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Interventions using mobile devices (phones, smart phones, or tablets) to improve adherence to treatment for HIV or tuberculosis (Protocol)

Roberts DJ, Rylands J, Sinclair D

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T A B L E   O F   C O N T E N T S

[Intervention Protocol]

Interventions using mobile devices (phones, smart phones, or tablets) to improve adherence to treatment for HIV or tuberculosis

David J Roberts[1], Joseph Rylands[2], David Sinclair[3]

[1]UK Cochrane Centre, Oxford, UK. [2]Arrowe Park Hospital, Liverpool, UK. [3]Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK

Contact address: David J Roberts, UK Cochrane Centre, Summertown Pavilion, Middle Way, Oxford, Oxfordshire, OX2 7LG, UK. david.roberts@cochrane.nhs.uk. davidjrobs@doctors.org.uk.

A B S T R A C T

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of adherence interventions delivered through mobile devices on adherence to treatment for HIV or tuberculosis (TB), compared with standard of care, non-mobile device adherence interventions, or alternative mobile device interventions.

B A C K G R O U N D

Description of the condition

Tuberculosis (TB) and HIV are infectious diseases that have broadly overlapping epidemiology and both require prolonged treatment with multiple drugs. People with TB are typically treated for six to 12 months with up to five drugs (WHO 2010), while people who are HIV-positive require lifelong antiretroviral therapy (ART) (WHO 2015b). Consequently, many people find it difficult to maintain adherence throughout treatment, and some people undergoing treatment fail to complete treatment programmes (WHO 2003; Munro 2007b). Interventions to improve adherence and retention in care are therefore important components of TB and HIV programmes. By improving the effectiveness of antimicrobial therapy, they have the potential to improve treatment

outcomes for the individual (Paterson 2000; WHO 2003; Sabin 2015), reduce disease transmission (Eaton 2012), and prevent the development of drug-resistant organisms (Friedland 1999; Moonan 2011).

HIV is primarily transmitted from person-to-person via sexual intercourse, although intravenous inoculation (via shared needles in people who inject drugs or unscreened blood transfusion), and vertical transmission (from mother to child at birth or via breast-feeding) are also important modes of transmission (WHO 2014). The early stages of HIV infection are commonly asymptomatic, but without treatment the virus causes progressive impairment of the immune system, and increasing susceptibility to both common and uncommon infections (WHO 2015d).

The infecting organism that causes TB is *Mycobacterium tuberculosis*, which is primarily transmitted via inhalation of respiratory droplets. Most infections are initially controlled by the immune

system but not fully eradicated; an asymptomatic state known as 'latent TB'. The latent mycobacteria may then become 'active' as a later time, particularly during impaired host immunity such as that caused by HIV, malnutrition, or diabetes (WHO 2016). The symptoms and signs of active TB depend on the organs affected, but the most common site is the lungs which typically presents as a progressive cough with weight loss and fever.

HIV and TB are major causes of death and continue to exact a substantial health burden across the globe. In 2014, TB was responsible for 1.5 million deaths, and HIV for 1.2 million (WHO 2015a). Of the 1.2 million HIV deaths, 0.4 million people who died were co-infected with TB, and of the 9.6 million people who were estimated to have developed active TB infection in 2014, 12% were HIV-positive (WHO 2015a). Of the 35 million people estimated to be infected with HIV globally in 2013, nearly 25 million were in the World Health Organization (WHO) African region (WHO 2013). The WHO African region had 28% of global TB cases in 2014, and cases in WHO South East Asia and Western Pacific regions collectively accounted for 58% of the global TB burden (WHO 2015a). Both diseases remain high on the international policy agenda; the United Nations (UN) Sustainable Development Goals (SDGs) call for an end to both epidemics by 2030 (UN 2015).

Description of the intervention

The use of mobile devices to support health care and public health practice has been labelled 'Mobile health' or 'mHealth' by the WHO (WHO 2011), and includes any mobile device that utilizes wireless technology or bluetooth (and is therefore not dependant on a wired connection). 'eHealth' is a broader term that covers the use of any information and communication technology (ICT) for health and health-related purposes (WHO 2015c).

Within mHealth, devices that are intended to be carried with a person at all times are particularly suited to adherence interventions, including pagers, mobile phones, smart phones, personal digital assistants (PDAs), and tablets. These devices support a variety of media: Short Messaging Services (SMS) or text messaging, voice or video calls, and specialized software applications (Apps) (Hamine 2015), which can be used to deliver a range of adherence interventions (see Table 1). Notably, many of these approaches are already implemented in TB and HIV control programmes through more traditional channels, and have been the subject of previous Cochrane reviews: letter or telephone reminder systems for improving adherence in TB (Liu 2014); face-to-face directly observed therapy for treating TB (Karumbi 2015); material incentives and enablers delivered through clinics and community health workers (Lutge 2015); and patient education and counselling delivered via telephone or face-to-face) (M'Imunya 2012). mHealth interventions therefore offer an alternative or additional approach to delivery of already complex packages of adherence support.

How the intervention might work

Behavioural theories can be used to understand why patients may or may not adhere to treatment. Cognitive perspective theories hold that an 'intention to adhere' results from a combination of 'personal factors':

- self-efficacy (a person's ability to cope with the challenge at hand); and
- the persons knowledge about the illness, treatment, and likely outcomes (Munro 2007a).

This intention to adhere may then be facilitated or inhibited by a variety of other factors (Munro 2007b):

- health system factors (for example, organization of care, geographical and financial access, side effects);
- structural factors (for example, poverty, gender, discrimination, law, finances);
- social context factors (for example, family, household, and community support and attitudes, stigma).

Adherence interventions seek to change behaviour by modifying these factors, and the 'active components' of behaviour change interventions have been classified and grouped hierarchically, based on similar mechanisms of action (Cane 2015):

- Group 1: scheduled consequences, reward and threat;
- Group 2: cues and cue responses;
- Group 3: covert learning and natural consequences; feedback and monitoring, goals and planning; social support and social comparison; shaping knowledge, self-belief, and identity (these subgroups are grouped together because they are considered to have less distinct mechanisms of action than those in Groups 1 or 2).

The adherence interventions identified in Table 1 are likely to operate through distinct theoretical mechanisms. They probably all influence the personal factors affecting adherence, but social support, monitoring, and incentive/enabler interventions may also act on the social factors, health system factors, and structural factors respectively (see Figure 1).

Figure 1. Logic model of factors influencing adherence to medication (adapted from Munro 2007a and Munro 2007b)
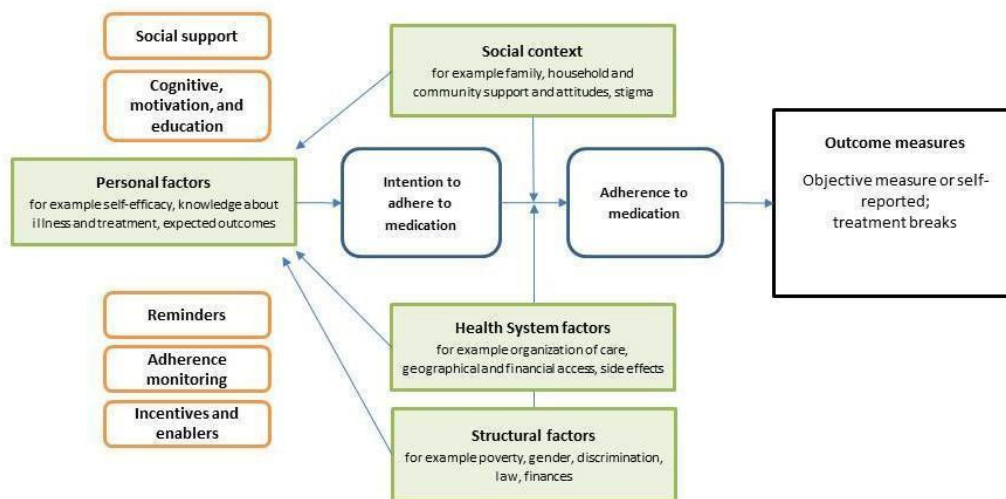
Why it is important to do this review

Mobile technology is already relatively widespread in low- and high-income countries, where 45% and 79% of the population had a mobile subscription by the end of 2014, respectively, and this is expected to grow to 56% and 81% by 2020, with particularly rapid growth predicted on the African continent (GSMA 2015). The users of social media platforms that deliver mHealth interventions are of diverse ethnic, racial, and income backgrounds (Taggart 2015), which increases the accessibility of interventions delivered in this way. Smart phones, which utilise data connections to access the internet, are rapidly being taken up in place of traditional mobile phones, including in developing countries and on mobile broadband networks, which extends the available interventions for mHealth adherence interventions (GSMA 2015; WHO 2015c). The potential value of mHealth approaches to TB prevention and care has been recognised by the WHO (WHO 2015c).

Despite decades of study, a recent Cochrane review of measures to improve adherence found there were few, if any, effective interventions with a clinically significant impact (Nieuwlaat 2014), and underlined that interventions also need to be affordable, and actionable in real world healthcare settings. mHealth interventions present an opportunity of an adherence intervention that is both affordable and actionable at large scale, and are a very active field of research, with multiple randomized controlled trials (RCTs) published (particularly for HIV (Mills 2015), or underway (for TB (WHO 2015c)), hence mHealth adherence intervention ef-fectiveness needs to be examined by a comprehensive systematic review.

It may be useful to combine studies in order to increase the power of our review to examine the effects of an intervention, if there are enough similarities between the population, type of intervention, and outcome measured. This review examines adherence in HIV and TB together for a number of reasons: HIV is a strong risk factor for TB and consequently they often occur together in the same person; they share the same or similar high prevalence settings, are relatively more common amongst marginalized groups, and consequently the health system factors and barriers to care (and adherence) are likely to be similar; both illnesses require prolonged treatment with multiple drugs, even when the patient feels well; and both illnesses can result in stigmatization of the person affected, potentially affecting treatment adherence (WHO 2003; Munro 2007b; Katz 2013). Though condition-related differences in treatment and support may differentially modify adherence between participants with TB or HIV, disease- or therapy-specific factors are not more important determinants of adherence than other factors such as socioeconomic position and access to health-care (WHO 2003; Kardas 2013), and similar reservations could apply when combining different studies within the same target infection. We will give careful consideration to similarities/differences in populations, co-interventions and outcomes measured when we combine studies for meta-analysis, to best ensure apparent differences in adherence intervention effectiveness are in fact attributable to the intervention being investigated.

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OBJECTIVES

To assess the effects of adherence interventions delivered through mobile devices on adherence to treatment for HIV or tuberculosis (TB), compared with standard of care, non-mobile device adherence interventions, or alternative mobile device interventions.

METHODS

Criteria for considering studies for this review

Types of studies

Individually randomized controlled trials (RCTs) and cluster-RCTs.

Types of participants

Adults or children prescribed treatment for HIV, active TB, or both.

Types of interventions

Intervention

Any intervention that utilizes a participant's mobile device to promote adherence to treatment, or adherence to a treatment programme. For the purposes of this Cochrane review, mobile device refers to devices that are intended to be carried on the person (for example, pager, phone, smart phone, personal digital assistants (PDA), or tablet). These interventions may be delivered via text messaging, voice, video, or smart phone applications and may include any combination of the following components: reminders; adherence monitoring; social support; financial incentives; cognitive-behavioural, motivational, or educational interventions.

We will exclude interventions that use an automated reminder device that do not rely on telecommunication, such as 'beepers'. We will exclude mobile health interventions bundled with other non-mobile health interventions unless we can analyse the mobile health intervention outcome data separately. We will only include interventions delivered using an internet-based platform if the intervention was designed and intended for use via a mobile device.

Control

Any alternative intervention aimed at increasing adherence, including both those delivered through standard (non-mobile device) approaches and alternative strategies that involve mobile devices. We will also include trials with inactive controls that do not receive an adherence intervention as part of their usual care.

Types of outcome measures

We will include trials with any measure of adherence to medication, or a treatment programme (both as a single event e.g. response to a single reminder text message to attend an appointment, or adherence across a treatment programme), but will only perform quantitative analysis of trials that report certain measures (for more detail on analysis of specific measures of adherence please see the 'Data extraction and management' section).

Primary outcomes

We will adopt adherence to medication or adherence to a treatment programme as our primary outcomes, rather than measures of treatment success. This will extend the potential pooling of trials because it is a shared outcome between TB and HIV participants, is more commonly measured and reported (particularly in trials from low- and middle-income countries) and therefore more easily pooled than biological measures, will have more power to detect potentially effective interventions than sparsely occurring endpoints such as death or TB treatment failure, and avoids confounding of biological measures of adherence due to co-morbidity, drug interaction, and drug resistance.

- Measures of adherence to medication:
    - 'objective' measures such as pharmacy refill data, pill count, electronic drug monitoring (EDM), and self-reported adherence measures such as number or proportion of doses missed, self-rated estimates of adherence;
- measures of programme adherence:
    - treatment completion (for TB);
    - attendance at clinic appointments (either a single appointment following an intervention, or a series of appointments, analysed as separate outcomes);
    - incidence of treatment breaks, where the trial authors define breaks;
    - loss to follow-up (participants who withdraw or are lost to follow-up in each treatment arm).

Secondary outcomes

For treatment of active tuberculosis:
- TB cure;
- TB survival;
- sputum conversion;
- incidence of drug resistance.

For treatment of HIV infection:
- proportion of participants achieving viral load suppression (at cut-offs defined by the trial authors, but which must be below the World Health Organization (WHO) suppression criteria of less than 1000 copies of HIV ribonucleic Acid (RNA) per mL (Bennett 2008);
- change in CD4 count;
- survival;

- incidence of drug resistance.

Adverse events

Adverse events of mobile device interventions: unwanted HIV or TB participant status disclosure; health system factors for failure to use the mHealth intervention as planned, for example technological failure or inadequate staff training; and participant factors for failure to use the mHealth intervention as planned, for example due to loss of device, poor network coverage, or language or literacy barriers.

Search methods for identification of studies

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

Electronic searches

We will search the following databases: Cochrane Infectious Disease Group (CIDG) Specialized Register; Cochrane Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library; MEDLINE (OVID); Embase (OVID); CINAHL (EBSCOHost); PsycInfo (EBSCOHost); LILACS (BIREME); Science Citation Index Expanded (SCI-EXPANDED, Web of Science), Social Sciences citation index (SSCI, Web of Science), and Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH, Web of Science), using the search terms detailed in Appendix 1, which we prepared in collaboration with the CIDG Information Specialist to offer both a sensitive and specific search strategy. We will also search the WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/search/en/) and ClinicalTrials.gov (https://clinicaltrials.gov/), to identify ongoing trials, using (tuberculosis OR TB) OR (HIV OR AIDS) and ("mobile phone" or cell phone or texting or SMS or smart phone) as search terms.

Searching other resources

We will search for additional trials by reviewing the reference lists of all included trials and relevant systematic reviews. We will also contact leading researchers to identify unpublished data.

Data collection and analysis

Selection of studies

Two review authors will each independently screen all the citations and abstracts of the literature search results to identify potentially eligible trials using a trial selection form. We will obtain the full-text reports of potentially eligible trials. We will assess them for inclusion in the review using a pre-designed eligibility form based on the inclusion criteria. We will resolve discrepancies through discussion or, if required, we will consult a third review author. Where necessary we will contact the trial authors for clarification of trial methods. We will list the excluded trials and the reasons for them in a 'Characteristics of excluded studies' table. Where there are multiple reports relating to the same trial, we will include all reports, but we will only extract data from the most up-to-date report that includes the specified outcome. We will detail the trial selection process in a PRISMA diagram.

Data extraction and management

We will independently extract data from the included trials using a piloted, tailored data extraction form. We will resolve any differences in data extraction through discussion or, if necessary, by consulting a third review author. After data extraction, we will enter these data into Review Manager (RevMan) (RevMan 2014). We will contact the authors of primary trials in case of any doubts regarding missing data or methodological details of the trial. From each included trial we will extract information on:

- trial design: start and end dates, trial location (country and setting), methods of random sequence generation, allocation concealment, blinding, participant monitoring and follow-up (self reported adherence, pill count, pharmacy records, or electronic monitoring), and funding (as stated by the trial authors);
- participant characteristics: age, gender, treatment regimen, co-morbidity, average educational attainment, average income if adults, baseline viral load, baseline adherence, occupation, and drug use;
- intervention details: mobile device intervention type (reminder; educational motivation or counselling; social support; incentive or enabler; mixed), media and device, content and format of intervention, frequency of intervention, how the intervention was delivered (for example, automated or by healthcare professional), period of intervention, fidelity of intervention delivered (extent to which intervention was delivered as described), training of staff and participants required, description of comparator/control arm, and any co-interventions, use of incentive if not primary intervention and differential between treatment arms, for example a gift or loan of a mobile phone as part of a Short Messaging Services (SMS) intervention, or subsidised medical treatment;
- outcome measurement: outcomes measured and time points measured, methodologies used (for example, for measuring medication adherence examples are self-reported, pill count, pharmacy record, or electronic drug monitoring (EDM)), if validated measures were used, and duration or assessment period for the measurement, for example doses missed in the

previous one week, 30 days, three months.

For dichotomous outcomes we will extract the number of participants randomized and analysed in each treatment arm. We will extract the number of participants that experience the event (numerator) and the total number of participants that start treatment (denominator).

For continuous outcomes we will extract the mean, the standard deviation (SD), and the number of people observed. For count data (for example, incidence of treatment breaks), we will extract the number of events in the treatment and control group and the person time at risk in each group, or the rate ratio and a measure of variance directly from the trial report.

For time-to-event outcomes we will extract the log hazard ratio and its standard error, or the hazard ratio with its confidence interval or P value if the trial only reports these data.

Cluster-RCTs

For cluster-RCTs, we will record the number of clusters, the average size of clusters, and the method used to adjust for clustering. If the trial authors adjusted for clustering appropriately, we will extract the cluster adjusted measure of effect and a measure of variance. For dichotomous outcomes, if the trial authors did not adjust for clustering we will extract the number of participants that experience the event and the number of participants randomized to each group. For continuous outcomes, we will extract the summary effect (mean or median) and the measure of variance (SD or range).

Assessment of risk of bias in included studies

Two review authors will independently assess the risk of bias of each included trial using the Cochrane 'Risk of bias' assessment tool (RevMan 2014), and discuss any differences of opinion. In the case of missing or unclear information, we will contact the trial authors for clarification.

The Cochrane approach assesses risk of bias across six domains: sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessors (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other potential biases. For 'other' biases, we will pay particular attention to the use of material incentives for participation, such as phone credit, given to participants dependent on intervention arm. We will also particularly consider if the included trials used validated instruments to measure outcomes, and, if we do not quantitatively synthesise trial results in meta-analysis, we will also consider whether trial authors demonstrated power to detect a meaningful difference in a measured outcome. For each domain we will record the methods used by the trial authors to reduce the risk of bias and assign a judgment of either 'low', 'high', or 'unclear' risk of bias.

For cluster-RCTs, we will also consider baseline imbalance in the appraisal of selection bias, loss of clusters in the appraisal of attrition bias, and consider the risk of contamination bias (where people living in the control areas also benefit from the intervention). We will summarize the 'Risk of bias' assessment results using the 'Risk of bias' summary and the 'Risk of bias' graph in addition to the 'Risk of bias' tables.

Measures of treatment effect

For dichotomous data, we will compare interventions using the risk ratio. Where trial authors present data as odds ratios, we will recalculate the effect. Where trial authors present dichotomous adherence data as the percentage of pills taken with various cut-off values, to avoid ceiling effects inflating estimates of intervention effect size, we will favour them in the following order: 95%, 90%, 80%, and 100%.

We will express count data as rate ratios. We will express time-to-event data as hazard ratios (HRs), and we will assume that the HR is constant across the follow-up period. For continuous data, we will compare arithmetic means using mean differences. We will present all measures with 95% confidence intervals (CIs). We will report medians and ranges in table format only.

Unit of analysis issues

Where cluster-RCTs have not adjusted their results for the effect of the cluster design, we will adjust the sample sizes using an estimate of the intra-cluster correlation coefficient (ICC) as described in Sections 16.3.4 and 16.3.6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Where possible, we will derive the ICC from the trial itself, or from a similar trial. If an appropriate ICC is unavailable, we will conduct sensitivity analyses to investigate the potential effect of clustering by imputing a range of values of ICC.

When a multi-arm trial contributes multiple comparisons to a particular meta-analysis, we will either combine treatment groups or split the 'shared' group as appropriate to avoid double counting.

Dealing with missing data

We will not apply any imputation measures for missing data. We will attempt to contact trial authors to obtain missing or unclear data.

Assessment of heterogeneity

We will inspect forest plots for overlapping CIs. We will also apply the Chi² test as a statistical test for the presence of heterogeneity, with a P value of 0.10 used to indicate statistical significance, and we will compute the I² statistic to quantify the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance).

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Assessment of reporting biases

We will examine the likelihood of reporting bias using funnel plots, provided that there is a sufficient number of included trials.

Data synthesis

We will analyse the data using RevMan (Review Manager 2014). We will conduct the primary analysis in pairwise comparisons (that is, mobile health interventions versus control/standard of care, mobile health interventions versus non-mobile health adherence interventions, and head-to-head comparison of alternative mobile health adherence interventions). When appropriate (that is, because populations, interventions, and outcome measure and time points measured are similar enough), we will combine trials across target infections (that is, participants infected with HIV or TB). We will also present analyses stratified by the target infection (HIV, TB, or co-infection with HIV and TB). We will also substratify by duration of follow-up of outcome measurement by grouping similar time points together in a single meta-analysis (for example, adherence in the shorter term up to six months, compared to longer term of over six months).

If an included trial reports several different validated measures of self-reported adherence, we will preferentially synthesize data from validated single-item self-rating scale (Likert type) instruments where responses are transformed to prespecified corresponding percentage adherence, then quantitative continua such as a visual analogue scale (VAS), shown to have greatest convergent validity with more objective measures such as electronic drug monitoring (EDM), and reduced ceiling effects, respectively (Stirrat 2015); other self-report instruments have similar convergent validity to EDM or ceiling effects (Stirrat 2015), so in this case we will select data collected using validated instruments with the most complete reporting, or flip a coin to make a random selection. Where multiple durations of adherence have been used in assessment of self-reported adherence (for example, adherence over the last seven days, and over the last 30 days), we will use the measure closest to 30 days because shorter durations may lead to ceiling effects (more participants self-reporting perfect adherence), and over longer durations recall may be inaccurate (Stirrat 2015).

Where both self-report and objective measures of medication adherence are available, we will use objective measures over self-reported measures, in the following order of favour due to increasing risk of bias (Nieuwlatt 2014): pharmacy record, electronic monitoring, pill count, and self-report. For objective measures, we will use the longest duration of measurement.

We will tabulate results from cluster-RCTs that we cannot adjust for clustering, and time-to-event data analysed with models other than a Cox proportional hazards model.

As we expect to find heterogenous participant populations and interventions, we plan to use a random-effects model for meta-analysis.

When it is unjustifiable to pool individual trials due to clinical or statistical heterogeneity, or reporting of an adherence measure unsuitable for quantitative analysis, we will instead present a narrative synthesis of trial findings.

Quality of the evidence

We will assess the quality of the evidence as it relates to the trials that contribute data to the meta-analyses for the prespecified outcomes, using the GRADE approach. We will construct 'Summary of findings' tables using the GRADEpro Guideline Development Tool (GDT) (available from https://gradepro.org/), and the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a; Schünemann 2011). We will present 'Summary of findings' tables for the primary outcomes. We will justify all decisions to downgrade the quality of the evidence in the included trials using footnotes and make comments to aid the reader's understanding of the review where necessary. We will consider whether there is any additional outcome information that we were unable to incorporate into the meta-analyses, note this in the comments, and state if it supports or contradicts the information from the meta-analyses.

Subgroup analysis and investigation of heterogeneity

We will document a variety of factors that may influence the effects of the interventions in the included trials. These will include:

● description of participants in terms of target infection, gender, age (child or adult), socioeconomic status defined by educational attainment or income, baseline adherence, treatment-naive or treatment-experienced at baseline; co-morbidities that may affect adherence and whose presence was dependent for participant enrolment for example, substance addiction, psychiatric disorder, and whether participants are from key groups ((1) men who have sex with men, (2) people who inject drugs, (3) people in prisons and closed settings, (4) sex workers, (5) transgender people, and (6) homeless), average cost of medical care to participants (where reported), trial country income (low-, middle-, or high-income as defined by World Bank criteria), and trial country out-of-pocket health expenditure (% of total expenditure on health, using World Bank data);

● description of the intervention, including all the associated interventions, in terms of:

○ the mechanism of action based on intervention behavioural change component (including reminders; motivational, educational, or counselling; incentive or enabler mechanism of interventions);

○ mobile device media used to deliver the intervention (voice, SMS, video, app, device);

○ format of intervention (text only, or pictorial/mixed);

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- ○ frequency (daily versus less than daily);
- ○ personalization of intervention content or schedule.

Where we pool trials by target infection or intervention duration, we will explore heterogeneity by subgroup analysis of interventions with the same mechanism of action (reminder; monitoring; motivational, educational, or counselling; incentive or enabler; mixed), and at longer duration of follow-up (for example, for 12 months or longer).

Sensitivity analysis

We will conduct sensitivity analyses on the robustness of the results to the 'Risk of bias' components.
We will explore the effects of including self-reported measures of medication adherence.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. New Table

Table 1. Adherence interventions, mHealth delivery media, factors for non-adherence impacted, and higher-order behavioural change technique groupings			
Adherence intervention	**mHealth media used to deliver intervention**	**Aherence factor impacted by intervention**	**Underpinning behavioural change technique(s) groupings**
Reminders to take medication and attend appointments	SMS; voice; App; device	Personal factors	Group 2: cues and cue responses
Adherence monitoring by health worker (not self-monitoring)	Two-way SMS; voice; video DOT; device (treatment monitor box)	Personal factors Health system factors	Group 1: scheduled consequences, reward and threat Group 3: feedback and monitoring
Social support and peer networks	SMS; voice; App (to connect to social support network)	Personal factors Social factors	Group 3: social support and social comparison
Material incentives or enablers to adhere of attend care	Phone enabled conditional cash transfer, free phone airtime	Personal factors Structural factors	Group 1: scheduled consequences; reward and threat
Cognitive-behavioural, motivational, or educational interventions	SMS; voice; video messaging; App	Personal factors	Group 3: feedback and monitoring, goals and planning; shaping knowledge, self belief, and identity

Abbreviations: DOT = directly observed therapy; SMS = short messaging services.

APPENDICES

Appendix 1. MEDLINE (OVID) search strategy

1 tuberculosis or TB.mp [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] .

2 Tuberculosis/dt, pc, th [Drug Therapy, Prevention & Control, Therapy]

4 Antitubercular agents.mp. or Antitubercular Agents/

5 anti-TB or anti-tuberculous or anti-tuberculosis.mp.

6 1 or 2 or 3 or 4 or 5

7 HIV infection.mp. or HIV Infections/

8 exp HIV/

9 human immunodeficiency virus.mp.

10 Acquired Immunodeficiency Syndrome/ or acquired immunodeficiency syndrome or AIDS.mp.

11 (acquired immun* and deficiency syndrome).mp.

12 (HIV* adj2 (people or person* or patient*)).mp.

13 Anti-Retroviral Agents/ or Antiretroviral Therapy, Highly Active/ or antiretroviral.mp. or Anti-HIV Agents/

14 "highly active antiretroviral therapy" OR "HAART".mp

15 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14

16 6 or 15

17 medication adherence.mp. or Patient Compliance/ or Medication Adherence/ or Self Care/

18 directly observed therapy.mp. or Directly Observed Therapy/ or DOT*.mp

19 incentives.mp. or Motivation/ or concordance.mp

20 reimbursement.mp. or Reimbursement, Incentive/

21 reminder systems.mp. or Reminder Systems/

22 patient adherence.mp. or Patient Compliance/

23 17 or 18 or 19 or 20 or 21 or 22

24 Telephone/ or Telemedicine/ or Cell Phones/ or mobile phone*.mp.

25 Wireless Technology/ or Text Messaging/ or Computers, Handheld/ or Smartphone/

26 ("cell phone*" or cellphone* or SMS* or MMS or "text message*" or texting or tablet* or "Iphone*" or "social media" or smart phone* or "multimedia messaging service" or "short messaging service*" or PDA or "mobile device*" or mHealth or telemedicine).mp.

27 24 or 25 or 26

28 16 and 23 and 27[1]

[1] We will use search terms in combination with the search strategy for retrieving trials developed by Cochrane (Lefebvre 2011).

This is the preliminary search strategy for MEDLINE (OVID). We will adapt it for other electronic databases. We will report all search strategies in full in the final version of the review.

CONTRIBUTIONS OF AUTHORS

DS, Paul Garner (CIDG Co-ordinating Editor), and DR contributed to the conception of the research question. All authors contributed to the design of the protocol and approved the final version.

DECLARATIONS OF INTEREST

DS, DR and JR have no known conflicts of interest.

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