (treat*)))
Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=1993-2013

# 9
429,171
#8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2
Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=1993-2013

# 10
73,117
#8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2
Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=1993-2013

# 11
62,215
Topic=(((manag* or support* or plan*) near/3 care))
Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=1993-2013
# 12
6,177
Topic=(("patient centered" or "patient centred"))
Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=1993-2013

# 13
480
Topic=(((Tuberculosis or TB) near/5 (nurs* or staff or team* or multidisciplinary or outreach or centre*1 or center*1 or clinic*1)))
Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=1993-2013

# 14
0
Topic=(((case or link) near/3 worker*1))
Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=1993-2013

# 15
30
Topic=(("treatment partner" or "treatment supporter"))
Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=1993-2013

# 16
105,321
#15 OR #14 OR #13 OR #12 OR #11 OR #10
Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=1993-2013

# 17
530,650
#16 OR #9
Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=1993-2013

# 18
266,738
#17 OR #8
Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=1993-2013

# 19
2,400,727
Topic=(((Adher* or nonadheren* or (non near/1 adheren*) or access or refus* or compliance or compli* or compli* or concordan* or default* or dropout*1 or drop out*1 or interrupt* or complet* or finish* or (follow* near/1 up*1) or (miss* near/2 appointment*1)))
Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=1993-2013
Notes: N/A
File Name: WOS1654.txt

Database: Health Economics Evaluation Database (HEED)
Host: via Wiley (through The Cochrane Library)
Data Parameters: Unspecified
Date Searched: 17/10/2013
Hits: 84

Search Strategy:

1. (Tuberculosis or TB) AND (directly observed) n=51

2. (Tuberculosis or TB) AND (DOT) n=26

3. (Tuberculosis or TB) AND (case management) n=7

Notes: the search terms used here reflect the core terms used for the interventions as represented by the key Cochrane reviews identified in scoping.
File Name: HEED.txt

Database: Cochrane CIDG Specialized register
Host: Cochrane CIDG
Data Parameters: 18/10/2013
Date Searched: 22/10/2013
Hits: 88
Search Strategy:

This resource is held by the Cochrane CIDG group. The search was conducted by Dr Vittoria Lutje, Information Specialist, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, www.liv.ac.uk/evidence

Notes: N/A
File Name: CIDG.txt