Directly observed therapy for treating tuberculosis (Review)

Volmink J, Garner P

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2008, Issue 2

http://www.thecochranelibrary.com

TABLE OF CONTENTS

Directly observed therapy for treating tuberculosis (Review)

Volmink J, Garner P

This record should be cited as:
Volmink J, Garner P. Directly observed therapy for treating tuberculosis. *Cochrane Database of Systematic Reviews* 2007, Issue 4. Art. No.: CD003343. DOI: 10.1002/14651858.CD003343.pub3.

This version first published online: 17 October 2007 in Issue 4, 2007.
Date of most recent substantive amendment: 13 August 2007

ABSTRACT

Background
For tuberculosis treatment, policies have been introduced to encourage adherence to treatment regimens. One such policy is directly observed therapy (DOT), which involves people directly observing patients taking their antituberculous drugs.

Objectives
To compare DOT with self administration of treatment or different DOT options for people requiring treatment for clinically active tuberculosis or prevention of active disease.

Search strategy
In May 2007, we searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (*The Cochrane Library* 2007, Issue 2), MEDLINE, EMBASE, LILACS, and *m*RCT. We also checked article reference lists and contacted relevant researchers and organizations.

Selection criteria
Randomized and quasi-randomized controlled trials comparing a health worker, family member, or community volunteer routinely observing people taking antituberculous drugs compared with routine self administration of treatment at home. We include people requiring treatment for clinically active tuberculosis or medication for preventing active disease.

Data collection and analysis
Both authors independently assessed trial methodological quality and extracted data. Data were analysed using relative risks (RR) with 95% confidence intervals (CI) and the fixed-effect model when there was no statistically significant heterogeneity (chi square P > 0.1). Trials of drug users were analysed separately.

Main results
Eleven trials with 5609 participants met the inclusion criteria. No statistically significant difference was detected between DOT and self administration in terms of cure (RR 1.02, 95% CI 0.86 to 1.21, random-effects model; 1603 participants, 4 trials), with similar results for cure plus completion of treatment. When stratified by location, DOT provided at home compared with DOT provided at clinic suggests a possible small advantage with home-based DOT for cure (RR 1.10, 95% CI 1.02 to 1.18; 1365 participants, 3 trials). There was no significant difference detected in clinical outcomes between DOT at a clinic versus by a family member or community health worker (2 trials), or for DOT provided by a family member versus a community health worker (1326 participants, 1 trial). Two small trials of tuberculosis prophylaxis in intravenous drugs users found no statistically significant difference between DOT and self administration (199 participants, 1 trial) or a choice of location for DOT for completion of treatment (108 participants, 1 trial).

Authors' conclusions
The results of randomized controlled trials conducted in low-, middle-, and high-income countries provide no assurance that DOT compared with self administration of treatment has any quantitatively important effect on cure or treatment completion in people receiving treatment for tuberculosis.

PLAIN LANGUAGE SUMMARY

Directly observing people taking their tuberculosis drugs did not improve the cure rate compared with people without direct monitoring of treatment

Tuberculosis is a very serious health problem with two million people dying each year, mostly in low-income countries. Effective drugs for tuberculosis have been available since the 1940s, but the problem still abounds. People with tuberculosis need to take the drugs for at least six months, but many do not complete their course of treatment. For this reason, services for people with tuberculosis often use different approaches to encourage people to complete their course of treatment. This review found no evidence that direct observation by health workers, family members, or community members of people taking their medication showed better cure rates that people having self administered treatment. The intervention is expensive to implement, and there appears to be no sound reason to advocate its routine use until we better understand the situations in which it may be beneficial.

BACKGROUND

Adherence in tuberculosis management

Effective drugs for tuberculosis have been available since the 1940s, but two million people continue to die each year, mostly in low-income countries (Dye 1999; Netto 1999). People with tuberculosis require treatment for at least six to eight months. Many find it difficult to complete their course of treatment and this serves as a major constraint to eradicating the disease (Fox 1958; Addington 1979; Cuneo 1989). Poor adherence to treatment can lead to prolonged infectiousness, drug resistance, relapse of tuberculosis, or even death. Incomplete treatment thus poses a serious risk for the individual as well as the community.

There are three groups of people for whom adherence is important: people under evaluation for suspected tuberculosis (to ensure they complete the diagnostic regimen or start treatment); people receiving prophylaxis (preventive therapy), where antituberculous drugs are given to people exposed to tuberculosis or thought to be at particular risk; and people with diagnosed tuberculosis in whom completion of treatment helps ensure cure.

Adherence to a tuberculosis treatment programme requires accessible and appropriate health care. People need to be diagnosed correctly, provided with information about their disease and the need for completion of treatment, and supplied with appropriate outpatient drugs. But even where these services are available, people may not adhere to the intended regimen. Healthcare providers have responded by developing a variety of specific measures to improve adherence (Cuneo 1989; CDC 1993; Sbarbaro 1994). These interventions are aimed at influencing the behaviour of healthcare personnel, the organization of the service, or the behaviour of the person with suspected or confirmed tuberculosis. Originally we included all these interventions in one Cochrane Review, but this approach did not allow us to consider the particulars of each of the following interventions, and why in one set of circumstances it may be effective and another it may not. This Cochrane Review is one of several planned or in progress to evaluate each type of intervention:

- Directly observed therapy (DOT): an appointed agent (health worker, community volunteer, family member) directly monitors people swallowing their antituberculous drugs (this review).
- Staff motivation and supervision: training and management processes that aim to improve how providers care for people with tuberculosis.
- Reminder systems and late patient tracers in the diagnosis and management of tuberculosis: routinely reminding patients to keep an appointment and actions taken when patients fail to keep an appointment (Liu 2007).
- Education and counselling for promoting adherence to the treatment of active tuberculosis: provision of information or one-to-one or group counseling about tuberculosis and the need to attend for treatment (M'Imunya 2007).
- Incentives and reimbursements: money or cash in kind to reimburse expenses of attending services, or to improve the attractiveness of visiting the service.
- Contracts: written or verbal agreements to return for an appointment or course of treatment (Bosch-Capblanch 2007).
- Peer assistance: people from the same social group helping someone with tuberculosis return to the health service by prompting or accompanying them.

DOT

DOT seeks to improve the adherence of people to tuberculosis treatment through health workers, family members, or community members directly observing them taking their antituberculous drugs. This approach was first adopted in studies in Madras, India, and Hong Kong as early as the 1960s (Bayer 1995), and a number of specialists now widely recommend DOT for the control of tuberculosis (Bass 1994; Maher 1997; Chaulk 1998; Enarson 2000). Indeed, Frieden and Sbarbaro state that it is essential and that it prevents relapse occurring and drug resistance developing (Frieden 2007).

The advantages of DOT are that people can be closely monitored and that there is a social process with peer pressure that may im-

prove adherence. On the other hand, the disadvantages associated with DOT are that it moves away from adherence models of communication with cooperation between patient and provider back to a traditional medical approach with the patient as the passive recipient of advice and treatment (Donovan 1992; Sumartojo 1993); resource implications for such a policy are substantial, particularly in low-income and middle-income countries where the case load is high; and it may make adherence worse if it is rigidly applied in an authoritarian setting or where people are expected to travel considerable distances to have their treatment supervised

Programmes that include DOT

Over the years DOT has come to mean much more than the supervised swallowing of drugs, causing considerable confusion. In the USA, DOT programmes are complex and consist of several components including social support, housing, food tokens, and jail for recalcitrant people (ATS 1992; Volmink 2000b).

The World Health Organization (WHO) promotes another version of DOT called 'directly observed therapy, short course' (DOTS). This is a comprehensive tuberculosis management programme that focuses on low-income countries. DOTS is a five-element strategy for the control of tuberculosis that consists of political commitment, improved laboratory analysis, direct patient observation while swallowing each dose of medication, a drug supply that provides for the correct complete short course antituberculous drug combination for free, and a reporting system that documents the progress in curing the patient (WHO 1997).

The WHO believes that direct observation is a key element for the success of DOTS and has retained it in more recent definitions of the DOTS strategy, although their documentation has clearly taken into account criticisms of their blanket policy. For example, the WHO states that the third component of their expanded strategic framework is "standardized short-course chemotherapy to all cases of TB [tuberculosis] under proper case-management conditions including direct observation of treatment" (WHO 2002). The 2004 progress report mentions direct observation for "at least" the first two months of treatment (WHO 2004). Even so, how this is interpreted in countries varies, and direct observation by a health worker remains national policy in China, for example.

In contrast, we have previously suggested that the benefits associated with DOT programmes found in observational studies may be attributable to simultaneous inputs rather than direct observation specifically (Volmink 1997a). An informed debate is important because direct observation has considerable resource implications; it therefore important to determine how important this intervention is for improving adherence to tuberculosis treatment and ensuring cure. Since our initial Cochrane Review (Volmink 1997b), which documented the absence of randomized controlled trials of DOT, several trials have been conducted aimed at disaggregating the effects of this specific intervention from those of accompanying inputs, and they are included in this review update.

Not only is there a debate about whether DOT is effective, there is also a debate about who should provide this. This may be contingent practically on an individual's circumstances, but the specialists are divided in their recommendations: some consider family members can help, whereas others regard family observation as a "seductive but risky concept" (Frieden 2007). We therefore also summarize trials comparing DOT through different providers and settings.

OBJECTIVES

To compare DOT with self administration of treatment or different DOT options for people requiring treatment for clinically active tuberculosis or prevention of active disease.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomized and quasi-randomized controlled trials.

Types of participants

People requiring treatment for clinically active tuberculosis *or* medication for preventing active disease (prophylaxis or preventive therapy).

Types of intervention

Intervention

Health worker, family member, or community volunteer routinely observes participants taking their antituberculous drugs.

Control

Routine self administration of treatment at home, with intermittent clinic visits for drugs with or without treatment adherence checks.

Where researchers explored different methods of implementing direct observation, the experimental method was allocated to the intervention group and the standard method to the control.

Types of outcome measures

Primary

- Cure.
- Completion of treatment.
- Development of clinical tuberculosis (in trials of drug prophylaxis).

Secondary

Keeping outpatient appointments.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Infectious Diseases Group methods used in reviews.

We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

Databases
We searched the following databases using the search terms and strategy described in Table 01: Cochrane Infectious Diseases Group Specialized Register (May 2007); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2007, Issue 2); MEDLINE (1966 to May 2007); EMBASE (1974 to May 2007); and LILACS (1982 to May 2007). We also searched the *meta*Register of Controlled Trials (*m*RCT) using 'tuberculosis AND DOT*' (May 2007).

Researchers and organizations
For unpublished and ongoing trials, we contacted individual researchers working in the field and the following organizations: World Health Organization (1997 and 2004), the International Union Against Tuberculosis and Lung Disease (IUATLD) (1997), and the Centers for Disease Control and Prevention (1997).

Reference lists
We also checked the reference lists of all studies identified by the above methods.

METHODS OF THE REVIEW

Trial selection
Both authors independently applied the inclusion criteria to all identified trials. We used the titles and abstracts of the identified citations to exclude trials that clearly did not meet the inclusion criteria. If either author judged that the trial might be eligible for inclusion, we obtained the full paper. We independently screened the full articles of selected trials to confirm eligibility and resolved any disagreements by discussion.

Assessment of methodological quality
We independently evaluated the methodological quality of each trial, classifying the generation of allocation sequence and concealment of allocation as adequate, inadequate, or unclear according to Juni 2001. We classified blinding as adequate if steps were taken to ensure the people recording the main outcome of the study were blind to the assigned interventions and inadequate if this was not the case or if there was no mention of attempts to blind the observers. We assessed completeness of follow up as adequate if 90% or more, inadequate if less than 90%, or unclear if not mentioned.

Data extraction
We independently extracted the data and checked whether authors had conducted an intention-to-treat analysis. Trialists were contacted to supply missing information and to clarify issues. We resolved discrepancies through discussion.

Data analysis
We used Review Manager 4.2 to analyse the data, using relative risk (RR) with 95% confidence intervals (CI) to assess estimates of effect. We used the fixed-effect model when there was no statistically significant heterogeneity (chi square P > 0.1).

DESCRIPTION OF STUDIES

Eleven trials with 5609 participants met the inclusion criteria (*see* 'Characteristics of included studies'). Twelve studies that initially seemed to fit the inclusion criteria were eventually excluded from our review; reasons for these decisions are provided in the 'Characteristics of excluded studies'.

Eight of the 11 trials were conducted in low-income and middle-income countries and evaluated DOT for treating people with active tuberculosis: Pakistan (Walley 2001); South Africa (Zwarenstein 1998; Zwarenstein 2000); Tanzania (Lwilla 2003; Wandwalo 2004); Nepal (Newell 2006); Thailand (Kamolratanakul 1999); and Swaziland (Wright 2004). Three trials were in high-income countries: one in Australia (MacIntyre 2003); and two in the USA that examined prophylaxis in intravenous drug users (Chaisson 2001; Malotte 2001). Two trials were cluster randomized (Lwilla 2003; Newell 2006). One trial used a quasi-random method of allocation (MacIntyre 2003).

Services for general populations

DOT versus self administration of treatment
Five trials compared DOT with self administration of treatment. There is some overlap of data in two of these trial reports, but we have taken this into account in the analyses: Zwarenstein 1998 combined data from two communities in which trials compared direct observation by nurses at clinics with self administration of treatment, while Zwarenstein 2000 described data from one of these trials that had three arms of direct observation by nurses, lay health workers, and self administration. Kamolratanakul 1999 allowed participants to choose between DOT by a health worker, community leader, or family member; most chose the latter. Walley 2001 compared DOT by a health worker or community health worker with DOT by a family member and with self administration of treatment. MacIntyre 2003 evaluated DOT by a family member.

Alternative DOT delivery options
A cluster-randomized trial from Tanzania (Lwilla 2003) compared a community health worker observing people at home with DOT at a health facility. Three trials compared DOT by a family member

with either DOT by a health worker at a health facility (Wandwalo 2004) or DOT by a community health worker (Wright 2004; Newell 2006).

Services for intravenous drug users
Two trials from the USA evaluated DOT in drug users on prophylaxis for latent tuberculosis (Chaisson 2001; Malotte 2001). Malotte 2001 studied intravenous and crack cocaine users, and compared DOT by an outreach worker at a site chosen by the participant (with or without a US$5 at each visit) with DOT at a community clinic with a US$5 at each visit. Chaisson 2001 involved intravenous drug users, and studied DOT by an outreach nurse with self administration either with monthly peer support or monthly clinic visits.

Outcomes
The numbers of people cured, cured and completed treatment, or completed treatment were the main outcomes assessed in the included trials.

Adjustment for clustering
Both cluster trials adjusted for clustering appropriately: standard error of the coefficients for clustering on units corrected using the Huber-White-Sandwich method (Lwilla 2003); and, in Newell 2006, using the coefficient of variation between clusters.

METHODOLOGICAL QUALITY

See Table 02 *for a summary of the assessment.*

Generation of allocation sequence
Seven trials used adequate methods – computer-generated random sequences (Zwarenstein 1998; Zwarenstein 2000; Walley 2001; Chaisson 2001), a random-number table (Kamolratanakul 1999), coin tossing (Wandwalo 2004), and random draws of paper from a basket (Newell 2006). One trial used alternate allocation, an inadequate method (MacIntyre 2003). The remaining trial reports did not provide information (Malotte 2001; Lwilla 2003; Wright 2004).

Allocation concealment
Four trials employed adequate methods for concealing allocation (Zwarenstein 1998; Zwarenstein 2000; Walley 2001; Malotte 2001). Allocation concealment was unclear in three trials (Chaisson 2001; Lwilla 2003; Wright 2004) and not used in the remaining trials (MacIntyre 2003; Kamolratanakul 1999; Wandwalo 2004; Newell 2006).

Blinding
Outcome assessment was blind in only four trials (Walley 2001; MacIntyre 2003; Wright 2004; Newell 2006).

Completeness of follow up
In two trials, more than 10% of participants were excluded from the analysis (Chaisson 2001; Lwilla 2003). A further four trials did not provide sufficient information to assess this aspect of study quality (Zwarenstein 2000; Malotte 2001; Walley 2001; MacIntyre 2003). In the rest of the trials follow up was adequate.

RESULTS

(1) Services for general public

DOT versus self administration of treatment
Treatment outcomes were similar among participants in the DOT and self administration of treatment arms. There was no statistically significant difference between the interventions for the number of people cured (1603 participants, 4 trials, Analysis 01.01), cured or completed treatment (1603 participants, 4 trials, Analysis 01.02), or completed treatment (173 participants, 1 trial, Analysis 01.03). There was significant heterogeneity between the trials for cure (chi squared 8.41; df = 3), but the point estimate of the RR was close to one, and no difference was demonstrated with either fixed-effect or random-effects models (Analysis 01.01).

We explored whether different effect sizes were associated with home-based and clinic-based DOT. Effect size was similar in the two groups (Analyses 02.01 and .02). Home-based DOT was strongly influenced by the trial from Thailand (Kamolratanakul 1999), and there was a statistically significant improvement in cure, but the difference was small (RR 1.10, 95% CI 1.02 to 1.18; 1365 participants, 3 trials, Analysis 02.01).

DOT: family member or community health worker versus at clinic
Wandwalo 2004 found cure or treatment completion to be similar for those observed by a family member compared with a health worker (587 participants, 1 trial, Analysis 03.01). A cluster-randomized trial, Lwilla 2003, which evaluated DOT by a community health worker, found no difference for sputum conversion at two months (OR 0.62, 95% CI 0.23 to 1.71) or cure at the end of treatment (OR 1.58, 95% CI 0.32 to 7.88; trial authors adjusted for design effects).

DOT: family member versus by a community health worker
Wright 2004 found no statistically significant difference in the number of people cured or who completed treatment (1326 participants, Analysis 04.01). A cluster-randomized trial, Newell 2006, which compared community-based DOT by a community health worker or village health worker with family-based DOT, found no statistically significant difference in success rates (cure and treatment completion) (85% vs 89%; OR 0.67, 95% CI 0.41 to 1.10; trial authors adjusted for design effects).

(2) Services for intravenous drug users
Chaisson 2001 found no statistically difference in the number of people who completed twice-weekly clinic-based DOT and those on daily self administration of treatment (199 participants, Analysis 05.01). For participants receiving prophylaxis, Malotte 2001

studied people receiving prophylaxis and found no statistically significant difference in the number who completed treatment between those allowed to choose their DOT location and those receiving DOT at a community clinic (108 participants, Analysis 06.01).

DISCUSSION

Direct observation of people taking their antituberculous drugs is widely advocated and forms part of the World Health Organization's 'directly observed therapy, short course' (DOTS) strategy. While this strategy includes a number of useful components, the available evidence does not provide strong support for the routine adoption of direct observation in favour of self administration of treatment either for people with active tuberculosis or those with latent tuberculosis requiring prophylaxis. There is also no evidence that one form of direct observation is better than another: direct, randomized comparisons between clinic-based DOT and community-based DOT did not demonstrate a difference; and, within community-based DOT, comparisons between DOT provided by a family member versus a community health worker had similar outcomes.

Given the prevailing support for DOT-based programmes, these findings are important. We have previously suggested that the benefits associated with DOT programmes in observational studies may be attributable to simultaneous interventions rather than direct observation being the key adherence-promoting strategy (Volmink 2000b). A qualitative study notes that the implementation of DOT is in the process of shifting from being a rigid model involving observation of drug swallowing to one that includes an array of incentives and enablers for supporting the patient (Macq 2003). Within such a package of patient-centred interventions it remains to be established whether direct observation is necessary at all. Of interest in this regard are the findings of a cluster-randomized trial in a rural South Africa in which motivation and support from a lay health worker (with or without DOT) was shown to be more effective in ensuring treatment than a conventional DOT-based service (Clarke 2005). People with tuberculosis are often poor and encounter numerous barriers to treatment adherence. Strategies aimed at reducing social and health system barriers may therefore be preferable to coercive approaches that impact negatively on patient autonomy. The encouraging results of a recent trial in Senegal using a multifaceted approach to address these challenges, which also included a flexible approach to DOT, lend support to this notion (Thiam 2007). Further rigorous trials, in particular those testing interventions social and family barriers to adherence, are needed (Garner 2007).

One of the trials included in our review found a modest improvement with DOT for cure and treatment completion (Kamolratanakul 1999), and one may speculate about the reasons for these findings. The Thai health system is relatively well resourced and has a tuberculosis control programme that is well organized. This is in contrast to the trials in South Africa (Zwarenstein 1998; Zwarenstein 2000) and Pakistan (Walley 2001) where the trials were conducted in areas with high disease burden, overcrowded tuberculosis clinics, and poorly motivated staff. On the other hand, DOT did not improve treatment completion rates in either Australia (MacIntyre 2003) or the USA (Chaisson 2001; Malotte 2001), both of which are low burden, highly resourced settings. A second reason one might posit is that cultural responses to supervision may vary with Thai people being more responsive to this approach. Finally, Kamolratanakul 1999 is so far the only trial to have allowed participants to choose their supervisor, and this patient-centred approach may also have influenced the effects.

Can adopting a DOT policy make adherence worse? The authors of the South African trial suggest an increasingly negative and demoralizing effect of direct observation on participants with tuberculosis (Zwarenstein 1998). This trial found that in participants with a first episode of tuberculosis, the outcomes were equivalent in DOT and self administration of treatment arms, while 'retreatment' participants who were assigned to DOT fared worse than those who self administered treatment. Given the small numbers of participants in the retreatment group, further research is warranted to confirm the findings.

Bias could have influenced the results in some of the trials. As outlined in the methodological quality assessment, the number of trials with adequate quality criteria was limited: four with adequate method for concealing treatment allocation; four with blinding of the outcome assessors; and two trials that excluded more than 10% of participants from the analysis. Nevertheless, these trials are not easy to implement and are a credit to the researchers who have worked hard to develop the evidence base for rational decision making.

AUTHORS' CONCLUSIONS

Implications for practice

Randomized controlled trials provide no assurance that the routine use of DOT in low- and middle-income countries improves cure or treatment completion in people with tuberculosis. There is also no rigorous evidence to support the use of DOT for prophylaxis in people with latent tuberculosis.

There appears to be no sound reason to advocate the allocation of resources to the routine use of DOT until we better understand the situations in which it may be beneficial. In the meantime, it could reasonably be argued that resources should be invested in interventions that have been shown to be effective for improving adherence, such as providing patient motivation and support, incentives, and defaulter action.

Implications for research

The relation between DOT and treatment outcome is complex. Factors that determine its usefulness in various settings require further study. The extent to which the quality of interaction between patients and their observers influences outcome would be a particularly fruitful topic for future research. It will also be worth testing whether DOT efficacy differs in people receiving tuberculosis treatment for the first time compared with those requiring retreatment, and in men compared with women. Comparisons of DOT in relation to other strategies aimed at improving adherence should be determined.

POTENTIAL CONFLICT OF INTEREST

None known.

ACKNOWLEDGEMENTS

To the Global Health Council and the Department of Arts, Culture, Science and Technology of South Africa for supporting Jimmy Volmink in the preparation of the review in the period before the 2006 update. This document is an output from a project funded by the UK Department for International Development (DFID) for the benefit of developing countries. The views expressed are not necessarily those of DFID.

SOURCES OF SUPPORT

External sources of support

- Department for International Development UK

Internal sources of support

- South African Medical Research Council SOUTH AFRICA
- Liverpool School of Tropical Medicine UK

REFERENCES

References to studies included in this review

Chaisson 2001 *{published data only}*

Chaisson RE, Barnes GL, Hackman J, Watkinson L, Kimbrough L, Metha S, et al.A randomized, controlled trial of interventions to improve adherence to isoniazid therapy to prevent tuberculosis in injection drug users. *American Journal of Medicine* 2001;**110**(8):610–5.

Kamolratanakul 1999 *{published data only}*

Kamolratanakul P, Sawert H, Lertmaharit S, Kasetjaroen Y, Akksilp S, Tulaporn C, et al.Randomized controlled trial of directly observed treatment (DOT) for patients with pulmonary tuberculosis in Thailand. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1999;**93**(5):552–7.

Lwilla 2003 *{published data only}*

Lwilla F, Schellenberg D, Masanja H, Acosta C, Galindo C, Aponte J, et al.Evaluation of efficacy of community-based vs. institutional-based direct observed short-course treatment for the control of tuberculosis in Kilombero district, Tanzania. *Tropical Medicine and International Health* 2003;**8**(3):204–10.

MacIntyre 2003 *{published data only}*

MacIntyre CR, Goebel K, Brown GV, Skull S, Starr M, Fullinfaw RO. A randomised controlled 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* 2003;**7**(9):848–54.

Malotte 2001 *{published data only}*

Malotte CK, Hollingshead JR, Larro M. Incentives vs outreach workers for latent tuberculosis treatment in drug users. *American Journal of Preventive Medicine* 2001;**20**(2):103–7.

Newell 2006 *{published data only}*

Newell JN, Baral SC, Pande SB, Bam DS, Malla P. Family-member DOTS and community DOTS for tuberculosis control in Nepal: cluster-randomised controlled trial. *Lancet* 2006;**367**(9514):903–9.

Walley 2001 *{published data only}*

Khan MA, Walley JD, Witter SN, Imran A, Safdar N. Costs and cost-effectiveness of different DOT strategies for the treatment of tuberculosis in Pakistan. *Health Policy and Planning* 2002;**17**(2):178–86.

*Walley JD, Khan MA, Newell JN, Khan MH. Effectiveness of direct observation component of DOTS for tuberculosis: a randomised controlled trial in Pakistan. *Lancet* 2001;**357**(9275):664–9.

Wandwalo 2004 *{published data only}*

Wandwalo E, Kapalata N, Egwaga S, Morkve O. Effectiveness of community-based directly observed treatment for tuberculosis in an urban setting in Tanzania: a randomised controlled trial. *International Journal of Tuberculosis and Lung Disease* 2004;**8**(10):1248–54.

Wright 2004 *{published data only}*

Wright J, Walley J, Phillip A, Pushpananthan S, Dlamini E, Newell J, et al.Direct observation of treatment for tuberculosis: a randomized controlled trial of community health workers versus family members. *Tropical Medicine and International Health* 2004;**9**(5):559–65.

Zwarenstein 1998 *{published data only}*

Zwarenstein M, Schoeman JH, Vundule C, Lombard CJ, Tatley M. Randomised controlled trial of self-supervised and directly observed treatment of tuberculosis. *Lancet* 1998;**352**(9137):1340–3.

Zwarenstein 2000 *{published data only}*

Zwarenstein M, Schoeman JH, Vundule C, Lombard CJ, Tatley M. A randomised trial of lay health workers as direct observers for treatment of tuberculosis. *International Journal of Tuberculosis and Lung Disease* 2000;**4**(6):550–4.

References to studies excluded from this review

Batki 2001

Batki SL, Gruber VA, Bradley JM, Bradley M, Delucchi K. A controlled trial of methadone treatment combined with directly observed isoniazid for tuberculosis prevention in injection drug users. *Drug and Alcohol Dependence* 2002;**66**(3):283–93.

Carroll 2004

Carroll K, Malefoasi G. Comparison of outcomes from a district tuberculosis control programme in the Pacific: before and after the implementation of DOTS. *Tropical Doctor* 2004;**34**(1):11–4.

Hwang 2004

Hwang TG, Kim SD, Yoo SH, Shin YC. Sputum smear conversion during mDOT. *Tuberculosis and Respiratory Diseases* 2004;**56**:485–94.

Jasmer 2004

Jasmer RM, Seaman CB, Gonzalez LC, Kawamura LM, Osmond DH, Daley CL. Tuberculosis treatment outcomes: directly observed therapy compared with self-administered therapy. *American Journal of Respiratory and Critical Care Medicine* 2004;**170**(5):561–6.

Lewin 2004

Lewin S, Dick J, Zwarenstein M, Lombard CJ. Staff training and ambulatory tuberculosis outcomes: a cluster randomized controlled trial in South Africa. *Bulletin of the World Health Organization* 2005; **83**(4):250–9.

Mathew 2002

Matthew AJ, Eicher A, Davies PD. Comparison of hospital checked directly observed therapy with family supervised and unchecked tuberculosis treatment in a rural setting in North India. *European Respiratory Journal* 2002;**20 Suppl 38**:215.

Moulding 2001

Moulding TS, Caymittes M. Managing medication compliance of tuberculosis patients in Haiti with medication monitors. *International Journal of Tuberculosis and Lung Disease* 2002;**6**(4):313–9.

Pungrassami 2002

Pungrassami P, Chongsuvivatwong V. Are health personnel the best choice for directly observed treatment in southern Thailand? A comparison of treatment outcomes among different types of observers. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2002; **96**(6):695–9.

Pungrassami P, Johnsen SP, Chongsuvivatwong V, Olsen J. Has directly observed treatment improved outcomes for patients with tuberculosis in southern Thailand?. *Tropical Medicine and International Health* 2002;**7**(3):271–9.

Sorete-Abore 2002

Sorete-Arbore A, Mihaescu T. Three years of DOTS strategy in Iasi county, Romania. *European Respiratory Journal* 2002;**20 Suppl 38**: 217.

Tandon 2002

Tandon M, Gupta M, Tandon S, Gupta KB. DOTS versus self adminstered therapy (SAT) for patients with pulmonary tuberculosis: a randomised trial at a tertiary care hospital. *Indian Journal of Medical Science* 2002;**56**(1):19–21.

Thiam 2007

Thiam S, LeFevre AM, Hane F, Ndiaye A, Ba F, Fielding KL, et al.Effectiveness of a strategy to improve adherence to tuberculosis treatment in a resource-poor setting: a cluster randomized controlled trial. *JAMA* 2007;**297**(4):380–6.

Toyota 2003

Toyota E, Kobayashi N, Houjou M, Yoshizawa A, Kawana A, Kudo K. Usefulness of directly observed therapy (DOT) during hospitalization as DOTS in Japanese style. *Kekkaku* 2003;**78**(9):581–5.

Additional references

Addington 1979

Addington WW. Patient compliance: The most serious remaining problem in the control of tuberculosis in the United States. *Chest* 1979;**76 Suppl 6**:741–3.

ATS 1992

American Thoracic Society/Centers for Disease Control and Prevention. Control of tuberculosis in the United States. *American Review of Respiratory Disease* 1992;**146**(6):1623–33.

Bass 1994

Bass JB Jr, Farer LS, Hopewell PC, O'Brien R, Jacobs RF, Ruben F, et al.Treatment of tuberculosis and tuberculosis infection in adults and children. American Thoracic Society and The Centers for Disease Control and Prevention. *American Journal of Respiratory and Critical Care Medicine* 1994;**149**(5):1359–74.

Bayer 1995

Bayer R, Wilkinson D. Directly observed therapy for tuberculosis: history of an idea. *Lancet* 1995;**345**(8964):1545–8.

Bosch-Capblanch 2007

Bosch-Capblanch X, Abba K, Prictor M, Garner P. Contracts between patients and healthcare practitioners for improving patients' adherence to treatment, prevention and health promotion activities. *Cochrane Database of Systematic Reviews* 2007, Issue 2.Art. No.: CD004808. DOI:10.1002/14651858.CD004808.pub3.

CDC 1993

Centers for Disease Control and Prevention (CDC). Approaches to improving adherence to antituberculosis therapy--South Carolina and New York, 1986-1991. *Morbidity and Mortality Weekly Report* 1993;**42**(4):74-5, 81.

Chaulk 1998

Chaulk CP, Kazandjian VA. Directly observed therapy for treatment completion of pulmonary tuberculosis: Consensus Statement of the Public Health Tuberculosis Guidelines Panel. *JAMA* 1998;**279**(12): 943–8.

Clarke 2005

Clarke M, Dick J, Zwarenstein M, Lombard CJ, Diwan VK. Lay health worker intervention with choice of DOT superior to standard TB care for farm dwellers in South Africa: a cluster randomised control trial. *International Journal of Tuberculosis and Lung Disease* 2005; **9**(6):673–9.

Cuneo 1989

Cuneo WD, Snider DE Jr. Enhancing patient compliance with tuberculosis therapy. *Clinics in Chest Medicine* 1989;**10**(3):375–80.

Donovan 1992

Donovan JL, Blake DR. Patient non-compliance: Deviance or reasoned decision-making?. *Social Science and Medicine* 1992;**34**(5): 507–13.

Dye 1999

Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. *JAMA* 1999;**282**(7):677–86.

Enarson 2000

Enarson DA, Rieder HL, Arnadottir T, Trebucq A. *Management of tuberculosis: a guide for low income countries*. 5th Edition. Paris: International Union Against Tuberculosis and Lung Disease, 2000.

Fox 1958

Fox W. The problem of self-administration of drugs: with particular reference to pulmonary tuberculosis. *Tubercle* 1958;**39**(5):269–74.

Frieden 2007

Frieden TR, Sbarbaro JA. Promoting adherence to treatment for tubercuoisis: the importance of direct observation. *Bulletin of the World Health Organization* 2007;**85**(5):407–9.

Garner 2007

Garner P, Smith H, Munro S, Volmink J. Promoting adherence to tuberculosis treatment. *Bulletin of the World Health Organization* 2007; **85**(5):404–9.

Higgins 2006

Higgins J, Green S, editors. Highly sensitive search strategies for identifying reports of randomized controlled trials in MEDLINE. Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006]; Appendix 5b. www.cochrane.org/resources/handbook/hbook.htm (accessed 1 May 2007).

Juni 2001

Juni P, Altman DG, Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. *BMJ* 2001;**323**(7303): 42–6.

Liu 2007

Liu Q, Abba K, Alejandria MM, Balanag VM, Berba RP, Lansang MA. Reminder systems and late patient tracers in the diagnosis and management of tuberculosis (Protocol). *Cochrane Database of Systematic Reviews* 2007, Issue 3.

M'Imunya 2007

M'Imunya MJ, Volmink J. Education and counselling for promoting adherence to the treatment of active tuberculosis (Protocol). *Cochrane Database of Systematic Reviews* 2007, Issue 3.

Macq 2003

Macq JC, Theobald S, Dick J, Dembele M. An exploration of the concept of directly observed treatment (DOT) for tuberculosis patients: from a uniform to a customised approach. *International Journal of Tuberculosis and Lung Disease* 2003;**7**(2):103–9.

Maher 1997

Maher D, Chaulet P, Spinaci S, Harries A. *Treatment of tuberculosis: guidelines for national programmes*. 2nd Edition. Geneva: World Health Organization, 1997.

Netto 1999

Netto EM, Dye C, Raviglione MC. Progress in global tuberculosis control 1995-1996, with emphasis on 22 high-incidence countries. Global Monitoring and Surveillance Project. *International Journal of Tubercle and Lung Disease* 1999;**3**(4):310–20.

Review Manager 4.2

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 4.2 for Windows. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2003.

Sbarbaro 1994

Sbarbaro JA, Sbarbaro JB. Compliance and supervision of chemotherapy of tuberculosis. *Seminars in Respiratory Infections* 1994;**9**(2): 120–7.

Sumartojo 1993

Sumartojo E. When tuberculosis treatment fails, a social behavioural account of patient adherence. *American Review of Respiratory Disease* 1993;**147**(5):1311–20.

Volmink 1997a

Volmink J, Garner P. Directly observed therapy [letter]. *Lancet* 1997; **349**(9062):1399–400.

Volmink 2000b

Volmink J, Matchaba P, Garner P. Directly observed therapy and treatment adherence. *Lancet* 2000;**355**(9212):1345–50.

WHO 1997
WHO Global Tuberculosis Programme. *TB : WHO report on the tuberculosis epidemic 1997*. Geneva: World Health Organization, 1997.

WHO 2002
WHO Global Tuberculosis Programme. *An expanded DOTS framework for effective tuberculosis control: stop TB communicable diseases*. World Health Organization: Geneva, 2002.

WHO 2004
World Health Organization, Stop TB Dept. *Progress report on the global plan to stop tuberculosis*. Geneva: World Health Organization, 2004.

References to other published versions of this review

Volmink 1997b
Volmink J, Garner P. Systematic review of randomised controlled trials of strategies to promote adherence to tuberculosis treatment. *BMJ* 1997;**315**(7120):1403–6.

Volmink 2000a
Volmink J, Garner P. Interventions for promoting adherence to tuberculosis management. *Cochrane Database of Systematic Reviews* 2000, Issue 4.Art. No.: CD000010. DOI:10.1002/14651858.CD000010.

Volmink 2001
Volmink J, Garner P. Directly observed therapy for treating tuberculosis. *Cochrane Database of Systematic Reviews* 2001, Issue 4.Art. No.: CD003343. DOI:10.1002/14651858.CD003343.pub3.

Volmink 2003
Volmink J, Garner P. Directly observed therapy for treating tuberculosis. *Cochrane Database of Systematic Reviews* 2003, Issue 1.Art. No.: CD003343. DOI:10.1002/14651858.CD003343.pub3.

Volmink 2006
Volmink J, Garner P. Directly observed therapy for treating tuberculosis. *Cochrane Database of Systematic Reviews* 2006, Issue 2.Art. No.: CD003343. DOI:10.1002/14651858.CD003343.pub3.

** Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	Chaisson 2001
Methods	Generation of allocation sequence: randomized, with factorial overlay; computer-generated random numbers Allocation concealment: not stated Blinding: none Completeness of follow up: 88%
Participants	Number: 300 randomized; 73% men; 85% unemployed; 27% with documented HIV infection Included: adult, intravenous drug users with positive tuberculin skin test (at least 10 mm induration or 5 mm if HIV positive); given isoniazid preventive therapy for 6 months Excluded: people with active tuberculosis
Interventions	(1) DOT twice weekly by outreach nurse at clinic or community location

Characteristics of included studies (*Continued*)

	(2) Daily self administration of treatment, monthly peer counselling group meetings with lunch, and clinical assessments by a nurse; peer counsellor was a former injection user who had completed preventive therapy, and who was trained in counselling and supervised by a health educator (3) Daily self administration of treatment with monthly clinic assessment; factorial design with immediate or deferred US$10 stipend at the end of each month; deferred payments credited each month and given when treatment completed or participant withdrew
Outcomes	(1) 6 months treatment completed, defined as 80% or more of treatments taken (observed for DOT group and 6 monthly visits plus reporting that at least 80% medication taken during a month for other groups) (2) Pill counts (3) Isoniazid metabolites in the urine (4) Electronically monitored bottle opening in a subset
Notes	Location: Baltimore City Health Department TB Clinic, USA Date: 1995-7 Duration of DOT duration not stated
Allocation concealment	B – Unclear

Study	**Kamolratanakul 1999**
Methods	Generation of allocation sequence: central block random allocation scheme prepared for each of 15 study sites; random-number table used Allocation concealment: none Blinding: no blinding of assessors Completeness of follow up: 100% (no losses)
Participants	Number: 837 randomized; 73% male Included: new smear positive adults (aged 15+)
Interventions	(1) Daily supervision: participants chose their supervisor from (a) health centre staff, (b) community members, or (c) family members; for (b) and (c) health workers visited homes twice monthly (first 2 months) or monthly for checking of treatment cards, pill counts, and urine tests (2) Self administration of treatment: 1 month drug supply given at diagnosis and after each follow-up visit; no treatment supervision between visits All participants received the same drug regimen: isoniazid-rifampicin-pyrazinamide-ethambutol for 2 months and isoniazid-rifampicin for 4 months
Outcomes	(1) Cure rate (primary outcome): completed 6 months antituberculous therapy, with 2 negative sputum exams, 1 at end of treatment (2) Treatment completion: completed 6 months antituberculous therapy but less than 2 sputum exams (3) Sputum conversion rate: negative sputum at end of third month (4) Percentage defaults (5) Percentage transfers (6) Caseholding rate
Notes	Location: Thailand Date: 1996-7 Duration of DOT not stated Informed consent not obtained as participants were not told that they were participating in a study Choice of supervisor for DOT participants: 352 chose a family member; 34 chose a community member; and 24 chose health centre staff One participant in daily supervision arm excluded due to protocol violation so not strictly intention-to-treat
Allocation concealment	C – Inadequate

Characteristics of included studies (*Continued*)

Study	**Lwilla 2003**
Methods	Cluster-randomized controlled trial: 9 pairs of centres matched by type and size Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: none Completeness of follow up: 87% at 2 months and 69% at 7 months
Participants	Number: 18 clusters randomized; 522 participants; mean age 35; 60% male Included: new smear positive adults
Interventions	(1) Community-based DOT: daily observation by community health volunteer (site not stated) for intensive 2-month treatment period; health worker visited volunteer every 2 weeks and district co-ordinator visited volunteer monthly; at each visit participants' treatment card checked and drugs counted (2) Institution-based DOT: required to attend health facility daily for 2 months, and then monthly after this Continuation phase of 6 months: both groups managed the same and expected to self administer treatment daily
Outcomes	(1) Sputum negative at 2 months (primary outcome) (2) Cure at 7 months (sputum negative at 2 months and at 5 to 7 months)
Notes	Location: Tanzania Date: 1999-2000 Duration of DOT not stated
Allocation concealment	B – Unclear

Study	**MacIntyre 2003**
Methods	Quasi-randomized controlled trial Generation of allocation sequence: alternate allocation Concealment of allocation: none Blinding: assessment of urinary isoniazid blinded Completeness of follow up: not stated
Participants	Number: 173 recruited, mostly foreign nationals; male 51%; mean age 41 (range 14 to 83) Included: new tuberculosis participants Excluded: multiple-drug resistant tuberculosis; relapsed tuberculosis; HIV-positive cases; and nontuberculous mycobacterial infections
Interventions	(1) Family-based DOT: daily observation by a nominated family member who received education and was expected to record participant compliance with pill taking; weekly phone calls from a nurse; nurse on call; nurse home visit every 2 weeks (2) Self administration of treatment: daily Both groups had monthly visits to health facilities and standardized recording charts
Outcomes	Treatment completion measured by: (1) Percentage clinic attendances to collect drugs (2) Urinary isoniazid (6 random checks over months; all had to be > 0)
Notes	Location: Australia Date: 1998 to December 2000 Duration of DOT not stated
Allocation concealment	C – Inadequate

Study	**Malotte 2001**
Methods	Generation of allocation sequence: randomized, blocks of 18 Allocation concealment: sequentially numbered, opaque, sealed envelopes

Characteristics of included studies (*Continued*)

	Blinding: none Completeness of follow up: not stated
Participants	Number: 163 randomized; 82% male Included: active or recent injection or crack cocaine users screened for tuberculosis with positive tuberculin skin test (at least 10 mm induration or 5 mm if HIV positive) Excluded: people with active tuberculosis
Interventions	(1) DOT by outreach worker (location decided by participant) plus US$5 at each visit (2) As (1) but no money (3) DOT at study community site plus US$5 All participants received isoniazid 2 times a week for 6 months or 1 year (depending on HIV status)
Outcomes	(1) Percentage medication taken on time; excludes medication taken late (next day) (2) Completion of medication
Notes	Location: Long Beach, California, USA Date: 1994-7 Lost to follow up included prison or moved and were included in outcome (1) but excluded completely from outcome (2)
Allocation concealment	A – Adequate

Study	**Newell 2006**
Methods	Cluster-randomized controlled trial Generation of allocation sequence: 5 randomly selected districts allocated to each arm; the name of each district was written on an individual paper and randomly drawn from a basket Allocation concealment: method not stated Blinding: laboratory technicians assessing the primary outcomes were blinded Completeness of follow up: 100% (no clusters or individuals lost)
Participants	Number: 10 districts with 907 people randomized; all smear positive; 67% male Included: people with tuberculosis (aged 15+); new smear-positive cases, diagnosed at health facilities in the study area; HIV-status not known
Interventions	(1) Community-based DOT: daily treatment supervised by a female community health worker (unpaid volunteer selected by the district health authority) or village health worker (community worker paid by government). Patients mainly visited at home, but occasionally patients met their supervisor at her home. Supervision was for the duration of treatment with drugs provided to the supervisor monthly. Tracing by the supervisor was undertaken for patients who discontinued treatment (2) Family-based DOT: daily supervision by a household member chosen by the participant with drugs provided to the supervisory weekly. Government workers traced those who discontinued treatment
Outcomes	(1) Treatment success: cure plus treatment completion [primary] (2) Treatment success compared with the World Health Organization target of 85% (3) Estimated case detection rate with the World Health Organization target of 70% (4) Compare the above rates in men and women
Notes	Location: hill and mountain districts of Nepal Date: 2002-3
Allocation concealment	C – Inadequate

Study	**Walley 2001**
Methods	Generation of allocation sequence: computer-generated random numbers Allocation concealment: opaque, sealed envelopes Blinding: assessors blinded

Characteristics of included studies (*Continued*)

	Completeness of follow up: not stated
Participants	Number: 497 randomized; 51.3% male Included: adults (aged 15+); new smear-positive cases
Interventions	(1) DOT by a health worker at a health facility that met "access criteria" or a community health worker at or near the participant's home: access criteria were return journey from the participant's home to facility < 2 km, < 2 h duration, and < 10 rupees, and for unmarried women an accompanying relative was available; participants had to attend a health facility or meet a community health worker 6 times per week for 2 months to take their drugs; thereafter they self administered drugs that the participants collected twice a month (2) DOT by a family member chosen by the participant (3) Self administration of drugs collected by participant fortnightly All participants received isoniazid-rifampicin-pyrazinamide-ethambutol for 2 months and isoniazid-ethambutol for 6 months
Outcomes	(1) Cure: sputum negative at 7 or 8 months and on at least 1 previous occasion (2) Treatment completion: treatment completed, but smear results not available on at least 2 occasions before completion of treatment (3) Treatment failure (4) Death (5) Default (6) Transferred out
Notes	Location: Pakistan Date: 1996-8
Allocation concealment	A – Adequate

Study	**Wandwalo 2004**
Methods	Generation of allocation sequence: coin tossing in each of 5 clinics Allocation concealment: none Blinding: none Completeness of follow up: 100% (no losses)
Participants	Number: 587 randomized; 322 smear positive, 182 smear negative, and 83 extrapulmonary tuberculosis; 57% male Included: people with tuberculosis (aged 5+); new smear positive, smear negative, and extrapulmonary cases; HIV-status not known Excluded: previously treated for tuberculosis; severe illness; transferred from another clinic; previously enrolled in the study
Interventions	(1) Community-based DOT: daily treatment supervised at home by 'guardian' (usually a family member) during 2-month intensive period; supervisors trained to observe drug taking, encourage participants to complete treatment, keep records, collect drugs, and assess drug side effects; during first 2 months participants received 'spot' visits by health workers who conducted treatment card checks and pill counts; during first 2 months participants also requested to attend clinic every 2 weeks for clinical review and progress monitoring (2) Health facility-based DOT: daily supervision at clinic by health workers during the 2 month intensive period Apart from the observation option participants received the same standardized management including drug therapy
Outcomes	(1) Treatment success: cure plus treatment completion (2) Cure: smear positive initially and negative at 7 or 8 months and on at least 1 previous occasion (3) Treatment completion: positive results initially, negative at 2 months and no results at end of treatment; or smear negative initially and received treatment on clinical grounds; or those who completed full course of treatment but had no initial or end-of-treatment results (4) Death: from all causes

	(5) Treatment failure: participants who remained or became smear positive or 5 months or later (6) Default: failed to collect medication for > 2 consecutive months (7) Transferred out: transferred to a clinic in another area
Notes	Location: Dar es Salaam, Tanzania Date: 2001-3
Allocation concealment	C – Inadequate

Study	**Wright 2004**
Methods	Generation of allocation sequence: unclear; stratified into adults and children; then, within each group, randomized by type of tuberculosis (sputum positive, sputum negative, extrapulmonary, relapse) Allocation concealment: unclear; sealed, sequentially numbered envelopes not stated if opaque Blinding: assessors of sputum results blinded Completeness of follow up: 98%
Participants	Number: 1353 randomized; 55% male; most 15+ years Included: adults and children with smear positive or negative, extrapulmonary tuberculosis, or relapse of previously treated tuberculosis Excluded: died before discharge; or too ill to receive outpatient treatment; lived in area without treatment supporter; or referred in after treatment commenced
Interventions	(1) DOT by community health worker: participants visited for observation daily; community health worker trained to provide daily treatment supervision, record adherence on Treatment Support Card, remind participants who did not report for treatment, and notify diagnostic centre about those who defaulted treatment (2) DOT by family member: family member or carer chosen by participant trained to provide daily treatment supervision, record adherence on Treatment Support Card, and remind participants who did not report for treatment; participants also required to visit the community health worker weekly to check side effects and adherence and receive health education; defaulters reported to the diagnostic centre
Outcomes	(1) Cure or treatment completion: cure defined as smear negative at 6 months and on at least 1 previous occasion; treatment completion defined as treatment completed but smear results not available on at least 2 occasions before treatment completion (2) Death (3) Treatment failure: remained or became smear positive at > = 5 months (4) Default: failed to collect medication for > 2 consecutive months (5) Transferred out: formally transferred to another centre
Notes	Location: Swaziland Date: 2000-2
Allocation concealment	B – Unclear

Study	**Zwarenstein 1998**
Methods	Generation of allocation sequence: computer-generated random numbers Allocation concealment: consecutively numbered, opaque, sealed envelopes in each of 5 clinics Blinding: none Completeness of follow up: 114/120 (95%) in 1 trial and 102/120 (85%) in other trial excluded from analysis
Participants	Number: 216 included in analysis; 62% male; 57% < 35 years Included: adults (aged 15+) with pulmonary tuberculosis; both new and retreatment cases Excluded: severe disease or multiple drug resistance; treatment at a non-study clinic for more than 2 weeks; need to be supervised at school or at the workplace; and leaving the area within a month
Interventions	(1) DOT by clinic nurses: participants asked to visit the clinic 5 days a week for 8 weeks (new participants) or for 12 weeks (retreatment participants); thereafter expected attendance was 3 days a week for the continuation phase; clinic visits restricted to normal working hours and adherence card signed and dated by a nurse at each visit and kept at the clinic

Characteristics of included studies (*Continued*)

	(2) Self administration of treatment: participants had to visit clinic once a week or send a relative to collect drugs; participants completed their own adherence card for every day of drug taking and a nurse recorded the weekly drug collection; adherence card handed to nurse at the weekly clinic visit New cases received Rifater (combined rifampicin-isoniazid-pyrazinamide) for 8 weeks followed by Rifinah 4 (combined rifampicin-isoniazid) plus additional isoniazid for 18 weeks Retreatment participants received Rifater plus ethambutol for 12 weeks and Rifinah plus rifampicin-ethambutol for 22 weeks
Outcomes	(1) "Successful treatment" included those who were cured and those who completed treatment; "cured" applied to those who converted from a positive smear and/or culture to a negative smear and/or culture at the end of treatment (6 months for new participants and 8 months for retreatment participants); "treatment completed" referred to participants who (a) completed the full course of treatment but had no pretreatment or post-treatment bacteriological results; (b) had negative pretreatment results and had been treated on clinical grounds; or (c) had positive pretreatment results, negative results after 2 months and no post-treatment results (2) "Treatment failure" applied to participants with a positive smear or culture at the end of treatment (3) "Treatment interrupters" applied to participants who stopped taking treatment for 8 or more weeks during the treatment period (4) Transfer to another treatment facility (5) Death from tuberculosis or other causes while on treatment
Notes	Location: 1 trial in each of 2 low-income communities near Cape Town, South Africa Date: 1994-5 Results combined 54 participants in 1 trial allocated to community supervision not reported in this paper Exclusions from analysis: trial 1 (6 cases of multiple drug resistance) and trial 2 (12 cases of multiple drug resistance and 6 not tuberculosis) Number of exclusions per arm of the 2 trials not given
Allocation concealment	A – Adequate

Study	**Zwarenstein 2000**
Methods	Generation of allocation sequence: computer-generated random numbers Allocation concealment: consecutively numbered, opaque, sealed envelopes Blinding: none Completeness of follow up: not stated
Participants	Number: 174 randomized Included: new or retreatment participants aged 15+ who were sputum or culture positive
Interventions	(1) DOT by clinic nurses (see Zwarenstein 1998) (2) Self administration (see Zwarenstein 1998) (3) DOT by lay health workers: participants took drugs at home of a lay health worker under supervision; if participant missed treatment for 1 day, a lay health worker visited participant's home and if necessary a member of the South African Tuberculosis Association (SANTA) also visited the participant
Outcomes	As for Zwarenstein 1998
Notes	Location: 4 clinics in a township near Cape Town, South Africa Date: 1994-5 18 participants excluded from analysis: 12 with multiple-drug resistant tuberculosis and 6 not tuberculosis
Allocation concealment	A – Adequate

DOT: directly observed therapy; HIV: human immunodeficiency virus

Characteristics of excluded studies

Study	Reason for exclusion
Batki 2001	Compared direct observation plus with methadone treatment for injecting drug users with routine tuberculosis treatment without methadone
Carroll 2004	Before-and-after study; no control group
Hwang 2004	Not randomized
Jasmer 2004	Different criteria for allocation to self administration or direct observation
Lewin 2004	An educational intervention was evaluated
Mathew 2002	Cohort study
Moulding 2001	Trial evaluating devices that monitor treatment using uranium along a strip of photographic film
Pungrassami 2002	2 publications reporting the same study; not randomly allocated
Sorete-Abore 2002	Cohort study
Tandon 2002	Described as a randomized trial, but the randomization led to very different numbers in the 2 groups; subsequently over 50 participants (out of a total of 379) crossed over from self treatment to direct observation and were excluded from the analysis; little detail for the rest of the study provided
Thiam 2007	Multifaceted intervention including directly observed therapy
Toyota 2003	Patients in hospital

ADDITIONAL TABLES

Table 01. Search strategies for databases

Search set	CIDG SR^	CENTRAL	MEDLINE^^	EMBASE^^	LILACS^^
1	tuberculosis	tuberculosis	tuberculosis	tuberculosis	tuberculosis
2	DOT*	PATIENT COMPLIANCE	PATIENT COMPLIANCE	PATIENT COMPLIANCE	DOT*
3	directly observed therapy	PATIENT PARTICIPATION	PATIENT PARTICIPATION	PATIENT MONITORING	supervision
4	2 or 3	patient monitoring	MOTIVATION	DOT$	2 or 3
5	1 and 4	MOTIVATION	DECISION SUPPORT TECHNIQUES	directly observed therapy	1 and 4
6	-	DECISION SUPPORT TECHNIQUES	DOT*	compliance	-
7	-	DOT*	directly observed therapy	motivation	-
8	-	directly observed therapy	compliance	patient$	-
9	-	compliance	patient*	defaulter$	-
10	-	defaulter*	defaulter*	adheren$	-
11	-	adheren*	adheren*	supervis$	-

Table 01. Search strategies for databases (*Continued*)

Search set	CIDG SR^	CENTRAL	MEDLINE^^	EMBASE^^	LILACS^^
12	-	supervision*	supervis*	2-11/or	-
13	-	2-12/or	2-12/or	1 and 12	-
14	-	1 and 13	1 and 13	Limit 13 to human	-
15	-	-	Limit 14 to human	-	-
	^Cochrane Infectious Diseases Group Specialized Register		^^Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Higgins 2006); upper case: MeSH or EMTREE heading; lower case: free text term		

Table 02. Methodological quality assessment^

Trial	Randomization type	Sequence^^	Concealment^^	Blinding (assessors)	Completeness^^
Chaisson 2001	Individual	Adequate	Unclear	Inadequate	Inadequate
Kamolratanakul 1999	Individual	Adequate	Inadequate	Inadequate	Adequate
Lwilla 2003	Cluster	Unclear	Unclear	Inadequate	Inadequate
MacIntyre 2003	Individual	Inadequate	Inadequate	Adequate	Unclear
Malotte 2001	Individual	Unclear	Adequate	Inadequate	Unclear
Newell 2006	Cluster	Adequate	Inadequate	Adequate	Adequate
Walley 2001	Individual	Adequate	Adequate	Adequate	Unclear
Wandwalo 2004	Individual	Adequate	Inadequate	Inadequate	Adequate
Wright 2004	Individual	Unclear	Unclear	Adequate	Adequate
Zwarenstein 1998	Individual	Adequate	Adequate	Inadequate	Adequate
Zwartenstein 2000	Individual	Adequate	Adequate	Inadequate	Unclear

^Details of methods in the 'Characteristics of included studies'; ^^Generation of allocation sequence, allocation concealment, and completeness of follow up

ANALYSES

Comparison 01. Direct observation versus self administration

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Cure	4	1603	Relative Risk (Random) 95% CI	1.02 [0.86, 1.21]
02 Cure or completion of treatment	4	1603	Relative Risk (Fixed) 95% CI	1.06 [1.00, 1.13]
03 Completion of treatment			Relative Risk (Fixed) 95% CI	Totals not selected

Comparison 02. Direct observation versus self administration: stratified by location of direct observation

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Cure			Relative Risk (Fixed) 95% CI	Subtotals only
02 Cure or completion of treatment			Relative Risk (Fixed) 95% CI	Subtotals only

Comparison 03. Direct observation: home versus clinic

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Cure or completion of treatment			Relative Risk (Fixed) 95% CI	Totals not selected

Comparison 04. Home-based direct observation: family member versus community health worker

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Cure or completion of treatment			Relative Risk (Fixed) 95% CI	Totals not selected

Comparison 05. Intravenous drug users: direct observation versus self administration

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Completion of treatment			Relative Risk (Fixed) 95% CI	Totals not selected

Comparison 06. Intravenous drug users: choose own location versus treatment centre

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Completion of treatment			Relative Risk (Fixed) 95% CI	Totals not selected

INDEX TERMS

Medical Subject Headings (MeSH)

Antitubercular Agents [*therapeutic use]; *Directly Observed Therapy; Randomized Controlled Trials as Topic; Tuberculosis, Pulmonary [*drug therapy]

MeSH check words

Humans

COVER SHEET

Title	Directly observed therapy for treating tuberculosis
Authors	Volmink J, Garner P
Contribution of author(s)	Jimmy Volmink initiated the review, wrote the protocol, applied the inclusion criteria, conducted the data extraction, and drafted the review. Paul Garner helped write the protocol, applied the inclusion criteria, constructed comparisons, and helped draft the review. Both authors remain actively involved in updating.
Issue protocol first published	2001/4
Review first published	2001/4
Date of most recent amendment	17 August 2007
Date of most recent SUBSTANTIVE amendment	13 August 2007
What's New	2007, Issue 4: added Newell 2006, with no change to the conclusions; added references to new tuberculosis adherence reviews in the 'Background' section and reworded objectives to clarify that the review encompasses comparisons between different types of directly observed therapy. 2006, Issue 2 (Volmink 2006): Lwilla 2003, MacIntyre 2003, Wandwalo 2004, and Wright 2004 added; no change to the conclusions. 2003, Issue 1 (Volmink 2003): Chaisson 2001 and Malotte 2001 added; no change to the conclusions. 2001, Issue 4 (Volmink 2001): first version of this review on directly observed therapy. 2000, Issue 4 (Volmink 2000a): original review split into a series of Cochrane Reviews, each focusing on particular intervention promotion strategies, such as directly observed therapy in this review. 1997, Issue 2: review first published as 'Interventions for promoting adherence to tuberculosis management'.
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
Contact address	Prof Jimmy Volmink Deputy Dean (Research) and SACC Director Faculty of Health Sciences Stellenbosch University PO Box 19063 Tygerberg Cape Town 7505 SOUTH AFRICA E-mail: jvolmink@sun.ac.za Tel: +27 21 938 9098 Fax: +27 21 938 9558

DOI 10.1002/14651858.CD003343.pub3

Cochrane Library number CD003343

Editorial group Cochrane Infectious Diseases Group

Editorial group code HM-INFECTN

GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Direct observation versus self administration, Outcome 01 Cure

Review: Directly observed therapy for treating tuberculosis

Comparison: 01 Direct observation versus self administration

Outcome: 01 Cure

Study	DOT n/N	Self n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Kamolratanakul 1999	315/414	283/422		41.5	1.13 [1.04, 1.24]
Walley 2001	199/335	100/162		34.2	0.96 [0.83, 1.12]
Zwarenstein 1998	18/53	31/61		11.2	0.67 [0.43, 1.05]
Zwarenstein 2000	55/112	18/44		13.1	1.20 [0.80, 1.79]
Total (95% CI)	914	689		100.0	1.02 [0.86, 1.21]

Total events: 587 (DOT), 432 (Self)

Test for heterogeneity chi-square=8.41 df=3 p=0.04 I^2 =64.3%

Test for overall effect z=0.21 p=0.8

Analysis 01.02. Comparison 01 Direct observation versus self administration, Outcome 02 Cure or completion of treatment

Review: Directly observed therapy for treating tuberculosis

Comparison: 01 Direct observation versus self administration

Outcome: 02 Cure or completion of treatment

Study	DOT n/N	Self n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kamolratanakul 1999	347/414	320/422		59.8	1.11 [1.03, 1.18]
Walley 2001	216/335	105/162		26.7	0.99 [0.87, 1.14]
Zwarenstein 1998	27/53	37/61		6.5	0.84 [0.60, 1.17]
Zwarenstein 2000	73/112	26/44		7.0	1.10 [0.83, 1.46]
Total (95% CI)	914	689		100.0	1.06 [1.00, 1.13]

Total events: 663 (DOT), 488 (Self)

Test for heterogeneity chi-square=4.25 df=3 p=0.24 I^2 =29.4%

Test for overall effect z=1.80 p=0.07

Analysis 01.03. Comparison 01 Direct observation versus self administration, Outcome 03 Completion of treatment

Review: Directly observed therapy for treating tuberculosis

Comparison: 01 Direct observation versus self administration

Outcome: 03 Completion of treatment

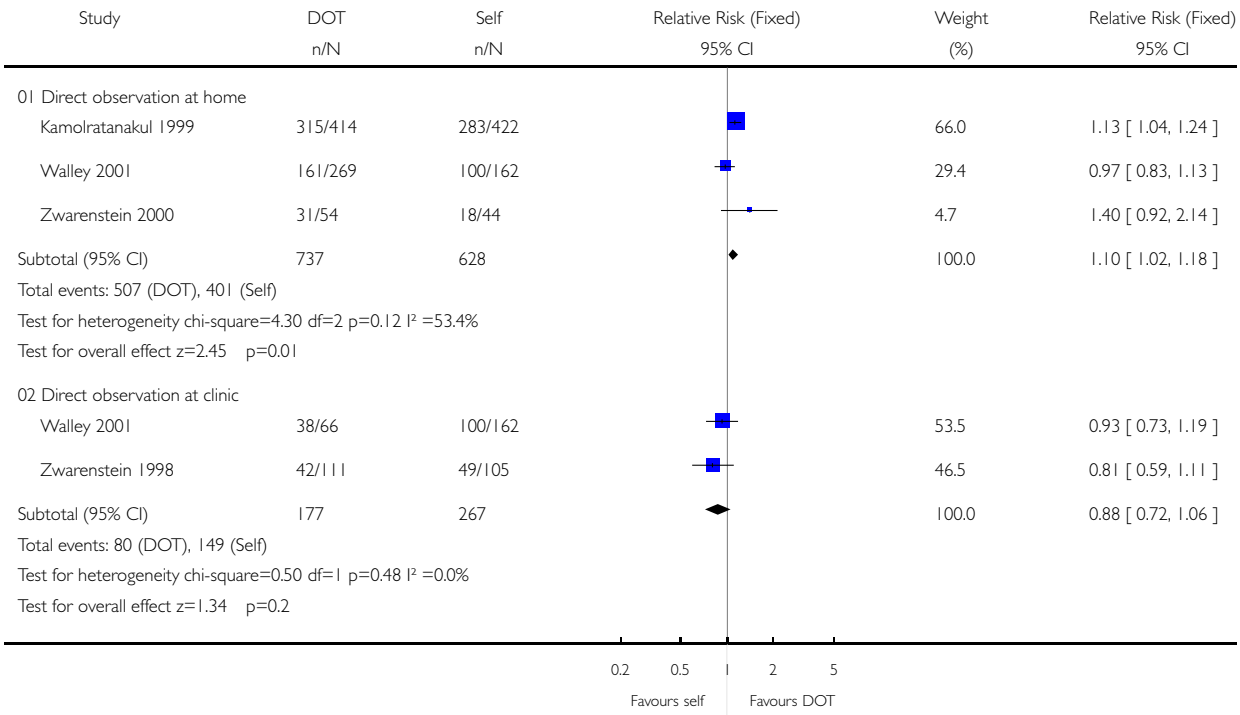
Study	DOT n/N	Self n/N	Relative Risk (Fixed) 95% CI	Relative Risk (Fixed) 95% CI
MacIntyre 2003	84/87	78/86		1.06 [0.98, 1.15]

Analysis 02.01. Comparison 02 Direct observation versus self administration: stratified by location of direct observation, Outcome 01 Cure

Review: Directly observed therapy for treating tuberculosis

Comparison: 02 Direct observation versus self administration: stratified by location of direct observation

Outcome: 01 Cure

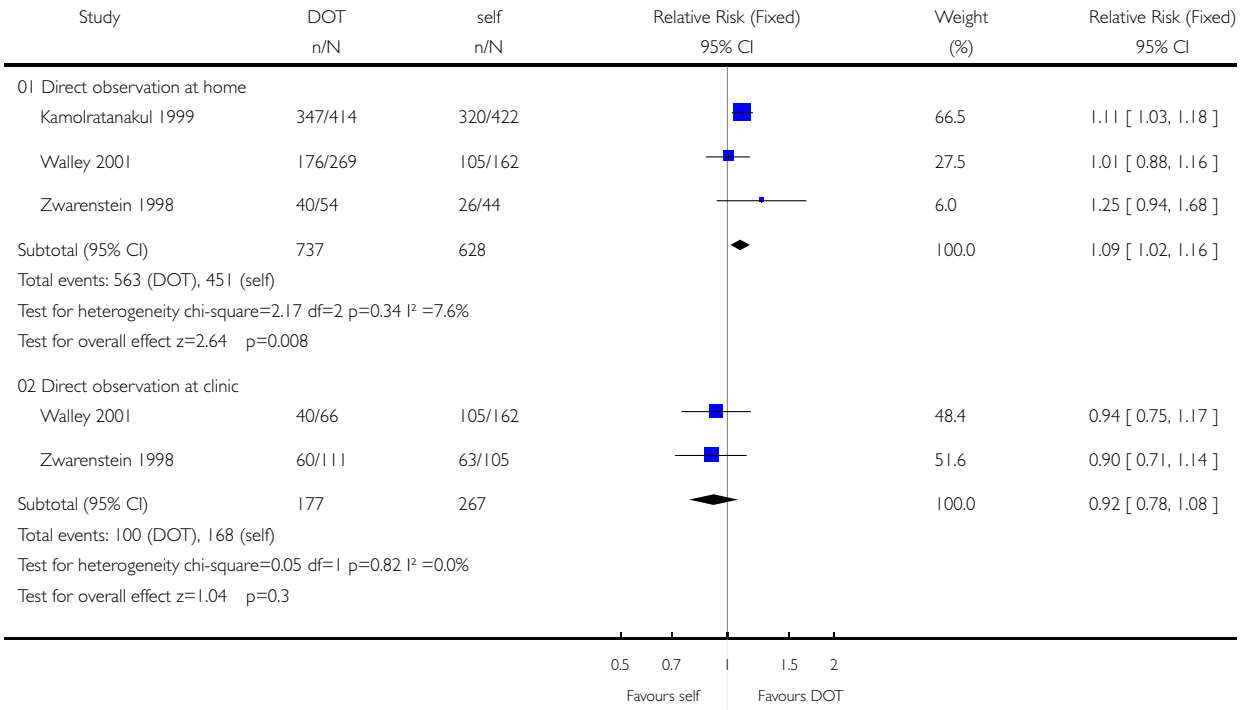


Analysis 02.02. Comparison 02 Direct observation versus self administration: stratified by location of direct observation, Outcome 02 Cure or completion of treatment

Review: Directly observed therapy for treating tuberculosis

Comparison: 02 Direct observation versus self administration: stratified by location of direct observation

Outcome: 02 Cure or completion of treatment

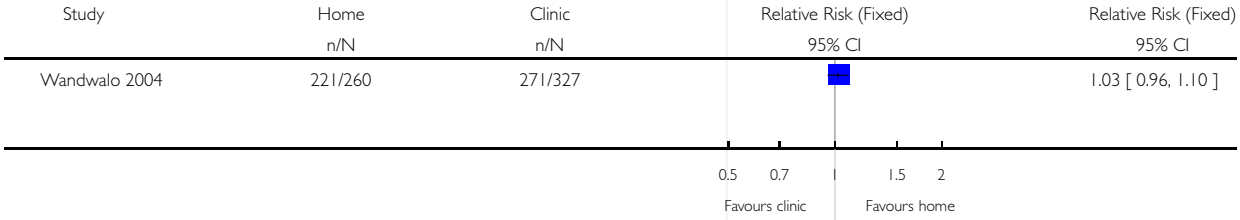


Analysis 03.01. Comparison 03 Direct observation: home versus clinic, Outcome 01 Cure or completion of treatment

Review: Directly observed therapy for treating tuberculosis

Comparison: 03 Direct observation: home versus clinic

Outcome: 01 Cure or completion of treatment

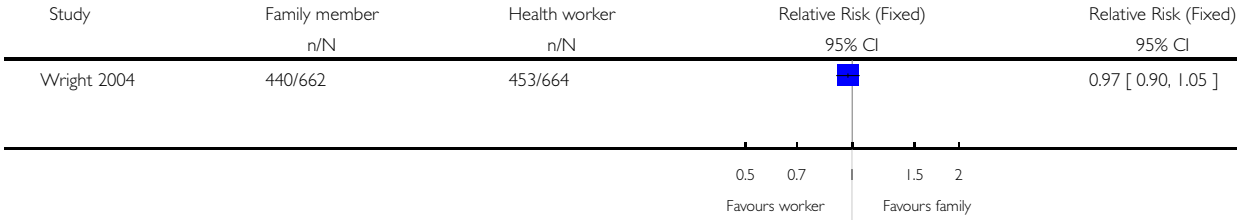


Analysis 04.01. Comparison 04 Home-based direct observation: family member versus community health worker, Outcome 01 Cure or completion of treatment

Review: Directly observed therapy for treating tuberculosis

Comparison: 04 Home-based direct observation: family member versus community health worker

Outcome: 01 Cure or completion of treatment

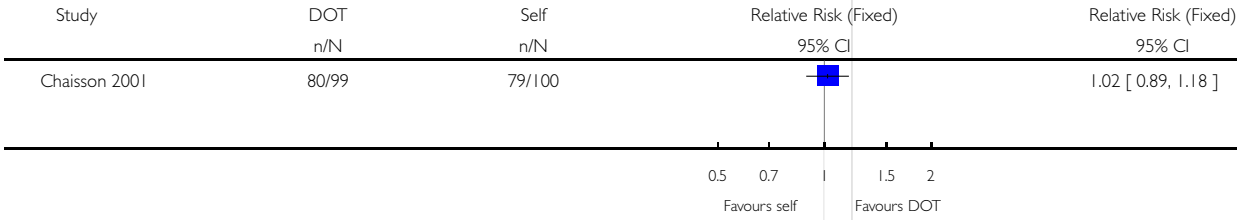


Analysis 05.01. Comparison 05 Intravenous drug users: direct observation versus self administration, Outcome 01 Completion of treatment

Review: Directly observed therapy for treating tuberculosis

Comparison: 05 Intravenous drug users: direct observation versus self administration

Outcome: 01 Completion of treatment



Analysis 06.01. Comparison 06 Intravenous drug users: choose own location versus treatment centre, Outcome 01 Completion of treatment

Review: Directly observed therapy for treating tuberculosis

Comparison: 06 Intravenous drug users: choose own location versus treatment centre

Outcome: 01 Completion of treatment