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

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

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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 (++), eight 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[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 (++)

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 (–)

2 Matteelli et al., 2000 (–)

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 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 study[7] 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[9] 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 (–)
9 Wade et al., 2012 (–)

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 treated[1-3].

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

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 (–)

Evidence statement 10: Cost-effectiveness of screening, LTBI treatment and DOPT for new entrants

There is good evidence from one (++) study[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.

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 study[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.

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 study[1] 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 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 (+)

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 England via https://www.gov.uk/government/organisations/public-health-england
- 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.

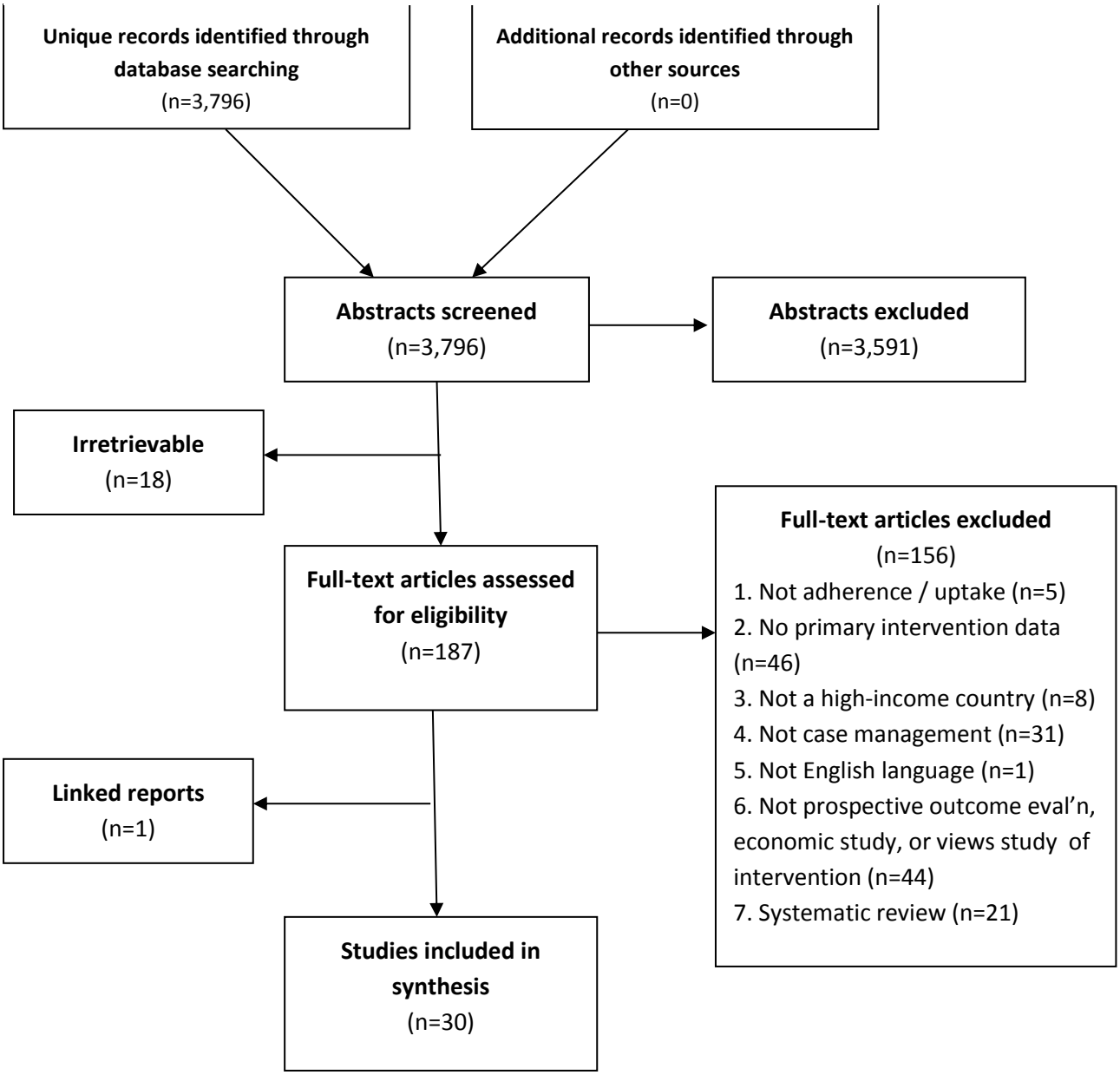
[1] These are: Australia, Austria, Belgium, Canada, Chile, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Korea, Luxembourg, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden, Switzerland,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

		Population			**Method of allocation to intervention/comparison**										**Outcomes**							**Analysis**					**Sum-mary**	
Reference	**Design**	**1.1**	**1.2**	**1.3**	**2.1**	**2.2**	**2.3**	**2.4**	**2.5**	**2.6**	**2.7**	**2.8**	**2.9**	**2. 10**	**3.1**	**3.2**	**3.3**	**3.4**	**3.5**	**3.6**	**4.1**	**4.2**	**4.3**	**4.4**	**4.5**	**4.6**	**5.1**	**5.2**
Batki et al., 2002	RCT	++	+	++	++	+	++	+	+	++	–	+	+	+	+	++	++	++	++	++	+	++	NR	++	++	++	++	+
Chaisson et al., 2001	RCT	+	+	–	++	++	++	+	+	NR	NR	+	+	+	+	++	+	+	++	+	++	++	NR	++	++	++	++	+
DeMaio et al., 2001	BA	–	–	–	–	–	NA	NR	–	+	NR	++	+	–	+	+	–	–	NA	–	NA	–	NR	–	–	–	–	–
Goldberg et al., 2004	BA	++	+	–	NA	++	NA	NA	+	NA	NA	+	+	+	+	+	+	+	+	++	NA	NA	NR	++	++	++	–	–
Graham et al., 1996	BA	+	+	–	NA	–	NA	NA	+	NA	NA	+	+	+	+	+	+	++	+	++	NA	NA	NR	++	+	++	–	–
Jin et al., 1993	RCT	–	–	–	+	–	NR	NR	–	–	+	+	–	–	–	+	+	–	NR	NR	+	–	–	+	–	–	–	–
MacIntyre et al., 2003	RCT	++	+	–	+	++	–	+	+	–	NR	+	+	+	+	+	+	++	++	+	–	++	–	++	–	++	++	+

Malotte et al., 2001	RCT	+	+	++	++	++	++	++	+	NR	NR	+	+	+	++	++	++	++	++	++	++	+	NR	++	++	++	++	+
Matteelli et al., 2000	RCT	+	–	NR	+	–	NR	+	+	NR	NR	–	+	–	–	–	+	–	++	+	++	–	+	–	–	–	–	–
Narita et al., 2002	BA	+	++	+	NA	+	NA	NA	–	NA	NA	++	+	+	++	+	+	+	+	++	NA	NA	NR	++	++	++	+	+
Nyamathi et al., 2006	RCT	++	+	++	++	++	NR	+	–	++	++	+	–	+	+	+	++	++	++	++	++	++	+	++	+	++	++	+
Rüütel et al. 2011	RCT	++	–	–	+	+	NR	NR	+	NR	NR	++	+	+	+	++	+	+	++	+	++	++	NR	++	++	++	++	+
Sterling et al., 2011	RCT	–	–	–	+	+	NR	++	+	NR	–	++	NR	+	+	+	+	++	++	++	++	++	++	++	+	++	+	–

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)

Reference	**Applicability**								**Overall judge-ment**	**Study limitations**											**Overall assess-ment**
	1.1	**1.2**	**1.3**	**1.4**	**1.5**	**1.6**	**1.7**	**1.8**		**2.1**	**2.2**	**2.3**	**2.4**	**2.5**	**2.6**	**2.7**	**2.8**	**2.9**	**2. 10**	**2. 11**	
Berkowitz et al., 2006	+	++	+	++	+	–	–	+	Partly applicable	+	–	+	+	–	+	–	–	+	+	NR	Very serious limitations
Burman et al., 1997	NR	++	+	++	+	–	–	+	Partly applicable	+	–	+	+	+	+	+	+	+	+	NR	Potentially serious limitations
Chaulk et al., 2000	NR	NR	+	NR	NR	–	–	–	Not applicable												
Gourevitch et al., 1998	++	++	+	+	+	–	–	+	Partly applicable	+	+	+	+	–	+	–	+	–	+	NR	Very serious limitations
Holland et al., 2009	+	+	+	+	+	–	++	+	Partly applicable	+	–	+	+	–	++	–	–	++	+	++	Very serious limitations
Jit et al., 2011	++	++	++	++	++	–	++	++	Directly applicable	+	+	+	+	+	+	+	+	++	++	++	Potentially serious limitations
Migliori et al., 1999	+	++	+	++	–	–	–	+	Partly applicable	–	–	–	–	–	+	+	–	–	–	NR	Very serious limitations
Moore et al., 1996	+	++	+	++	+	–	–	++	Partly applicable	+	–	+	–	+	+	+	+	+	+	NR	Potentially serious limitations
Palmer et al.,	++	+	+	++	+	–	–	+	Partly applicable	+	+	+	+	+	+	+	+	+	+	NR	Potentially serious

1998																					limitations
Perlman et al., 2001	++	+	+	–	+	–	–	+	Partly applicable	+	+	–	+	–	+	+	–	++	–	NR	Very serious limitations
Porco et al., 2006	++	+	+	++	++	–	++	+	Directly applicable	++	+	++	+	+	++	+	+	++	++	NR	Minor limitations
Synder & Chin, 1999a	+	++	+	++	+	–	–	+	Partly applicable	+	–	–	+	+	+	–	–	++	+	NR	Very serious limitations
Snyder et al., 1999b	++	++	+	++	+	–	–	+	Partly applicable	+	+	+	+	–	+	+	+	+	+	NR	Potentially serious limitations
Wade et al., 2012	++	++	+	+	–	–	–	+	Partly applicable	–	–	–	+	+	–	+	+	++	++	++	Very serious limitations
Weis et al., 1999	++	++	+	+	+	–	–	+	Partly applicable	–	–	–	+	+	+	+	++	–	–	NR	Very serious limitations
Wilton et al., 2001	++	+	+	+	+	–	–	+	Partly applicable	+	–	+	+	–	+	–	–	–	+	NR	Very serious limitations

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)

Reference	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Overall
Craig et al., 2008	Y	Y	?	?	N	N	N	?	N	?	N	Y	Y	Y	–
Wade et al., 2012	Y	Y	Y	Y	N	Y	Y	Y	N	Y	N	Y	Y	Y	+

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 4. Summary of the effectiveness studies (N=13)

Ref.	Des.	QA	Country	Population	Intervention / comparison	Outcomes	Direction of effect
Batki et al., 2002	RCT	++	USA	Drug users	DOPT, methadone, counselling / DOPT, methadone / usual care	Completion	Effective
						Active TB	No difference
Chaisson et al., 2001	RCT	++	USA	Drug users	DOPT / peer support / usual care	Adherence	No difference
						Completion	No difference
DeMaio et al., 2001	BA	–	USA	Patients with active TB	Standard DOT / videophone DOT	Adherence	No difference
Goldberg et al., 2004	BA	–	USA	Refugees	Case management	Uptake	Effective
						Completion	Effective
Graham et al., 1996	BA	–	USA	Drug users	DOPT	TB	Effective
Jin et al., 1993	RCT	–	S Korea	Patients with active TB	Intensified supervision for staff / usual supervision	Tests performed	Effective
						Adherence	Effective
						Completion	Effective
						Treatment success	Effective
MacIntyre et al., 2003	RCT	++	Aust-ralia	Patients with active TB	Family-based DOT / usual care	Adherence	No difference
						Completion	No difference
Malotte et al., 2001	RCT	++	USA	Drug users	Outreach DOPT, incentive / outreach DOPT alone / on-site DOPT, incentive	Adherence	Effective (incentive groups)
						Completion	Effective (incentive groups)
Matteelli et al., 2000	RCT	–	Italy	Immigrants	Supervised drug collection / usual care	Completion	Adverse
Narita et al., 2002	BA	+	USA	HIV+ people with LTBI	DOT	Completion	Effective
Nyamathi et al., 2006	RCT	++	USA	Homeless people with LTBI	Education, tracking of defaulters, DOT, incentives / DOT, incentives	Knowledge	Effective
						Completion	Effective
Rüütel et al. 2011	RCT	++	Estonia	Drug users	Active referral, incentive / passive referral	Attendance at TB clinic	Effective
Sterling et	RCT	+	Multi.	People with	DOT / SAT	Completion	Effective

al., 2011				LTBI		TB	Effective
						Death	No difference

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 of 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).

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 (–)
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 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)

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

Wade et al., 2012	–	Patients with active TB	Videophone DOT / in-person DOT	Cost per successful care episode
Weis et al., 1999	–	Patients with active TB	DOT / SAT	Net cost savings
Wilton et al., 2001	–	Patients with MDR-TB	DOT / 'conventional therapy'	Net cost savings

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$

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

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-adminstered 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 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 study[7] 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[9] 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 (–)

9 Wade et al., 2012 (–)

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 treated[1-3].

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

in terms of net costs, taking into account further treatment costs, and in terms of cost per QALY.

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 7. Findings from Porco et al., 2006 (++)

Beginning with …	Choose between …	Best choice
1. Treat only active cases; detect them only passively	(1) Offer LTBI treatment to TB2s or TB4s, or (2) send letters to improve evaluation	Send letters (2.7 QALYs gained, $10 000 in net savings)
2. Send letters; treat active cases	(1) Offer LTBI treatment to TB2s, (2) Offer LTBI treatment to TB4s, or (3) make phone calls to improve evaluation rates	Treat TB4s (3.2 QALYs gained, $11 000 in net savings)
3. Treat active cases and TB4s; improve evaluation by letters	(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	Improve starting rates (1.3 QALYs saved, $1 800 in net savings)
4. Treat active cases and TB4s; improve evaluation rates by letters; improve starting rates	(1) send letters to improve evaluation rates further, (2) treat TB2s, or (3) improve completion rates by DOPT	Treat TB2s (0.7 QALYs saved, $3 000 in net cost)
5. Treat active cases, TB2s, and TB4s; improve evaluation by letters; improve rates of starting therapy	(1) Further improve evaluation rates by phone calls, or (2) improve rates of completing therapy (by targeted DOPT)	Phone calls (0.5 QALYs saved, approximately $1 000 in net savings)
6. Treat active cases, TB4s, and TB2s; improve evaluation by letters and phone calls	(1) Further improve evaluation rates by home visits, or (2) improve rates of completing therapy by using targeted DOPT	Home visits (0.3 QALYs saved, approximately $1 000 in net cost)
7. Treat active cases, TB4s, and TB2s; improve evaluation by letters and phone calls	(1) improve rates of completing therapy by using targeted DOPT	> $100 000 per QALY saved; no further intervention

Evidence statement 10: Cost-effectiveness of screening, LTBI treatment and DOPT for new entrants

There is good evidence from one (++) study[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.

1 Porco et al., 2006 (++)

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.

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

There is weak evidence from one (–) cost-effectiveness study[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.

1 Berkowitz et al., 2006 (–)

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)

Ref.	QA	Country	Population	Intervention	Methods
Craig et al., 2008	–	UK	Staff in agencies working with people with TB	Social outreach case management with TB link worker	Interviews; focus groups
Wade et al., 2012	+	Australia	Clinical and other staff delivering service; patients with TB	Videophone DOT	Interviews

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 study[1] 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 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.

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7 Appendix A. Evidence tables

7.1 Effectiveness studies

Study Details	Population and setting	Method of allocation to intervention/control	Outcomes and methods of analysis:	Results	Notes
Authors: Batki SL, Gruber VA, Bradley JM, Bradley M, Delucci K **Year:** 2002 **Citation:** 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. **Country of study:** USA **Aim of study:**	**Source population/s:** Drug users accessing methadone treatment in San Francisco **Eligible population:** 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. **Selected population:** 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	**Method of allocation:** Concealed randomization **Intervention/s description:** 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	**Outcomes:** Treatment completion (defined as ≥80% doses taken, measured by observation in intervention groups and by receipt of medication in usual-care group) Duration of therapy (retention) Active TB cases **Follow up periods:** 7 months for completion, 4 years for TB incidence **Method of analysis:** intention-to-treat. Pearson chi-squared. Pearson correlation coefficients for predictors	**Results for all relevant outcomes:** 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 ($p < 0.0001$); no sig diff between Standard MT and Minimal MT. Duration of INH preventive therapy: 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) ($P< 0.0001$). Active tuberculosis cases (4 years after study entry): Non-completers: n=2 of 57	**Limitations identified by author:** 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. **Limitations identified by review team:** Generally robust. Some minor reporting issues. Population may not be widely generalizable. **Evidence gaps and/or recommendations for future research:** Testing DOPT vs methadone, with and without incentives. Different dosing schedules. Cost-effectiveness research.

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:** +	methadone treatment. **Excluded population:** (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. **Sample characteristics:** 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	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. **Control/comparison/s description:** Routine care: Standard referral with self-administered preventive treatment. Methadone not provided, but participants in this group could seek methadone maintenance treatment elsewhere. **Sample sizes:** **Total**: N=111 **Standard MT**: N=37 **Minimal MT**: N=35 **Routine care**: N=39 **Baseline comparisons:** Usual care group significantly older and worse mental health than either intervention group. Otherwise no significant differences w/r/t gender, ethnicity, marital status, education, income, drug/alcohol abuse or other risk factors **Study sufficiently powered?** NR		(3.5%) (n=1 from the minimal MT arm; n=1 from routine care); Completers n=0 of 54. **Results on inequalities:** 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. **Attrition details:** Unclear. Apparently 0 for TB incidence outcome (which was measured by clinic records)	**Source of funding:** National Institute on Drug Abuse

Study Details	Population and setting	Method of allocation to intervention/control	Outcomes and methods of analysis:	Results	Notes
Authors Chaisson RE, Barnes GL, Hackman J, et al.` **Year:** 2001 **Citation:** 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. **Country of study:** USA **Aim of study:** To determine the effect of several interventions on adherence	**Source population/s:** Injecting drug users in Baltimore **Eligible population:** 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 **Selected population:** 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. **Excluded population:** Patients who had active TB; a history of serious adverse reactions to INH; previous INH therapy for 6 months or longer; serum alanine aminotrans-ferase level more than 5 times normal; or HIV disease with CD4 <200/mm. **Sample characteristics:**	**Method of allocation:** Randomisation by computer algorithm. **Intervention/s description:** 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	**Outcomes:** Therapy completion Adherence at 80%, 90% and 100% levels (DOPT group observed, other groups self-report validated by pill count) **Follow up periods:** 6 months **Method of analysis:** intention-to-treat. Chi-square, Fisher's exact, t-test, Wilcoxon rank sum. Log linear model for predictors.	**Results for all relevant outcomes:** Completion: DOPT = 80%; Peer support =78%; Routine care = 79%. DOPT vs. peer support: p = 0.73; DOPT vs. routine care: p = 0.86; Peer support vs. routine care sig NR 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 Took at least 90% of doses: DOPT =80%; Peer support = 51%; Routine care = 77%. DOPT vs. peer support: p <0.001;DOPT vs. routine care: p-value= 0.63; Peer support vs. routine care sig NR Took 100% of the doses: DOPT = 77%; Peer support = 6%; Routine care =10%. DOPT vs. peer support: p <0.001; DOPT vs. routine care: p <0.001; Peer support vs. routine care sig NR Doses taken, as ascertained	**Limitations identified by author:** NR **Limitations identified by review team:** 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. **Evidence gaps and/or recommendations for future research:** More research on promoting adherence and cost-effectiveness, especially using short-course regimens **Source of funding:** National Institute on Drug Abuse; National Institute of Allergy and Infectious Diseases.

to tuberculosis preventive therapy by injection drug users in Baltimore treated at a public tuberculosis clinic. **Study design:** RCT **Quality Score:** ++ **External validity:** +	Age (years, mean SD): Supervised= 41 +/- 7; Peer= 41 +/- 9; Routine= 42 +/- 8 Female sex: Supervised=27%; Peer= 26%; Routine= 27% Black race: Supervised=88%; Peer= 92%; Routine= 91% HIV seropositive: Supervised=18%; Peer= 24%; Routine= 17% Unemployed: Supervised=85%; Peer= 81%; Routine= 88% Less than high school education: Supervised=42%; Peer= 49%; Routine= 53%.	thereafter. 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		by electronic monitoring of pill bottle caps: DOPT = not used; Peer support = 57%; Routine care = 49%; Peer support vs. routine care: p <0.001. Urine testing: DOPT: not used; Peer support: 47% positive; Routine care: 55% positive. Peer support vs routine care: p=0.11 **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	Population and setting	Method of allocation to intervention/control	Outcomes and methods of analysis:	Results	Notes
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	**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:** 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:** 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 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%	**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

Quality Score: – **External validity: –**					

Study Details	Population and setting	Method of allocation to intervention/control	Outcomes and methods of analysis:	Results	Notes
Authors: Goldberg SV, Wallace J, Jackson JC, Chaulk CP, Nolan CM **Year:** 2004 **Citation:** Cultural case management of latent tuberculosis infection. *International Journal of Tuberculosis and Lung Disease 8*(1): 76-82. **Country of study:** USA **Aim of study:** To evaluate the effectiveness of cultural case management for LTBI in refugee populations	**Source population/s:** Refugees in King County, WA, USA **Eligible population:** All refugees newly arriving in King County who presented to Public Health's Refugee Screening Program, with LTBI **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 **Excluded population:** Program had age cut-off of 35; nothing specific to study **Sample characteristics:** Approx 60% male; approx 70% 15-34yo, 12% >34yo, 13%-19% 5-14yo [Note: some inconsistency in age figures, and also don't appear to line up with incl criteria] National origin: pre test former Soviet N=139, former	**Method of allocation:** N/A. Pre-test data comes from historical comparison (post 1999-2000, pre 1996-1998) **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. **Control/comparison/s description:** Standard 'clinic-centered' approach to treatment of LTBI. Refugees reported to TB clinic for test readings and other	**Outcomes:** Treatment start (delivery of initial supply of medication) Treatment completion **Follow up periods:** 9 months **Method of analysis:** chi-square .	**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<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<0.001) (Subgroups. Former Soviet pre 45%, post 76% (p<0.001); former Yugoslavia pre 60%, post 94% (p<0.001); Somalia pre 34%, post 88% (p<0.001); other pre 31%, post 63% (p<0.001) Note: 80% of refugees actually received cultural case management (outcome figures include all participants that started treatment) **Attrition details:** NR	**Limitations identified by author:** Effect might have resulted from broader diffusion in communities, behaviour of other patients and staff. Different individuals pre and post. **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 **Source of funding:** Federal Refugee Program, Annie E Casey Foundation, Firland Foundation, Nesholm Foundation

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			

Study Details	Population and setting	Method of allocation to intervention/control	Outcomes and methods of analysis:	Results	Notes
Authors: Graham NMH, Galai N, Nelson KE, et al. **Year:** 1996 **Citation:** Effect of isoniazid chemo-prophylaxis on HIV-related mycobacterial disease. *Archives of Internal Medicine 156*(8): 889. **Country of study:** USA **Aim of study:** Describe trends in TB and other mycobacterial infections; evaluate the effect of expanded access to isoniazid chemo-	**Source population/s:** Injecting drug users, Baltimore, MD, USA **Eligible population:** Unclear (recruitment from separate study, not described in detail in report of this study) **Selected population:** 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. **Excluded population:** NR **Sample characteristics:** 81% male, 89% Black, 72% injected drugs in month before enrolment, >84% not receiving treatment for drug dependency at enrolment, 24% HIV+	**Method of allocation:** N/A **Intervention/s description:** 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. **Control/comparison/s description:** N/A **Sample sizes:** N=2960 **Baseline comparisons:** N/A **Study sufficiently powered?** NR	**Outcomes:** Incidence of TB and *M. avium* **Follow up periods:** Approx. 2 years at cohort level; unclear at individual level **Method of analysis:** Relative risks	**Results for all relevant outcomes:** 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) **Attrition details:** NR	**Limitations identified by author:** Small sample **Limitations identified by review team:** Non-comparative design; main aim of study is to describe trends rather than evaluate intervention. Limited information on sampling. Very little information on intervention. No adherence/compliance outcome. Outcomes calculated as incidence rates per person-years of treatment, rather than at individual level, and full outcome data are not reported. **Evidence gaps and/or recommendations for future research:** NR **Source of funding:** National Institute on Drug Abuse; Centers for Disease Control and Prevention

prophylaxis on tuberculosis incidence **Study design:** One-group **Quality Score:** – **External validity:** –					

Study Details	Population and setting	Method of allocation to intervention/control	Outcomes and methods of analysis:	Results	Notes
Authors: Jin BW, Kim SC . Mori T, Shimao T **Year:** 1993 **Citation:** The impact of intensified supervisory activities on tuberculosis treatment. *Tubercle and Lung Disease 74*:267-272 **Country of study:** South Korea **Aim of study:** to determine the importance of the motivation of the tuberculosis personnel in improving the results of a treatment programme. **Study design:**	**Source population/s:** Unclear – apparently general population **Eligible population:** 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. **Selected population:** 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. **Excluded population:** NR **Sample characteristics:** Urban 49.8% Initial positive bacteriology 46% Male 68.8% Age <29 years 31.7%, 30-39	**Method of allocation:** Randomisation at level of the subcentres within health centres (methods of randomisation not stated); only post test data reported **Intervention/s description:** In addition to comparator programme, a special type of supervision or motivation was given to the workers. This additional supervision included the closer checking of the workers' tasks by the Health Centre director and the subsection chief, and periodic sessions for discussion of the achievements of each worker held at the Health Centre, sometimes attended by the supervisory medical officer. Note: the details of what the patients actually received is not described, only the process of providing the additional motivation to the staff **Control/comparison/s description:** Staff were instructed to follow the usual case	**Outcomes:** Number of patient examinations Drug collection rates Delayed drug collection Treatment completion Treatment success (conversion rates) **Follow up periods:** NR **Method of analysis:** Student's t-test and chi-square test. The Mantel-Haenszel test was used when comparisons were made with stratification for each group. The basis of the analysis is not given. It appears to be completers rather than ITT	**Results for all relevant outcomes:** Patient examinations: X-rays I 98.0%, C 80.2%; sputum smear and culture I 97.6%, C 70.2% (significance NR) Drug collection rates; I 87.9%, C 77.1% ($p<0.01$) Drug collection delayed by 7 days or more: I 4.7%, C 12.2% ($p<0.01$) Treatment completion: I 78.8%, C 65.2% ($p<0.01$) Treatment success (bacteriological conversion): I 75.2%, C 45.8% ($p<0.01$) Inequalities: For patient examination, greater effect in rural than urban areas; for completion, greater in urban than rural. No significant difference by sex or age. **Attrition details:** N/A – only post test reported	**Limitations identified by author:** NR **Limitations identified by review team:** Details of the treatment the patients were receiving is not described. Details of the source population are not provided. 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 sub centre within the health centre and so staff may have had contact with each other **Evidence gaps and/or recommendations for future research:** NR **Source of funding:** Partly funded by the World Health Organization. Western Pacific Regional Office, Manila.

Randomised controlled trial (cluster randomised) **Quality Score:** – **External validity:** –	years 16.2%, 40-49 years 16.8%, 50-59 years 14.5%, 60 years or more 20.7% Prevous treatment 17.5% [Characteristics of health centre staff (who were the group initially targeted by the intervention) NR]	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			

Study Details	Population and setting	Method of allocation to intervention/control	Outcomes and methods of analysis:	Results	Notes
Authors: MacIntyre CR, Goebel K, Brown GV, Skill S, Starr M, Fullinfaw RO **Year:** 2003 **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. **Country of study:** Australia **Aim of study:** To assess the	**Source population/s:** People under treatment for TB in Victoria, Australia **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). Percentage agreed to participate: NR. **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. **Excluded population:** Patients with MDR-TB; HIV co-infection; non-TB mycobacterial infections **Sample characteristics:** Mean age: 41 years (median 38 years, range 14–83); Sex: 51% male (n=89/73); Countries of birth: Vietnam (29%),	**Method of allocation:** Alternating (i.e. quasi-random) **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. **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. **Sample sizes:** **Total** N=173 **Intervention** N=87	**Outcomes:** Completion of treatment (measured by drug collection) 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) **Follow up periods:** Minimum of 6 months or until treatment was completed **Method of analysis:** Intention-to-treat (but per-protocol also reported)	**Results for all relevant outcomes:** (58% of those allocated to FDOT actually received it (50/87), most due to not having a suitable family member.) Non-completion: I 3.4%, C 9.3% (p=0.11) 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 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<0.05). Non-compliance by electronic pill bottles: 13% of doses missed, not analysed by group Regression analysis shows that employment status or needing an interpreter did not	**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). **Limitations identified by review team:** Generally robust other than limitations noted by authors. Differences in baseline NR. Not true random allocation. **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. **Source of funding:** NR

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 out-patient 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.		significantly predict compliance. **Attrition details:** Unclear	

Study Details	Population and setting	Method of allocation to intervention/control	Outcomes and methods of analysis:	Results	Notes
Authors: Malotte CK, Hollingshead JR, Larro M **Year:** 2001 **Citation:** Incentives vs outreach workers for latent tuberculosis treatment in drug users. *American Journal of Preventive Medicine*, *20*(2):103-107. **Country of study:** USA **Aim of study:** To compare the independent and combined effects of monetary incentives and outreach worker	**Source population/s:** Active drug users (injecting or crack cocaine) with LTBI in Long Beach, California, USA **Eligible population:** Unclear - recruitment via another study. Setting was a 'storefront facility' conducting research and risk-reduction programmes for drug users. **Selected population:** 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 isonazid. **Excluded population:** Participants with active disease or medical contraindications. **Sample characteristics:** 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%	**Method of allocation:** Concealed random allocation in blocks of 18 **Intervention/s description:** 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 Condition 3: Twice weekly DOT at the study community site; and $5 monetary incentive if they appeared for the prescribed doses. **Control/comparison/s description:** As above **Sample sizes:** Total: N=163; condition 1 N=53, condition 2 N=55, condition 3 N=55 **Baseline comparisons:**	**Outcomes:** Treatment completion (participants were counted as non-completers if lost to follow-up) Percentage of medication taken on time **Follow up periods:** 8-12 months **Method of analysis:** ANOVA, chi-square; intention-to-treat	**Results for all relevant outcomes:** Treatment completion c1 52.8%; c2 3.6%; c3 60%. C1 vs c2 p<0.0001; c3 vs c2 p<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<0.001, but unclear what comparison this refers to] No binge drinking and earlier recruited participants associated with increased completion. **Attrition details:** Unclear; dropouts were counted as non-completers	**Limitations identified by author:** NR **Limitations identified by review team:** Generally robust study. Sampling not well-defined in this report. **Evidence gaps and/or recommendations for future research:** NR **Source of funding:** National Institute of Drug Abuse.

provision of DOT (for LTBI) treatment in a sample of active drug users. **Study design:** RCT **Quality Score:** ++ **External validity:** +		No statistically significant differences at baseline in demographic or drug use variables **Study sufficiently powered?** NR			

Study Details	Population and setting	Method of allocation to intervention/control	Outcomes and methods of analysis:	Results	Notes
Authors: Matteelli A, Casalini C, Raviglione MC, et al. **Year:** 2000 **Citation:** Supervised preventive therapy for latent tuberculosis infection in illegal immigrants in Italy. *American Journal of Respiratory and Critical Care Medicine 162*(5):1653-1655. **Country of study:** Italy **Aim of study:** To conduct a comparative prospective study to assess adherence to one supervised,	**Source population/s:** 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). **Eligible population:** Unclear. No details on recruitment or percentage agreed to participate **Selected population:** 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 >10 mm 72 h after intradermal injection of 5 international units of PPD. **Excluded population:** Exclusion criteria included pregnancy, age older than 35 yr, and liver enzymes (AST, ALT) five times or more than the upper normal values.. **Sample characteristics:** Male	**Method of allocation:** Random by randomization list **Intervention/s description:** Regimen A: Supervised isoniazid (900 mg twice weekly) for 6 months. Subjects were invited to report twice weekly to the clinical service sites (either the tuberculosis clinic or the clinic for migrants) to collect the drugs [NB it is unclear how this was 'supervised IPT']. Drugs were free to patients **Control/comparison/s description:** Regimen B: Unsupervised isoniazid 900 mg twice weekly for 6 months Regimen C: Unsupervised isoniazid regimen of 300 mg daily for 6 months; standard treatment. **Sample sizes:** **Total** N=208 **Regimen A**: n=82 patients **Regimen B**: n=73 patients **Regimen C**: n=53 patients **Baseline comparisons:**	**Outcomes:** Completion of treatment (defined as 80% or more of the prescribed medications taken over 26 weeks; measured by reporting to sites and returned medication for group A, and by urine testing for groups B and C). Time to dropout **Follow up periods:** 26 weeks **Method of analysis:** t-test; chi-square; for time to dropout, survival analysis using Kaplan-Meier plot	**Results for all relevant outcomes:** Treatment completion: Regimen A: 7.3%; Regimen B: 26%; Regimen C: 41% (A vs B p=0.006; A vs C p=0.001; B vs C significance NR) Mean time to dropout: Regimen A 3.8 weeks, Regimen B 6 weeks, Regimen C 6.2 weeks (p=0.003, although unclear which comparison this refers to) Adherence was not associated with study site, patient's sex or age, country of origin, alcohol/drug use, marital status, employment status or religion. **Attrition details:** N=127 lost to follow-up (61.1%)	**Limitations identified by author:** Small sample size. **Limitations identified by review team:** Recruitment and sampling not well-defined. Very little detail on intervention content, and unclear whether 'super-vised' is an accurate description of intervention arm **Evidence gaps and/or recommendations for future research:** Efficacy of short-term multidrug regimens delivered through outreach DOPT to illegal immigrants **Source of funding:** Italian Tuberculosis Project of the Istituto Superiore di Sanità.

medical service based, twice weekly regimen of isoniazid in illegal migrants in Northern Italy. **Study design:** RCT **Quality Score:** – **External validity:** –	sex- Regimen A: 48 (58.5%); Regimen B: 48 (65.7%); Regimen C: 32 (60.3%) Age 15-24yr- Regimen A: 26 (31.7%); Regimen B: 22 (30.2%); Regimen C: 16 (30.2%) Age 25-35yr- Regimen A: 56 (68.3%); Regimen B: 51 (69.8%); Regimen C: 37 (69.8%) Country of Origin – Africa- Regimen A: 60 (73.2%); Regimen B: 50 (68.5%); Regimen C: 37 (69.8%) Country of Origin – Other- Regimen A: 22 (26.8%); Regimen B: 23 (31.5%); Regimen C: 17 (32%)	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.			

Study Details	Population and setting	Method of allocation to intervention/control	Outcomes and methods of analysis:	Results	Notes
Authors: Narita M, Kellman M, Franchini DL, McMIllian ME, Hollender ES, Ashkin D **Year:** 2002 **Citation:** Short-Course Rifamycin and Pyrazinamide treatment for latent tuberculosis infection in patients with HIV infection: The 2-Year experience of a comprehensive community-based program in Broward County, Florida. *Chest 122*(4):1292-1298. **Country of study:** USA	**Source population/s:** HIV infected patients in Broward County, Florida community HIV clinics **Eligible population:** 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. **Selected population:** 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. **Excluded population:** NR **Sample characteristics:** Mean age pre 38, post 42 Male 57% pre, 67% post Black 90% pre, 83% post	**Method of allocation:** N/A. Pre-test data come from retrospective cohort **Intervention/s description:** Pre: self-administered therapy (isoniazid). Post: twice-weekly DOT observed by clinic staff (rifamycin and pyrazinamide) **Control/comparison/s description:** N/A **Sample sizes:** Post N=135 Pre N=93 **Baseline comparisons:** N/A **Study sufficiently powered?** NR	**Outcomes:** Treatment completion (defined as drug collection for pre group) **Follow up periods:** 24 months at individual level **Method of analysis:** t-test, Mann-Whitney rank sum test, Fisher exact test	**Results for all relevant outcomes:** Treatment completion pre 61%, post 93% ($p<0.001$) **Attrition details:** Pre 5%; post 17% at 12 months, 53% at 24 months (individual level; N/A at cohort level)	**Limitations identified by author:** 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. **Limitations identified by review team:** Non-comparative design. Main focus of study is not on DOT and there is limited information on it. **Evidence gaps and/or recommendations for future research:** NR **Source of funding:** NR

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:** +					

Study Details	Population and setting	Method of allocation to intervention/control	Outcomes and methods of analysis:	Results	Notes
Authors: Nyamathi AM, Christiani A, Nahid P , Gregerson P, Leake B. **Year:** 2006 **Citation**: A randomized controlled trial of two treatment programs for homeless adults with latent tuberculosis infection. *International Journal of Tuberculosis and Lung Disease* *10*(7):775–782 (linked paper: Nyamathi et al 2008, *Nursing Research* *57*(1):33-39) **Country of study:** Los Angeles, US	**Source population/s:** homeless adults residing in the Skid Row region of Los Angeles, US from 1998 to 2003 **Eligible population:** People attending homeless emergency and residential recovery shelters; recruited by flyers at intervention sites **Selected population:** 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 **Excluded population:** None **Sample characteristics:** 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	**Method of allocation:** Random allocation (details NR) by site, stratified by type, stability of population, and size **Intervention/s description:** 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.	**Outcomes:** Treatment completion (directly observed) TB knowledge **Follow up periods:** 6 months **Method of analysis:** Wilcoxon two-sample test; chi-square; t-test; logistic regression for modelling predictors	**Results for all relevant outcomes:** Treatment completion: I 61.5%, C 39.3% (p<0.01) TB knowledge improvement: I 3.8±3.5, C 2.0±4.2 (p<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<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) Unadjusted results of treatment completion	**Limitations identified by author:** Cannot identify precise contributions of different intervention components; may be bias in self-report outcomes **Limitations identified by review team:** Generally robust. Some minor limitations in methods; cluster randomisation not taken into account in analysis; some unclarity on recruitment of sites **Evidence gaps and/or recommendations for future research:** Additional studies are needed to assess cost effectiveness, program portability, and the feasibility of using lay personnel. **Source of funding:** The National Institute on Drug Abuse

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)			

Study Details	Population and setting	Method of allocation to intervention/control	Outcomes and methods of analysis:	Results	Notes
Authors: Rüütel K, Loit HM, Sepp T, Kliiman K, McNutt LA, Uusküla A **Year:** 2011 **Citation:** Enhanced tuberculosis case detection among substitution treatment patients: a randomized controlled trial. *BMC Research Notes 4*(1), 192. **Country of study:** Estonia **Aim of study:** To evaluate a case manage-ment inter-vention aimed at increasing tuberculosis screening and treatment entry among injecting	**Source population/s:** Drug users in Estonia **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. **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. **Excluded population:** NR **Sample characteristics:** 64.9% male, mean age 26.2 (83.9% <30), 9.8% Estonian ethnicity	**Method of allocation:** Randomization conducted by study nurses **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). **Control/comparison/s description:** Passive referral. Instructed to schedule an appointment with TB services themselves. **Sample sizes:** **Total** N=112 **Intervention** N=56 **Control** N=56 **Baseline comparisons:** No sig differences w/r/t	**Outcomes:** Attendance at TB services **Follow up periods:** 2 months **Method of analysis:** Wilcoxon rank-sum test or Fisher exact test; univariate and multivariable logistic regressions.	**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 **Attrition details:** NR	**Limitations identified by author:** Small sample recruited from one centre, and low response rate, may limit generalizability **Limitations identified by review team:** None to add to authors'. **Evidence gaps and/or recommendations for future research:** Methods for screening among IDUs not in contact with harm reduction services. **Source of funding:** National Institute for Health Development, Estonia; European Commission; National HIV/AIDS Strategy; National Tuberculosis Control Program; Estonian Ministry of Education and Research; New York State International Training and Research Program; National Institutes of Health; Fogarty International Center; National Institute on Drug Abuse.

drug users referred from a methadone drug treatment program. **Study design:** RCT **Quality Score:** ++ **External validity:** +		gender, age, ethnicity, education, employment, TB exposure, or risk factors **Study sufficiently powered?** NR			

Study Details	Population and setting	Method of allocation to intervention/control	Outcomes and methods of analysis:	Results	Notes
Authors: Sterling TR, Villarino ME, Borisov AS, et al. **Year:** 2011. **Citation:** Three months of rifapentine and isoniazid for latent tuberculosis infection. *New England Journal of Medicine 365*(23):2155-2166. **Country of study:** USA, Canada, Brazil, Spain **Aim of study:** To evaluate rifapentine plus isoniazid compared to isoniazid alone **Study design:** Randomised controlled trial	**Source population/s:** People at high risk of TB in USA, Canada, Brazil and Spain **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. **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 **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	**Method of allocation:** Simple randomization (by household for those recruited and treated by household, individually for others) **Intervention/s description:** DOT using combination therapy (rifapentine and isoniazid once weekly). No information on context or delivery of DOT. **Control/comparison/s description:** Self-administered treatment using isoniazid only (daily). **Sample sizes:** **Total** N=7,731 **Intervention** N=3,986 **Control** N=3,745 **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 **Study sufficiently powered?** Yes. A sample	**Outcomes:** Treatment completion Incidence of TB Death **Follow up periods:** 33 months **Method of analysis:** Chi-square. Both intention-to-treat and per-protocol analyses conducted.	**Results for all relevant outcomes:** Treatment completion: I 82.1%, C 69.0% (p<0.001) 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) 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) Death: C 0.8%, I 1.0% (p=0.22) **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.	**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. **Limitations identified by review team:** Sampling and recruitment unclear. Study authors conceptual-ize the comparison as between two drug regimens rather than between DOT and SAT. **Evidence gaps and/or recommendations for future research:** NR **Source of funding:** Centers for Disease Control and Prevention (CDC)

Quality Score: + **External validity:** –	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

Study Details	Population and setting	Intervention/ comparator	Outcomes and methods of analysis:	Results	Notes
Authors: Berkowitz FE, Severens JL, Blumberg HM **Year:** 2006 **Citation:** Exposure to tuberculosis among newborns in a nursery: decision analysis for initiation of prophylaxis. *Infection Control and Hospital Epidemiology, 27*(6): 604-611 **Aim of study:** "to use decision analysis to examine whether administration of isoniazid prophylaxis against tuberculosis would be preferable to no administration of prophylaxis in a situation in which infants had a low probability of acquiring	**Source population/s:** [NB this is a pure modelling study rather than an economic evaluation – the intervention, population and setting are hypothetical.] Neonates **Setting:** Hospital nursery **Data sources:** All from the literature **Sample characteristics:** NR	**Intervention/s description:** 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 **Comparator/control/s description:** Isoniazid administered by parents 7 days/week No intervention (each arm is compared to no prophylaxis) **Sample sizes:** N/A	**Outcomes:** Cost per death prevented **Time horizon:** 4 years **Discount rates:** 5% **Perspective:** Healthcare system **Measures of uncertainty:** Probability of infection, of progress to disease, of death, of hepatotoxicity (adverse effect), of death from hepatotoxicity **Modelling method:** Decision tree model incorporating: Probability of infection Probability of disease given infection Effect of DO and non-DO prophylaxis Survival	**Primary analysis:** 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 **Secondary analysis:** 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	**Limitations identified by author:** Only survival and death taken into account, not e.g. impairment as a result of tuberculous meningitis, or costs of litigation [*sic*]. **Limitations identified by review team:** 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. **Evidence gaps and/or recommendations for future research:** Data on probability of infection, of hepatotoxicity

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

Study Details	Population and setting	Intervention/ comparator	Outcomes and methods of analysis:	Results	Notes
Authors: Burman WJ, Dalton CB, Cohn DL, Butler JRG, Reves RR **Year:** 1997 **Citation:** A cost-effectiveness analysis of directly observed therapy vs self-administered therapy for treatment of tuberculosis. *Chest 112*(1):63-70. **Aim of study:** To compare the costs and effectiveness of directly observed therapy (DOT) vs self-administered therapy (SAT) for the treatment of active tuberculosis **Type of economic analysis:** cost-effectiveness	**Source population/s:** A hypothetical cohort of 100 patients with active tuberculosis **Setting:** Health service **Data sources:** Retrospective data from Denver Metro Tuberculosis Clinic, unpublished data from Denver General Hospital, Medical Consumer Price Index, literature **Sample characteristics:** NR	**Intervention/s description:** The DOT treatment arm uses the "Denver regimen," a 62-dose, largely intermittent regimen of isoniazid, rifampin, pyrazinamide, and streptomycin. DOT delivered by nurses, either on outpatient basis in specialist clinic, or in patients' homes. **Comparator/control/s description:** 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. **Sample sizes:** **Total** 100 **Intervention** 100 **Control** N/A	**Outcomes:** Average net cost **Time horizon:** None for model itself; 6-24 months considered for some probabilities **Discount rates:** 0%, 5% and 8% considered **Perspective:** programme and healthcare system **Measures of uncertainty:** One-way threshold analysis of a number of parameters **Modelling method:** Decision tree	**Primary analysis:** Programme perspective: DOT net costs US$1,405, SAT $2,314 per patient treated (=relative cost saving from DOT of $909) 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) 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). **Secondary analysis:** Threshold analysis calculate values required for SAT to overturn DOT's advantage. Cost of medications used for	**Limitations identified by author:** 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. **Limitations identified by review team:** Model is very simplified. Effect and baseline data from programme only. **Evidence gaps and/or recommendations for future research:** Effectiveness and cost-effectiveness of DOT in developing countries **Source of funding:** NR

Economic perspective: programme and healthcare system **Quality score:** + **Applicability:** +				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 ($): model=7662, TBp=n/a, hc=not found Cost of hospitalization for a MDR treatment failure ($): model=15740, TBp=n/a, 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	

Study Details	Population and setting	Intervention/ comparator	Outcomes and methods of analysis:	Results	Notes
Authors: Gourevitch MN, Alcabes P, Wasserman WC, Arno PS **Year:** 1998 **Citation:** 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 **Aim of study:** To define whether costs associated with directly observed preventive therapy (DOPT) of tuberculosis are justified by cases and costs of tuberculosis prevented among persons at high risk for active disease. **Type of**	**Source population/s:** Drug users enrolled in a methadone maintenance treatment program in the Bronx, New York **Setting:** Drug treatment programme which provides comprehensive medical services **Data sources:** Literature, clinic records **Sample characteristics:** HIV-seropositive (n=159): Male 58%; Hispanic 69%, Black 16%, White 14%, Other race 1%; PPD+ve 16%; anergic 37%; PPD-ve (non-anergic) 47%. HIV-seronegative (n=348): Male 59%; Hispanic 66%, Black	**Intervention/s description:** 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+). **Comparator/control/s description:** Implicitly, self-administered therapy **Sample sizes:** **Total** N=507 (screening); N=151 (chemoprophylaxis) **Intervention** As above **Control** N/A	**Outcomes:** Net cost savings per patient receiving chemoprophylaxis **Time horizon:** 5 years **Discount rates:** 3% **Perspective:** programme **Measures of uncertainty:** INH (isoniazid) effectiveness, TB prevalence, TB hazard in HIV-seropositive PPD+ve. HIV prevalence, TB cases in HIV-seropositive anergics, inclusion of outpatient costs, inclusion of multi-drug resistance costs **Modelling method:** Not explicitly reported, seems like a discrete-time	**Primary analysis:** 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.) **Secondary analysis:** Figures are calculated, denoting money saved per TB case prevented. Base model: $398295/11=$36209 Lower TB prevalence (PPD prevalence drop from 16% and 29%, to 10% and 15% respectively for HIV sero+ve and –ve patients): $333645/9=$37072 TB hazard in HIV-seropositive PPD+ve halved: $283012/8=$35376.5 (lower	**Limitations identified by author:** 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. **Limitations identified by review team:** 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. **Evidence gaps and/or**

economic analysis: Cost-effectiveness **Economic perspective:** programme **Quality score:** – **Applicability:** +	15%, White 19%, Other race 1%; PPD+ve 29%; anergic 6%; PPD-ve (non-anergic) 66%.		compartmental model	than baseline) Lower prevalence of HIV infection (drop from 31% to 5%): $117096/4=$29274 (lower than baseline) No TB in HIV-seropositive anergic: $244584/7=$34941 (lower than baseline) Include out-patient costs ($3009.90): $431395/11=$39218 Include multi-drug resistance costs (13 cases at a cost of $100000 per case): $498370/11=$45306.36	**recommendations for future research:** Applicability of model to other settings; effect of diminishing TB incidence on outcomes; cost-effectiveness of prevention compared with case finding and treatment **Source of funding:** National Institute of Drug Abuse, NY State AIDS Institute, and New York City Department of Health

Study Details	Population and setting	Intervention/ comparator	Outcomes and methods of analysis:	Results	Notes
Authors: Holland DP, Sanders GD, Hamilton CD, Stout JE **Year:** 2009 **Citation:** Costs and Cost-effectiveness of Four Treatment Regimens for Latent Tuberculosis Infection. *American Journal of Respiratory and Critical Care Medicine 179:*1055–1060 **Aim of study:** To evaluate the costs and cost-effectiveness of regimens for the treatment of LTBI **Type of economic analysis:** Cost-effectiveness	**Source population/s:** hypothetical cohort, no information on source **Setting:** NR **Data sources:** Most from literature, some from other programme records **Sample characteristics:** Recent contacts of infectious TB cases; average age 39 years.	**Intervention/s description:** (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 **Comparator/control/s description:** No treatment **Sample sizes:** N/A	**Outcomes:** Net costs; cost per QALY **Time horizon:** None for model itself; some outcomes considered up to 9 months **Discount rates:** 3% **Perspective:** Not explicitly stated, appears to be healthcare perspective **Measures of uncertainty:** One-way sensitivity analyses on Risk of TB, Adherence, Efficacy, Toxicity and Costs **Modelling method:** Markov	**Primary analysis:** 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 ICERs: 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 **Secondary analysis:** [Detailed quantitative data not provided for sensitivity analyses, mostly reported verbally] Risk of TB. 2x risk: 4R (SAT) and 3HP (DOT) dominate; 3HP more CE thean 4R at $20,099 per QALY. 5.2x risk: 3HP (DOT) dominates. 10x risk: 3HP (DOT) cost-saving wrt 9H (SAT) Adherence: 4R (SAT) dominates all except 3HR	**Limitations identified by author:** Limited data on efficacy and adherence for 3HP. **Limitations identified by review team:** 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). **Evidence gaps and/or recommendations for future research:** NR **Source of funding:** NR

Economic perspective: Not explicitly stated, appears to be healthcare perspective **Quality score:** – **Applicability:** +				(DOT) if completion >54% for 4R; 3HP (DOT) if both SAT regimens have low compliance (<34% for 9H, <37% for 4R) Efficacy: [only SAT regimens considered] Toxicity: not sensitive to changes in toxicity rates Costs: if DOT <$1.00/dose, 3HP (DOT) dominates 4R (SAT). [Analysis on drug costs not considered here.]	

Study Details	Population and setting	Intervention/ comparator	Outcomes and methods of analysis:	Results	Notes
Authors: Jit M, Stagg HR, Aldridge RW, White PJ, Abubakar I, for the Find and Treat Evaluation Team **Year:** 2011 **Citation:** Dedicated outreach service for hard to reach patients with tuberculosis in London: observational study and economic evaluation. *BMJ 343*:d5376 **Aim of study:** To evaluate the cost-effectiveness of the Find and Treat service from September 2007 to July 2010 in London **Type of economic analysis:** Cost-effectiveness	**Source population/s:** Individuals with active pulmonary tuberculosis screened or managed by the service with record dates between September 2007 and September 2010 **Setting:** Health services **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 **Sample characteristics:** Excluded cases: cases of extrapulmonary tuberculosis, latent tuberculosis, and	**Intervention/s description:** 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 **Comparator/control/s description:** Usual care, i.e. patients who presented to usual TB services of their own accord **Sample sizes:** **Total:** N=668 **Intervention:** 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) **Control:** N=252	**Outcomes:** Cost per QALY **Time horizon:** 5 years **Discount rates:** 3.5% **Perspective:** "healthcare taxpayer" **Measures of uncertainty:** 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 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	**Primary analysis:** £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 **Secondary analysis:** Increased mobile screening unit costs: F&T=£6,700/QALY, mobile screening=£20,000, case management=£4,100; Increased treatment costs: F&T=£7,600, mobile screening=£18,000, case management=£5,600; Improved QoL for untreated TB and poor QoL for treated TB: F&T=£6,500, mobile screening=£19,000, case management=£4,200; Asymptomatic mobile screening unit cases do not always progress to symptomatic disease: F&T=£6,500, mobile screening=£22,000, case management=£4,100; Cases referred to F&T for enhanced cases management have lower rate of loss to follow-up than those not referred: F&T=£7,100, mobile	**Limitations identified by author:** Absence of a trial randomising TB cases to be either managed or not managed by the F&T service. Methods used for modelling do not fully capture the benefits of the F&T service (because transmission not taken into account). Did not measure the effect of the F&T service on reducing the likelihood of patients developing and transmitting acquired drug resistance (as a result of poor treatment adherence) **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.) **Evidence gaps and/or recommendations for future research:** Point of care testing within

Economic perspective: "healthcare taxpayer" **Quality score:** + **Applicability:** ++	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.		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%) **Modelling method:** discrete, multiple age cohort, compartmental model	screening=£18,000, case management=£4,600; Case referred to F&T service for loss to follow-up could passively re-engage with treatment: F&T=£7,500, mobile screening=£18,000, case management=£4,700. Combination of all most unfavourable components: F&T £10,000/QALY, mobile screening £26,000, case management £6,800	community outreach settings; community-based delivery of treatment; randomised trial of F&T service **Source of funding:** English Department of Health, MRC, NIHR

Study Details	Population and setting	Intervention/ comparator	Outcomes and methods of analysis:	Results	Notes
Authors: Migliori, GB, Ambrosetti M, Besozzi G, et al. **Year:** 1999 **Citation:** Cost-comparison of different manage-ment for tuberculosis patients in Italy. *Bulletin of the World Health Organization* *77*(6): 467–476 **Aim of study:** To perform an economic analysis of changes to TB management policies in Italy **Type of economic analysis:** Cost-comparison **Economic perspective:** Two perspectives used: social perspective and health perspective	**Source population/s:** 41 TB-reporting units in Italy; no further information **Setting:** 17 outpatient units, 10 inpatient units, 14 in- and outpatient units. **Data sources:** Questionnaires collected from the units **Sample characteristics:** not described. 15 centres were in the North, 13 in the Centre and 13 in the South and the Islands	**Intervention/s description:** 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. **Comparator/control/s description:** 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. To each of these scenarios different provision of DOT was assumed (1) No DOT, (2) DOT no additional staff (3) DOT + additional staff + no incentives (4) DOT no additional staff + incentives (5) DOT additional	**Outcomes:** Cost per case cured **Time horizon:** 1 year **Discount rates:** None **Perspective:** Health; social **Measures of uncertainty:** 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	**Primary analysis:** 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 / 11438 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.] **Secondary analysis:** Test Positive, scenario 1: For no DOT the range was	**Limitations identified by author:** 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. **Limitations identified by review team:** 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. **Evidence gaps and/or recommendations for future research:** NR **Source of funding:** Istituto Superiore di Sanità, Rome

Quality score: – **Applicability:** +		staff and incentives. Incentives were the provision of a meal and 5 US dollars. Smear positive and smear negative were also analysed seperately. 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"]	

Study Details	Population and setting	Intervention/ comparator	Outcomes and methods of analysis:	Results	Notes
Authors: Moore RD, Chaulk P, Griffiths R, Cavalcante S, Chaisson RE **Year:** 1996 **Citation:** 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 **Aim of study:** To compare 3 alternative strategies for a 6 month course of treatment for tuberculosis; DOT, self administered fixed-dose combination durg therapy and self-administered conventional individual drug therapy.	**Source population/s:** (hypothetical cohort) No information on population; cost data taken from population under TB treatment in Baltimore **Setting:** NR; costs include an assumption of one on-site TB clinic visit and 50 subsequent outreach visits **Data sources:** 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. **Sample characteristics:** NR	**Intervention/s description:** DOT included one on-site visit and 50 subsequent patient outreach visits (drug regimen was rifampin, ethambutol, pyrazinamide). Observed by nurse, for 6 months **Comparator/control/s description:** Self administered individual conventional = isoniazid, rifampin, ethambutol, pyrazinamide – 6 months Self administed fixed dose combination = rifater, rifamate, ethambutol, isoniazid – 6 months **Sample sizes:** NR	**Outcomes:** Cost per relapse averted and Cost per life saved **Time horizon:** Unclear (relapse rates assume 2-year window) **Discount rates:** 4% **Perspective:** 'urban public health' **Measures of uncertainty:** 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	**Primary analysis:** Cost per relapse averted $17,305 for conventional $15,446 for fixed dose $14,378 for DOT Cost per life saved $15,200 for conventional $14,068 for fixed dose $13,966 for DOT **Secondary analysis:** 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	**Limitations identified by author:** 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. **Limitations identified by review team:** Description of the model is limited. Description of the population and estimates of effect are limited. The effects are not taken from the same sources as the costs drawing instead on the literature. The methods of identifying these effects are not described. **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	fixed dose intervention 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 probablility 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	**Source of funding:** Supported in part by Marion Merrell Dow, Inc

Study Details	Population and setting	Intervention/ comparator	Outcomes and methods of analysis:	Results	Notes
Authors: Palmer CS, Miller B, Halpern MT, Geiter LJ **Year:** 1998 **Citation:** A model of the cost effectiveness of directly observed therapy for treatment of tuberculosis. *Journal of Public Health Management Practice 4*(3):1-13 **Aim of study:** To compare universal DOT with partial DOT (15%) and no DOT (100% patient responsible therapy) **Type of economic analysis:** Cost-effectiveness **Economic perspective:** Health (direct costs of curative and preventative TB treatment)	**Source population/s:** Hypothetical cohort of 25,000 TB patients using data taken from 178 patient records **Setting:** Outpatient **Data sources:** 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. **Sample characteristics:** Outpatient data from Newark (n=35), San Fransisco (N=86), Los Angeles (n=36), Mississippi (n=21). Males = 73%, White = 32%, US born 58%, mean age 44. Noted to be somewhat	**Intervention/s description:** DOT observed either in clinic or in other site, by a health professional (100%) **Comparator/control/s description:** Partial DOT (15%) No DOT (all 'patient responsible' (i.e. self-administered therapy). Details of DOT or patient responsible therapy not described. The following is noted about the sources of the patient records: 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. **Sample sizes:** **Total:** 178	**Outcomes:** Cost per TB case cured **Time horizon:** 10 years **Discount rates:** 3% **Perspective:** Health **Measures of uncertainty:** 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 **Modelling method:**	**Primary analysis:** 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 **Secondary analysis:** 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	**Limitations identified by author:** 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

Quality score: + **Applicability:** +	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)

Study Details	Population and setting	Intervention/ comparator	Outcomes and methods of analysis:	Results	Notes
Authors: Perlman DC, Gourevitch MN, Trihn C, Salomon N, Horn L, Des Jarlais DC **Year:** 2001 **Citation:** Cost-effectiveness of tuberculosis screening and observed preventative therapy for active drug injectors at a syringe-exchange programme. *Journal of Urban Health 78*(3): 550-67 **Aim of study:** To examine the cost-effectiveness of a screening and DOPT programme, and of incentives to increase adherence **Type of economic analysis:** Cost-effectiveness	**Source population/s:** hypothetical cohort of 1000 patients, based on the characteristics of people visiting a needle exchange programme in New York City, USA. **Setting:** needle exchange centre **Data sources:** Most from records collected at the needle exchange. Treatment effect of DOPT taken from Gourevitch 1998, which itself appears to be assumption. Drug efficacy from literature **Sample characteristics:** These are the characteristics of the 974 people at the needle exchange agreeing to TB screening. Male 67%,	**Intervention/s description:** 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. **Comparator/control/s description:** No intervention **Sample sizes:** 1000 (offered screening); 175 (receive DOPT) [hypothetical cohort]	**Outcomes:** Cost per case of TB averted; net cost savings **Time horizon:** 3 years, 5 years **Discount rates:** None **Perspective:** healthcare (implicitly) **Measures of uncertainty:** Sensitivity analyses varying the decrees of INH effectiveness and CXR referral adherence and as a function of the role of anergy in TB incidence. Further, one scenario ignored anergy, the second included testing for anergy and assumed that HIV infected anergic patients had a moderately increased risk of developing TB (but no DOPT), the third	**Primary analysis:** 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	**Limitations identified by author:** Uncertainties in input data; otherwise NR **Limitations identified by review team:** 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) **Evidence gaps and/or recommendations for future research:** NR **Source of funding:** National Institute on Drug Abuse. New York City Department of Health (intervention costs)

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 a 'analysed in a relational database' (Paradox, Borland).	savings $123.081 **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	

Study Details	Population and setting	Intervention/ comparator	Outcomes and methods of analysis:	Results	Notes
Authors: Porco TC, Lewis B, Marseille E, Grinsdale J, Flood JM, Royce SE **Year:** 2006 **Citation:** Cost-effectiveness of tuberculosis evaluation and treatment of newly-arrived immigrants. *BMC Public Health* *6*:157 **Aim of study:** To evaluate the cost-effectiveness of domestic follow-up of suspected LTBI cases among new immigrants to California **Type of economic analysis:** Cost-effectiveness **Economic perspective:** 'Domestic all-payer'	**Source population/s:** [NB hypothetical cohort rather than evaluation data.] Immigrants to California with LTBI ('TB4') or inactive TB ('TB2') **Setting:** Health services **Data sources:** Most from the literature; cost data from Medi-Cal reimbursement standards **Sample characteristics:** No info, other than clinical characteristics	**Intervention/s description:** 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) **Comparator/control/s Description:** None as such, but a range of different programme components considered – see Table 9 **Sample sizes** N/A; hypothetical cohort N=1000	**Outcomes:** Cost/QALY **Time horizon:** 20 years **Discount rates:** 3% (5% considered in sensitivity analysis) **Perspective:** 'Domestic all-payer' **Measures of uncertainty:** Sensitivity analysis on a range of combinations of screening rate, starting (uptake) rate, and completion rate; also on treatment delay, screening delay, % active cases, % baseline smear-positive, transmission rates, hospitalization rates, reactivation rates, cost multipliers, DOT costs, TST specificity, % INH resistance, risk multiplier for	**Primary analysis:** Screening programme yields net cost saving of US$25,000, and yielded 7.7 net QALYs The results regarding programmes to improve the efficiency of the programme (Table 9) show that most CE intervention component is sending letter reminders (2.7 QALYs, save $10,000); next is to treat people with inactive TB (3.2 QALYs, save $11,000); next is to improve starting rates for preventive therapy (although unclear what this means in practice) (1.3 QALYs, save $1,800); next is to treat people with inactive TB (0.7 QALYs, cost $3,000); next is to improve evaluation rates by phone calls (0.5 QALYs, save $1,000); next is to improve evaluation rates by home visiting (0.3 QALYs, cost $1,000); and only then to use targeted DOT to improve completion rates (>$100,000 per QALY saved). **Secondary analysis:** Full three-way analysis on	**Limitations identified by author:** 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. **Limitations identified by review team:** 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 **Evidence gaps and/or recommendations for future research:** NR **Source of funding:** Centers for Disease Control and Prevention

(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 **Modelling method:** Continuous time, discrete event model	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	

				QALYs, save $24,000 TST specificity 0.875 (reference 0.99): 7.6 QALYs, save $21,000 Fraction INH resistant 0.2 (reference (0.13): 6.7 QALYs, save $16,000 Risk multiplier for severe hepatitis 3x more: 7.6 QALYs, save $17,000 Disutility for hepatitis hospitalization 0.9 (reference 0.4): 8.0 QALYs, save $23,000 Disutility for outpatient hepatitis 0.5 (reference 0.265): 8.0 QALYs, save $24,000 Disutility for other INH side-effects 0.2 (reference 0.1): 7.4 QALYs, save $22,000 Disutility for untreated TB 0.2 (reference 0.1): 9.0 QALYs, save $22,000 QALY loss from one month INH 0.01 (reference 0): lose 16 QALYs, save $22,000 Disutility multiplier for TB hospitalization 0.5 (reference 1): 7.9 QALYs, save $24,000 Disutility multiplier for outpatient TB 0.5 (reference 1): 8.3 QALYs, save $21,000 Discount rate 5% (reference 3%): 5.9 QALYs, save $16,000 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%	

Study Details	Population and setting	Intervention/ comparator	Outcomes and methods of analysis:	Results	Notes
Authors: Snyder DC, Chin DP **Year:** 1999 **Citation:** 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 **Aim of study:** 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) **Type of economic analysis:** Cost-effectiveness	**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 **Setting:** TB services **Data sources:** Retrospective cohort study for population data; previous cost-effectiveness analysis for treatment effect	**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 **Comparator/control/s description:** Self-administered therapy daily for 24wk **Sample sizes:** **Total** N=1,377	**Outcomes:** Cost per patient treated, per patient cured **Time horizon:** Effects estimated with reference to 2-year horizon (time horizon of model itself unclear) **Discount rates:** 4% **Perspective:** Programme / healthcare system **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 **Modelling method:** Decision tree, 1 time cycle	**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) **Secondary analysis:** SAT probability of default 0%, incremental net cost $51,234 per cure; 40%, net cost saving of $2,160 per cure DOT effectiveness in preventing default 50%, incremental net cost $42,406 per cure; 100%, $39,165 Relapse rate on SAT 6.0%, incremental net cost $11,182; 1.5%, $307,862 Contacts with active disease 0%, $42,158; 1.5%, $39,851 Patients with TB hospitalized 10%, $44,833; 100%, $30,790 Cost of hospitalization for MDR-TB, $20,000, incremental net cost $42,786 per cure; $200,000, $17,371	**Limitations identified by author:** Benefits of DOT not fully measured **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 **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 **Source of funding:** NR

Economic perspective: Programme / healthcare system **Quality score:** – **Applicability:** +	and other transition probabilities; cost data mainly from Medi-Cal reimbursement rates **Sample characteristics:** None reported beyond inclusion criteria				

Study Details	Population and setting	Intervention/ comparator	Outcomes and methods of analysis:	Results	Notes
Authors: Snyder DC, Paz EA, Mohle-Boetani JC, Fallstad R, Black RL, Chin DP **Year:** 1999 **Citation:** Tuberculosis prevention in methadone maintenance clinics: effectiveness and cost-effectiveness. *American Journal of Respiratory and Critical Care Medicine160:* 178-185 **Aim of study:** To evaluate the effectiveness of a DOT programme implemented in a methadone clinic **Type of economic analysis:** Cost-effectiveness **Economic**	**Source population/s:** People attending methadone maintenance clinic in San Francisco **Setting:** Methadone clinic **Data sources:** 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 **Sample characteristics:** 59% M; 58% non-Hispanic white, 27% African-American, 12% Latino, 2% Asian/Pacific Is-lander, 1% other; median age 40 (range	**Intervention/s description:** 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 **Comparator/control/s description:** N/A **Sample sizes:** **Total** N=2689 (total seen by programme); N=417 (commenced preventive therapy)	**Outcomes:** Net cost saving (i.e. cost of DOT programme minus costs of treatment and contact tracing averted) **Time horizon:** 10 years **Discount rates:** 3% **Perspective:** Healthcare system **Measures of uncertainty:** Sensitivity analysis on: rates of hospitalization; completion rates; rates of return for test reading; rates of uptake of preventive therapy; receipt of medical evaluation **Modelling method:** Markov model; 1-year cycles; 4 states (remain well, develop TB and survive, develop TB and die,	**Primary analysis:** 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 **Secondary analysis:** 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	**Limitations identified by author:** Data for model inputs derived from other (i.e. non-IDU) populations **Limitations identified by review team:** Health states not valued in model. No comparison group. Model structure is simple **Evidence gaps and/or recommendations for future research:** NR **Source of funding:** NR

perspective: Healthcare system **Quality score:** + **Applicability:** +	18-77); 63% HIV–, 18% HIV+, 19% unknown HIV status		die of other causes)		

Study Details	Population and setting	Intervention/ comparator	Outcomes and methods of analysis:	Results	Notes
Authors: Wade VA, Karnon J, Eliott JA, Hiller JE **Year:** 2012 **Citation:** Home videophones improve direct observation in tuberculosis treatment: a mixed methods evaluation. *PLoS ONE 7*(11): e50155 **Aim of study:** "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; o determine the acceptability,	**Source population/s:** TB cases commencing treatment at Royal Adelaide Hospital Chest Clinic **Setting:** Hospital specialist TB service **Data sources:** Retrospective cohort study based on clinical records **Sample characteristics:** Video group: 55% M, 45% F; 41% <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% <30 years; 17% African origin, 16% Australian, 9% European, 7% E Asian, 31% SE Asian,	**Intervention/s description:** 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.) **Comparator/control/s description:** In-person 'drive-around' directly observed therapy service delivered by nurses (site unclear, but presumably patients' homes) **Sample sizes:** **Total** N=128 **Intervention** N=58 **Control** N=70	**Outcomes:** Cost per successful observation **Time horizon:** N/A **Discount rates:** N/A **Perspective:** Healthcare system **Measures of uncertainty:** 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 **Modelling method:** Decision tree analysis	**Primary analysis:** 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 **Secondary analysis:** Only reported qualitatively. Number of patients: reduced number makes video service more costly but still favours video; increased number favours video Type of patients: if noncompliance reduced from 25% to 10%, ICER unchanged; if increased to 40%, favours in-person Driving time: 5 mins driving time assumed; any increase favours video Cost of technology: Decreasing cost favours video Staff salaries: Reducing salaries slightly favours in-person Weekend service: Reducing weekend service favours in-	**Limitations identified by author:** 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. **Limitations identified by review team:** Lack of health status outcomes limits usefulness for this review. **Evidence gaps and/or recommendations for future research:** Large-scale RCT of video observation; research on use of mobile technologies

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:** +	20% S Asian; 56% proficient in English			person, increasing favours video Length of service: If in-person service increased to same length of time as video service, video becomes dominant	**Source of funding:** Royal District Nursing Service of South Australia; Australian Government (postgraduate award)

Study Details	Population and setting	Intervention/ comparator	Outcomes and methods of analysis:	Results	Notes
Authors: Weis SE, Foresman B, Matty KJ, et al. **Year:** 1999 **Citation:** 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 **Aim of study:** To compare costs of DOT and 'traditional' (self-administered) therapy **Type of economic analysis:** Cost-comparison **Economic perspective:** Healthcare system	**Source population/s:** All TB cases reported in Tarrant County, Texas, between 1980-1985 (traditional therapy) and 1987-1994 (DOT) **Setting:** TB care services **Data sources:** All based on a retrospective cohort study; data drawn from patient charts and hospital records **Sample characteristics:** Non-DOT group: 24% aged <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 <30; 30% white, 41% black, 19%	**Intervention/s description:** 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.) **Comparator/control/s description:** Limited information; self-administered therapy **Sample sizes:** **Total** N=659 **Intervention** N=402 **Control** N=257	**Outcomes:** Net costs **Time horizon:** N/A (retrospective study) **Discount rates:** N/A (retrospective study) **Perspective:** Healthcare system **Measures of uncertainty:** None **Modelling method:** None – analysis is based purely on descriptive data about service use in the two periods	**Primary analysis:** Total net cost per patient US$11,260 in DOT group, US$27,630 in 'traditional' group **Secondary analysis:** None	**Limitations identified by author:** 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. **Limitations identified by review team:** Purely descriptive analysis; health states are not valued, or projected into the future using modelling **Evidence gaps and/or recommendations for future research:** NR **Source of funding:** NR

Quality score: – **Applicability:** +	Hispanic, 10% Asian; 64% male; 22% foreign-born; 22% history of alcohol abuse; 29% history of drug abuse; 10% HIV+				

Study Details	Population and setting	Intervention/ comparator	Outcomes and methods of analysis:	Results	Notes
Authors: Wilton P, Smith RD, Coast J, Millar M, Karcher A **Year:** 2001 **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 **Aim of study:** To develop an economic model of DOT for MDR-TB **Type of economic analysis:** Cost-effectiveness analysis **Economic perspective:**	**Source population/s:** [Hypothetical cohort and intervention.] Not clearly defined; USA and South Africa (only USA data considered here) **Setting:** Not clearly defined **Data sources:** All from literature **Sample characteristics:** NR	**Intervention/s description:** DOT, not further defined **Comparator/control/s description:** 'Conventional therapy', not further defined **Sample sizes:** N/A	**Outcomes:** Cost savings based on costs of healthcare per patient treated **Time horizon:** Unclear **Discount rates:** None **Perspective:** Healthcare system **Measures of uncertainty:** Second-line drug costs **Modelling method:** Monte Carlo model incorporating cure rates, death rates and probability of progressing to more severe forms of drug-resistance	**Primary analysis:** DOT total mean cost US$18,932 (SD $2,329) 'Conventional therapy' total mean cost US$20,720 (SD $2,070) **Secondary analysis:** DOT remains more cost-effective when protocol regarding resistance to second-line drugs is altered	**Limitations identified by author:** 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. **Limitations identified by review team:** Some concerns regarding reliability and applicability of input data. Very little information on intervention content, esp. comparator. **Evidence gaps and/or recommendations for future research:** Use of Markov modelling to encompass more complex impacts; application of model to other countries **Source of funding:** Global Forum for Health Research, Geneva

Healthcare system **Quality score:** – **Applicability:** +					

7.3 Views studies

Study details	Research parameters	Population and sample selection	Outcomes and methods of analysis Results	Notes by review team
Authors: Craig GM, Booth H, Hall J, et al. **Year:** 2008 **Citation:** Establishing a new service role in tuberculosis care: the tuberculosis link worker. *Journal of Advanced Nursing 61*(4): 413-424. **Quality score:** –	**Report the research questions:** Process evaluation of a social outreach model of care including a link worker to develop collaborative care pathways. **Report theoretical approach:** NR **State how the data were collected:** **What method(s):** Group discussions and interviews, face-to-face or by telephone (for stakeholders; NB patient data is quantitative, so not considered here). **By whom:** NR **What setting(s):** NR **When:** NR	**Report population were the sample recruited from:** Stakeholders with experience of collaborative working from agencies "representative of the type of referrals made by the [link worker] and patients' presenting problems" (p415) **Report how were they recruited:** Written invitation **Report how many participants were recruited:** N=8 individual i/vs (44% response rate), N=1 group i/v (exact total N NR) **State specific inclusion criteria:** NR **State specific exclusion criteria:** NR	**Brief description of methods and process of analysis:** Analysed "in relation to the questions in the interview schedule" using N*Vivo **Key themes relevant to this review:** 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.	**Limitations identified by author:** NR for qualitative aspect of the study **Limitations identified by review team:** 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. **Evidence gaps and/or recommendations for future research:** NR **Source of funding:** King's Fund, The Henry Smith's Charity, The Sir Halley Stewart Trust, The Kirby Laing Foundation, The Adint Charitable Trust.

			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)	

Study details	Research parameters	Population and sample selection	Outcomes and methods of analysis Results	Notes by review team
Authors: Wade VA, Karnon J, Eliott JA, Hiller JE et al. **Year:** 2012 **Citation:** Home videophones improve direct observation in tuberculosis treatment: A mixed methods evaluation. *PLoS ONE* *7*(11):e50155 **Quality score:** +	**Report the research questions:** To investigate the implementation of a videophone DOT intervention, and identify reasons for successful uptake **Report theoretical approach:** NR **State how the data were collected:** **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)	**Report population were the sample recruited from:** Clinicians and other staff involved in delivering the service; patients **Report how were they recruited:** Patients recruited by service staff and then contacted by researcher; staff recruited by email or direct contact **Report how many participants were recruited:** N=44 staff; N=11 patients **State specific inclusion criteria:** Staff: any delivering or associated with the service. Patients: had been receiving service at least 1 month **State specific exclusion criteria:** NR	**Brief description of methods and process of analysis:** Used NVivo for analysis. "Realist" thematic analysis method. Staff reviewed transcripts. **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.	**Limitations identified by author:** Only patients receiving intervention included, not comparison group (in-person DOT). Interpreters not used for patients who did not speak fluent English. **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.	

8 Appendix B: Search annex

Database	Hits
MEDLINE	2189
MEDLINE In Process	173
EMBASE	2886
ASSIA	124
BL Ethos	7
British Nursing Index	191
CINAHL	396
Cochrane Library	204
TRoPHI	0
ERIC	6
HEED	84
HMIC	47
OpenGrey	1
Social Policy and Practice	2
Sociological Abstracts	27
Web of Science	1654
Cochrane CIDG Specialized register	88
Total	**8079**
De-duplication	**-4283**
Unique Records for Screening	**3796**

Search Annex

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

#	Searches	Results
1	(Tuberculosis or TB).ti,ab,kw.	146098
2	exp Tuberculosis/	157772
3	1 or 2	195113
4	*Directly Observed Therapy/	700
5	(DOT$ or (directly observ$ adj3 (therap$ or treat$))).ti,ab,kw.	33781
6	(short$ course$ adj3 (therap$ or treat$)).ti,ab,kw.	2162

7	((observ$ or supervis$ or watch$ or witness$ or see$ or monitor$ or check$) adj3 (therap$ or treat$)).ti,ab,kw.	109079
8	((record$ or report$) adj3 (therap$ or treat$)).ti,ab,kw.	44221
9	or/4-8	185231
10	Case Management/	8381
11	((case or care or treatment) adj3 manage$).ti,ab,kw.	55577
12	((manag$ or support$ or plan$) adj3 care).ti,ab,kw.	60941
13	Managed Care Programs/	23650
14	("patient centered" or "patient centred").ti,ab,kw. or Patient-Centered Care/	14718
15	((Tuberculosis or TB) adj5 (nurs$ or staff or team$ or multidisciplinary or outreach or centre$1 or center$1 or clinic$1)).ti,ab,kw.	2900
16	((case or link) adj3 worker$1).ti,ab,kw.	647
17	("treatment partner" or "treatment supporter").ti,ab,kw.	37
18	"Continuity of Patient Care"/	14553
19	or/10-18	128394
20	9 or 19	311034
21	(uptake or up-take or (up adj1 tak$) or takeup or take-up).ti,ab,kw.	264424
22	(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.	2447803
23	*Medication Adherence/	4269
24	*Patient Compliance/	19401
25	*PATIENT DROPOUTS/	2374
26	*TREATMENT REFUSAL/	5293
27	or/21-26	2689187
28	3 and 20 and 27	2759
29	limit 28 to yr="1993 -Current"	2559
30	limit 29 to english language	2205
31	exp animals/ not humans.sh.	4050082
32	30 not 31	2196
33	(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.	3037295
34	32 not 33	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:

#	Searches	Results
1	(Tuberculosis or TB).ti,ab,kw.	9499
2	exp Tuberculosis/	0
3	1 or 2	9499
4	*Directly Observed Therapy/	0
5	(DOT$ or (directly observ$ adj3 (therap$ or treat$))).ti,ab,kw.	6461
6	(short$ course$ adj3 (therap$ or treat$)).ti,ab,kw.	128
7	((observ$ or supervis$ or watch$ or witness$ or see$ or monitor$ or check$) adj3 (therap$ or treat$)).ti,ab,kw.	6621
8	((record$ or report$) adj3 (therap$ or treat$)).ti,ab,kw.	3317
9	or/4-8	16206
10	Case Management/	0
11	((case or care or treatment) adj3 manage$).ti,ab,kw.	3532
12	((manag$ or support$ or plan$) adj3 care).ti,ab,kw.	3595
13	Managed Care Programs/	0
14	("patient centered" or "patient centred").ti,ab,kw. or Patient-Centered Care/	814
15	((Tuberculosis or TB) adj5 (nurs$ or staff or team$ or multidisciplinary or outreach or centre$1 or center$1 or clinic$1)).ti,ab,kw.	169
16	((case or link) adj3 worker$1).ti,ab,kw.	45
17	("treatment partner" or "treatment supporter").ti,ab,kw.	4
18	"Continuity of Patient Care"/	0
19	or/10-18	6516
20	9 or 19	22501
21	(uptake or up-take or (up adj1 tak$) or takeup or take-up).ti,ab,kw.	14072
22	(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	164094

	drop out$1 or interrupt$ or complet$ or finish$ or (follow$ adj1 up$1) or (miss$ adj2 appointment$1)).ti,ab,kw.	
23	*Medication Adherence/	0
24	*Patient Compliance/	0
25	*PATIENT DROPOUTS/	0
26	*TREATMENT REFUSAL/	0
27	or/21-26	176314
28	3 and 20 and 27	185
29	limit 28 to yr="1993 -Current"	184
30	limit 29 to english language	173
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.	71030
32	30 not 31	173

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:

#	Searches	Results
1	(Tuberculosis or TB).ti,ab,kw.	171381
2	exp tuberculosis/	192490
3	1 or 2	236380
4	*directly observed therapy/	364
5	(DOT$ or (directly observ$ adj3 (therap$ or treat$))).ti,ab,kw.	43277
6	(short$ course$ adj3 (therap$ or treat$)).ti,ab,kw.	2814
7	((observ$ or supervis$ or watch$ or witness$ or see$ or monitor$ or check$) adj3 (therap$ or treat$)).ti,ab,kw.	149954
8	((record$ or report$) adj3 (therap$ or treat$)).ti,ab,kw.	63236
9	or/4-8	253687
10	case management/	7291

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 takeup 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*1))
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
Data Parameters: Not Specified
Date Searched: 15/10/2013
Hits: 8
Search Strategy:

((Tuberculosis or TB) and (DOT)) n=4
((Tuberculosis or TB) and (directly observed therapy)) n=2
((Tuberculosis or TB) and (case management)) n=2

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

Results: 1313°

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: 69693*

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

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

Set#: S22
Searched 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 witness* 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")

S15. ((Tuberculosis or TB) N5 (nurs* or staff or team* or multidisciplinary or outreach or centre*1 or center*1 or clinic*1))
S16. ((case or link) N3 worker*1)
S17. ("treatment partner" or "treatment supporter")
S18. (MH "Continuity of Patient Care")
S19. S10 or s11 or s12 or s13 or s14 or s15 or s16 or s17 or s18
S20. S9 or s19
S21. (uptake or up-take or (up NEAR/1 tak*) or takeup or take-up)
S22. (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))
S23. (MH "Medication Compliance")
S24. (MH "Patient Compliance")
S25. (MH "Patient Dropouts")
S26. (MH "Treatment Refusal")
S27. S21 or s22 or s23 or s24 or s25 or s26
S28. S3 and S20 or S27
S29. Limit to English Language
S30. Limit 1993-2013

Notes: N/A
File Name: CINAHL396.txt

Database: Cochrane Library
Host: The Cochrane Library via http://www.thecochranelibrary.com/view/0/index.html
Data Parameters: CENTRAL: **Issue 9 of 12, Sept 2013; CDSR: Issue 10 of 12, October 2013; DARE: Issue 3 of 4, Jul 2013; NHS EEDS: Issue 3 of 4 Jul 2013; HTA: Issue 3 of 4 Jul 2013; Cochrane Groups: Issue 9 of 12, Sept 2013.**
Date Searched: 15/10/2013
Hits: (CDSR: 45; DARE 11; CENTRAL 112; Methods 3; NHS EEDS 33) 204 hits
Search Strategy:

#1 Tuberculosis or TB:ti,ab,kw (Word variations have been searched) 2869
#2 MeSH descriptor: [Tuberculosis] explode all trees 1539
#3 #1 or #2 2877
#4 MeSH descriptor: [Directly Observed Therapy] this term only 117
#5 (DOT* or (directly observ* near/3 (therap* or treat*))) 2525
#6 (short* course* near/3 (therap* or treat*)) 1674
#7 ((observ* or supervis* or watch* or witness* or see* or monitor* or check*) near/3 (therap* or treat*)) 16831
#8 ((record* or report*) near/3 (therap* or treat*)) 10468
#9 #4 or #5 or #6 or #7 or #8 28359
#10 MeSH descriptor: [Case Management] explode all trees 591
#11 ((case or care or treatment) near/3 manage*) 6082
#12 ((manag* or support* or plan*) near/3 care) 7052

#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 takeup or take-up) 10368
#24 (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)) 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:

Select	Search #	Search	No of hits
	1	Freetext: "((Tuberculosis or TB) and (DOT)) "	0
	2	Freetext: "((Tuberculosis or TB) and (directly observed therapy)) "	0
	3	Freetext: "((Tuberculosis or TB) and (case management)) "	0

Notes: N/A
File Name: N/A

Database: ERIC
Host: ProQuest
Data Parameters: 1966 - current
Date Searched: 15/10/2013
Hits: 6
Search Strategy:

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:

#	Searches	Results
1	(Tuberculosis or TB).ti,ab.	776
2	Tuberculosis.mp.	886
3	1 or 2	905
4	Directly Observed Therap*.mp.	20
5	(DOT$ or (directly observ$ adj3 (therap$ or treat$))).ti,ab.	84
6	(short$ course$ adj3 (therap$ or treat$)).ti,ab.	16
7	((observ$ or supervis$ or watch$ or witness$ or see$ or monitor$ or check$) adj3 (therap$ or treat$)).ti,ab.	817
8	((record$ or report$) adj3 (therap$ or treat$)).ti,ab.	524
9	4 or 5 or 6 or 7 or 8	1375
10	Case Management.mp.	842
11	((case or care or treatment) adj3 manage$).ti,ab.	5194
12	((manag$ or support$ or plan$) adj3 care).ti,ab.	8534
13	Managed Care Programs.mp.	3
14	("patient centered" or "patient centred").ti,ab. or Patient-Centered Care.mp.	1037
15	((Tuberculosis or TB) adj5 (nurs$ or staff or team$ or multidisciplinary or outreach or centre$1 or center$1 or clinic$1)).ti,ab.	38
16	((case or link) adj3 worker$1).ti,ab.	138
17	("treatment partner" or "treatment supporter").ti,ab.	1
18	Continuity of Patient Care.mp.	333
19	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	11045
20	9 or 19	12336
21	(uptake or up-take or (up adj1 tak$) or takeup or take-up).ti,ab.	2587
22	(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.	34162
23	Medication Adherence.mp.	80
24	Patient Compliance.mp.	476
25	PATIENT DROPOUTS.mp.	1
26	TREATMENT REFUSAL.mp.	9
27	21 or 22 or 23 or 24 or 25 or 26	36130
28	3 and 20 and 27	50

29	limit 28 to yr="1993 -Current"	47
30	limit 29 to english	47
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.	1015
32	30 not 31	47

Notes: N/A
File Name: HMIC47.txt

Database: OpenGrey
Host: 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:

#	Searches	Results
1	(Tuberculosis or TB).ti,ab.	139
2	Tuberculosis.mp.	169
3	1 or 2	180
4	Directly Observed Therap*.mp.	4
5	(DOT$ or (directly observ$ adj3 (therap$ or treat$))).ti,ab.	76
6	(short$ course$ adj3 (therap$ or treat$)).ti,ab.	2
7	((observ$ or supervis$ or watch$ or witness$ or see$ or monitor$ or check$) adj3 (therap$ or treat$)).ti,ab.	728
8	((record$ or report$) adj3 (therap$ or treat$)).ti,ab.	580

9	4 or 5 or 6 or 7 or 8	1354
10	Case Management.mp.	1390
11	((case or care or treatment) adj3 manage$).ti,ab.	4541
12	((manag$ or support$ or plan$) adj3 care).ti,ab.	9413
13	Managed Care Programs.mp.	1
14	("patient centered" or "patient centred").ti,ab. or Patient-Centered Care.mp.	179
15	((Tuberculosis or TB) adj5 (nurs$ or staff or team$ or multidisciplinary or outreach or centre$1 or center$1 or clinic$1)).ti,ab.	4
16	((case or link) adj3 worker$1).ti,ab.	266
17	("treatment partner" or "treatment supporter").ti,ab.	0
18	Continuity of Patient Care.mp.	2
19	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	11418
20	9 or 19	12728
21	(uptake or up-take or (up adj1 tak$) or takeup or take-up).ti,ab.	2343
22	(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.	41154
23	Medication Adherence.mp.	84
24	Patient Compliance.mp.	10
25	PATIENT DROPOUTS.mp.	0
26	TREATMENT REFUSAL.mp.	8
27	21 or 22 or 23 or 24 or 25 or 26	43046
28	3 and 20 and 27	2

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
Searched 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
Topic=(((case or care or treatment) near/3 manage*))
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
Topic=((uptake or up-take or (up near/1 tak*) or takeup or take-up))
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 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=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=1993-2013

20
2,641,480
#19 OR #18
Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=1993-2013

21
1,768
#20 AND #17 AND #1
Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=1993-2013

22
1,654
#20 AND #17 AND #1
Refined by: Languages=(ENGLISH)
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