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[Intervention Protocol]

Tai Chi plus standard care versus other exercise plus standard care for people with schizophrenia or related disorders

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To systematically assess the effects of Tai Chi plus standard care versus other exercise plus standard care for people with schizophrenia.

BACKGROUND

Description of the condition

Schizophrenia is a chronic psychiatric disorder that affects approximately 24 million people worldwide (Abi-Dargham 2014). Schizophrenia is characterised by positive symptoms (including hallucinations, delusions), negative symptoms (such as avolition, affective flattening), cognitive impairments (such as working memory, attention, information processing deficits), and social dysfunction (Owen 2016). More severe cognitive impairment and higher negative symptoms are related to poorer functional outcome (Lin 2013; Ventura 2009).

The mainstay treatment is antipsychotic medication, but the overall management of schizophrenia usually depends largely on a combination of medications, psychosocial interventions, and support in the community (Huhn 2014). Antipsychotics are effective for the positive symptoms of schizophrenia but are not as successful for the negative symptoms and cognitive impairment (Gold 2004; Leucht 2009). Moreover, antipsychotics are associated with a wide range of side effects including increased risk of weight gain and obesity, impaired glucose tolerance and new-onset diabetes, hyperlipidaemia, and cardiovascular disease (Henderson 2015). A number of studies have shown that physical exercise such as running, swimming, or team sports has physical, psychological, and social functioning benefits (Firth 2015; Firth 2016; Holley 2011; Vera-Garcia 2015). However, people with psychiatric disorders often experience a range of barriers to these types of physical exercise due to limitations on physical exertion, motor control, and muscle dexterity (Fogarty 2005). Tai Chi, an exercise sequence with a psychological emphasis, is a less physically demanding exercise and can improve co-ordination, balance, and flexibility in practitioners (Hong 2000). Recent research suggests that Tai Chi could improve symptoms and cognitive impairments in schizophrenia (Kang 2016; Vera-Garcia 2015).

Description of the intervention

Tai Chi (also known as Tai Chi Quan or Tai chi exercise) has long been believed to have originated in China, in the late Ming and early Qing dynasties (Guo 2014). The essential principles of Tai Chi are based on Taoist philosophy, which stresses the natural balance in all things and the interchangeability of yin and yang (Li 2014). Yin and yang are two opposite cosmic energies, and all things in nature evolve through the interaction of yin and yang (Li 2014). Tai Chi links yin and yang concepts to martial arts to describe the interplay between stillness and motion, softness and hardness, and emptiness and fullness, and routine starts with continuous movements accompanied by deep and regular breathing, not with muscular force, but with inner energy and concentration (Li 2014). All movements are performed with control of the inner force. Performing Tai Chi this way will lead to mental concentration, peace, and serenity of mind, which can alleviate high blood pressure and improve psychological well-being (Sun 2015; Wang 2010).

Exercise is a subset of physical activity that is "planned, structured, repetitive, and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective" (Caspersen 1985). Physical fitness is a set of attributes that are either health- or skill-related, such as cardiorespiratory fitness, muscular endurance, muscular strength,

body composition, flexibility, and neuromotor fitness (Caspersen 1985). As Tai Chi is technically defined as an 'exercise', we consider 'other exercise' as any other exercise, encompassing broad categories of skill-related fitness, health-related fitness, and body-mind fitness, as well as physical activities that are not specifically fitness focused.

How the intervention might work

Through making people with schizophrenia more physically active and less sedentary, exercise may increase cardiorespiratory fitness and metabolic health and reduce physical health problems such as obesity and diabetes (Gorczyński 2010). Exercise can increase several growth factors in the brain such as brain-derived neurotrophic factor (BDNF) (Firth 2017), which is relevant for neurogenesis and maintaining optimal brain function (Ahmed 2015; Firth 2017), and insulin-like growth factor type 1 (IGF-1) and vascular endothelial growth factor (VEGF), which are associated with the functional connectivity in the temporal cortex in elderly humans (Voss 2013). Exercise can lead to benefits in schizophrenia through psychological changes such as social support, sense of autonomy, improved perceptions of competence, enhanced body image, self-efficacy, and distraction (Vancampfort 2014). Tai Chi, as a kind of exercise, could be beneficial for schizophrenia in these ways. In addition, people with schizophrenia experience abnormal hypothalamic-pituitary-adrenal (HPA) axis functioning in the form of altered cortisol levels (Mondelli 2010), which was a neuroendocrine indicator of stress response (Gunnar 2007), and is related to more severe negative symptoms in schizophrenia, Hempel 2010, and poorer quality of life (Brenner 2011). Tai Chi can lead to serenity of mind and help to reduce stress and anxiety, improving psychological well-being which in turn reduces symptoms of schizophrenia (Wang 2014). Tai Chi also involves cognitive activities such as movement recall, switching, and spatial orientation that require attention and executive control (Rogers 2009), and so could improve cognitive impairments in schizophrenia through these cognitive activities.

Why it is important to do this review

Antipsychotic drugs treatments are not fully effective, particularly for the chronic negative symptoms and cognitive impairment in schizophrenia (Gold 2004), and are associated with side effects (Henderson 2015). Additional interventions that help with these issues are needed. Increasingly evidence has shown that physical exercise, including Tai Chi, has positive effects on people with schizophrenia (Ho 2012; Kang 2016). Furthermore, Tai Chi is a relatively inexpensive exercise and is easy to perform. In the current economic situation of healthcare delivery and resource constraints, it is important to assess the effects of Tai Chi compared to other exercise for people with schizophrenia. This review aims to provide a most comprehensive answer to this issue.

OBJECTIVES

To systematically assess the effects of Tai Chi plus standard care versus other exercise plus standard care for people with schizophrenia.

METHODS

Criteria for considering studies for this review

Types of studies

We will consider all relevant randomised controlled trials (RCTs). We will include RCTs meeting our inclusion criteria and reporting useable data in analyses. We will consider trials that are described as 'double-blind' - in which randomisation is implied - and include or exclude once we have carried out a sensitivity analysis (see [Sensitivity analysis](#)). We will exclude quasi-randomised studies, such as those that allocate intervention by alternate days of the week. Where people are given additional treatments as well as Tai Chi, we will only include data if the adjunct treatment is evenly distributed between groups and Tai Chi is the only intervention that is randomised.

Types of participants

Adults, however defined, with schizophrenia or related disorders, including schizophreniform disorder, schizoaffective disorder, and delusional disorder, by any means of diagnosis. We are interested in ensuring that the information is as relevant as possible to the current care of people with schizophrenia, and so aim to highlight the current clinical state clearly (acute, early postacute, partial remission, remission), as well as the stage (prodromal, first episode, early illness, persistent), and whether the studies primarily focused on people with particular problems (e.g. negative symptoms, treatment-resistant illnesses).

Types of interventions

1. *Tai Chi plus standard care therapy*

Participants receiving Tai Chi plus standard care. Different forms of Tai Chi (e.g. training based on Chen, Yang, Wu, Li, Su and Wudang's style, or exercise programmes incorporating principles of Tai Chi philosophy) will be acceptable.

Standard care is defined as treatment a participant would receive had they not been involved in any research trial, given a diagnosis of schizophrenia. This typically includes a biological, psychological, and social approach to care including antipsychotic medication and utilisation of services including hospital stay, day hospital attendance, and community psychiatric nursing involvement.

2. *Other exercise plus standard care therapy*

Participants receiving other exercise plus standard care. This will include broad categories of exercise focused on health-related fitness, skills-related fitness, mind-and-body fitness, and other physical activity not necessarily focused on fitness. We propose to keep each of the above categories separate, as they represent quite different approaches.

Types of outcome measures

We aim to divide all outcomes into short term (less than six months), medium term (seven to 12 months), and long term (over 12 months). We will endeavour to report binary outcomes recording clear and clinically meaningful degrees of change (e.g. global impression of much improved, or more than 50% improvement on a rating scale - as defined within the trials) before any others. We will thereafter list other binary outcomes and then those that are continuous.

Primary outcomes

1. Global state

1.1 Clinically important change in global state

2. Functioning

2.1 Clinically important change in general functioning

3. Adverse effects

3.1 Any clinically important adverse effect (including weight gain and obesity, impaired glucose tolerance and diabetes, hyperlipidaemia, and cardiovascular disease)

Secondary outcomes

1. Global state

1.1 Any change in global state (as defined by individual studies)

1.2 Average endpoint/change score on global state scale

2. Functioning

2.1 General

2.1.1 Any change in overall functioning

2.1.2 Average endpoint/change score on general functioning scale

2.2 Specific (e.g. social, cognitive, daily living)

2.2.1 Clinically important change

2.2.2 Any change in specific aspects of functioning

2.2.3 Average endpoint/change score on specific aspects of functioning scale

3. Mental state (overall or specific)

3.1 Clinically important change in mental state

3.2 Any change in mental state

3.3 Average endpoint/change score on mental state scale

4. Quality of life

4.1 Clinically important change in quality of life

4.2 Any change in quality of life

4.3 Average endpoint/change score on quality of life scales

5. Adverse effect/event(s)

5.1 General

5.1.1 At least one adverse effect/event

5.1.2 Average endpoint score on adverse effect/event scale

5.2 Specific

5.2.1 Incidence of specific effect(s)

6. Leaving the study early

6.1 Any reason

6.2 For specific reason

7. Costs of care

7.1 Direct costs of care

7.2 Indirect costs of care

8. Effect on standard care

8.1 Any change in reported adverse effects of standard care

8.2 Any change in the level of standard care required to manage condition

9. Physical health

9.1 Clinically important change in physical health (as defined by individual studies)

9.2 Any change in physical health

10. Service use

10.1 Hospital admission

10.2 Length of stay in hospital

11. Disability

11.1 Clinically important change in disability

11.2 Any change in disability

'Summary of findings' table

We will use the GRADE approach to interpret findings ([Schünemann 2011](#)), employing [GRADEpro GDT](#) to export data from our review to create a 'Summary of findings' table. These tables provide outcome-specific information concerning the overall certainty of evidence from each included study in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on all outcomes we rate as important to patient care and decision making. We aim to select the following main outcomes for inclusion in the 'Summary of findings' table.

1. Global state: clinically important change in global state
2. Functioning: clinically important change in general functioning
3. Mental state: clinically important change in mental state
4. Adverse effects: clinically important adverse effect
5. Quality of life: clinically important change in quality of life
6. Leaving the study early
7. Cost of care
8. Physical health: clinically important change in physical health

If data are not available for these prespecified outcomes but are available for ones that are similar, we will present the closest outcome to the prespecified one in the table but take this into account when grading the finding.

Search methods for identification of studies

Electronic searches

Cochrane Schizophrenia Group's Study-Based Register of Trials

The Information Specialist will search the register using the following search strategy:

Tai Chi in Intervention Field of STUDY

In such study-based register, searching the major concept retrieves all the synonyms and relevant studies because all the studies have already been organised based on their interventions and linked to the relevant topics ([Shokraneh 2017](#)).

This register is compiled by systematic searches of major resources (Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL (Cumulative Index to Nursing and Allied Health Literature), US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov, Embase, MEDLINE, PsycINFO, PubMed,

World Health Organization International Clinical Trials Registry Platform) and their monthly updates, ProQuest Dissertations and Theses A&I and its quarterly update, Chinese databases (CBM (Chinese Biomedical Literature Database), CNKI (China National Knowledge Infrastructure), and Wanfang) and their annual updates, handsearches, grey literature, and conference proceedings (see [Group's website](#)). There is no language, date, document type, or publication status limitations for inclusion of records into the register.

Searching other resources

1. Reference searching

We will inspect references of all included studies for further relevant studies.

2. Personal contact

We will contact the first author of each included study for information regarding unpublished trials. We will note the outcome of this contact in the 'Characteristics of included studies' or 'Characteristics of studies awaiting classification' tables.

Data collection and analysis

Selection of studies

Review authors LJ and SJ will independently inspect citations from the searches and identify relevant abstracts; ZQ will independently re-inspect a random 20% sample of these abstracts to ensure reliability of selection. Where disputes arise, we will acquire the full report for more detailed scrutiny. LJ and SJ will then obtain and inspect the full reports of the abstracts or reports meeting the review criteria. ZQ will re-inspect a random 20% of these full reports in order to ensure reliability of selection. Where disagreements cannot be resolved by discussion, we will attempt to contact the authors of the study concerned for clarification.

Data extraction and management

1. Extraction

Review authors LJ and SJ will extract data from all included studies. In addition, to ensure reliability, ZQ will independently extract data from a random sample of these studies, comprising 10% of the total. We will attempt to extract data presented only in graphs and figures whenever possible, but will include these data only if two review authors independently obtain the same result. If studies are multicentre, where possible we will extract data relevant to each centre. Any disagreements will be discussed and decisions documented. If necessary, we will attempt to contact authors through an open-ended request to obtain missing information or for clarification. ZQ will help clarify issues regarding any remaining problems, and these final decisions will be documented.

2. Management

2.1 Forms

We will extract data onto standard, predesigned, simple forms.

2.2 Scale-derived data

We will include continuous data from rating scales only if:

- a) the psychometric properties of the measuring instrument have been described in a peer-reviewed journal ([Marshall 2000](#));

b) the measuring instrument has not been written or modified by one of the trialists for that particular trial; and
c) the instrument should be a global assessment of an area of functioning and not subscores which are not, in themselves, validated or shown to be reliable. However, there are exceptions: we will include subscores from mental state scales measuring positive and negative symptoms of schizophrenia.

Ideally the measuring instrument should be either i) a self-report or ii) completed by an independent rater or relative (not the therapist). We realise that this is not often reported clearly; we will note in the 'Description of studies' section if this is the case or not.

2.3 Endpoint versus change data

There are advantages to both endpoint and change data: change data can remove a component of between-person variability from the analysis, however calculation of change needs two assessments (baseline and endpoint), which can be difficult to obtain in unstable and difficult-to-measure conditions such as schizophrenia. We have decided to primarily use endpoint data, and only use change data if the former are not available. If necessary, we will combine endpoint and change data in the analysis, as we prefer to use mean differences (MDs) rather than standardised mean differences (SMDs) throughout (Deeks 2011).

2.4 Skewed data

Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we will apply the following standards to relevant continuous data before inclusion.

For endpoint data from studies including fewer than 200 participants:

a) when a scale starts from the finite number zero, we will subtract the lowest possible value from the mean, and divide this by the standard deviation (SD). A value lower than one strongly suggests that the data are skewed, and we will exclude these data. A ratio higher than one but less than two suggests that the data are skewed: we will enter these data and test whether their inclusion or exclusion would change the results substantially. If these data change the results, we will enter as 'other data'. Finally, if the ratio is larger than two, we will include these data, because it is less likely that they are skewed (Altman 1996; Higgins 2011a);

b) if a scale starts from a positive value (such as the Positive and Negative Syndrome Scale (PANSS), which can have values from 30 to 210) (Kay 1986), we will modify the calculation described above to take the scale starting point into account. In these cases skewed data are present if $2\text{ SD} > (S - S_{\text{min}})$, where S is the mean score and 'S min' is the minimum score.

Please note: we will enter all relevant data from studies of more than 200 participants in the analysis irrespective of the above rules, because skewed data pose less of a problem in large studies. We will also enter all relevant change data, as when continuous data are presented on a scale that includes a possibility of negative values (such as change data), it is difficult to tell whether or not data are skewed.

2.5 Common measurement

In order to facilitate comparison between trials we aim, where relevant, to convert variables that can be reported in different metrics, such as days in hospital (mean days per year, per week, or per month) to a common metric (e.g. mean days per month).

2.6 Conversion of continuous to binary

Where possible, we will attempt to convert outcome measures to dichotomous data. This can be done by identifying cut-off points on rating scales and dividing participants accordingly into 'clinically improved' or 'not clinically improved'. It is generally assumed that if there is a 50% reduction in a scale-derived score such as the Brief Psychiatric Rating Scale (BPRS), Overall 1962, or the PANSS, Kay 1986, this could be considered as a clinically significant response (Leucht 2005a; Leucht 2005b). If data based on these thresholds are not available, we will use the primary cut-off presented by the original authors.

2.7 Direction of graphs

Where possible, we will enter data in such a way that the area to the left of the line of no effect indicates a favourable outcome for Tai Chi plus standard care. Where keeping to this makes it impossible to avoid outcome titles with clumsy double-negatives (e.g. 'not unimproved'), we will report data where the left of the line indicates an unfavourable outcome and note this in the relevant graphs.

Assessment of risk of bias in included studies

Review authors LJ and SJ will independently assess risk of bias using the criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess trial quality (Higgins 2011b). This set of criteria is based on evidence of associations between potential overestimation of effect and the level of risk of bias of the article that may be due to aspects of sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting, or the way in which these 'domains' are reported.

If the raters disagree, we will make the final rating by consensus. Where details of randomisation and other characteristics of trials are inadequate, we will attempt to contact the authors of the studies to obtain further information. We will report non-concurrence in quality assessment, but if disputes arise regarding the category to which a trial is to be allocated, this will be resolved by discussion.

We will note the level of risk of bias in the text of the review, Figure 1, Figure 2, and the 'Summary of findings' table/s.

Measures of treatment effect

1. Binary data

For binary outcomes, we will calculate a standard estimation of the risk ratio (RR) and its 95% confidence interval (CI), as it has been shown that RR is more intuitive than odds ratios (Boissel 1999), and that odds ratios tend to be interpreted as RR by clinicians (Deeks 2000). Although the number needed to treat for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH), with their CIs, are intuitively attractive to clinicians, they are problematic to calculate and interpret in meta-analyses (Hutton 2009). For binary

data presented in the 'Summary of findings' table/s, we will, where possible, calculate illustrative comparative risks.

2. Continuous data

For continuous outcomes, we will estimate MD between groups. We prefer not to calculate effect size measures (SMD). However, if scales of very considerable similarity are used, we will presume there is a small difference in measurement, and we will calculate effect size and transform the effect back to the units of one or more of the specific instruments.

Unit of analysis issues

1. Cluster trials

Studies increasingly employ 'cluster randomisation' (such as randomisation by clinician or practice), but analysis and pooling of clustered data poses problems. Authors often fail to account for intraclass correlation in clustered studies, leading to a unit of analysis error whereby P values are spuriously low, CIs unduly narrow, and statistical significance overestimated (Divine 1992). This causes type I errors (Bland 1997; Gulliford 1999).

Where clustering has been incorporated into the analysis of primary studies, we will present these data as if from a non-cluster-randomised study, but adjust for the clustering effect.

Where clustering is not accounted for in primary studies, we will present data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. We will attempt to contact first authors of studies to obtain intraclass correlation coefficients (ICCs) for their clustered data and to adjust for this by using accepted methods (Gulliford 1999).

We have sought statistical advice and have been advised that the binary data from cluster trials presented in a report should be divided by a 'design effect'. This is calculated using the mean number of participants per cluster (m) and the ICC: thus design effect = $1 + (m - 1) * ICC$ (Donner 2002). If the ICC is not reported, we will assume it to be 0.1 (Ukoumunne 1999).

If cluster studies have been appropriately analysed and taken ICCs and relevant data documented in the report into account, synthesis with other studies will be possible using the generic inverse-variance technique.

2. Cross-over trials

A major concern of cross-over trials is the carry-over effect. This occurs if an effect (e.g. pharmacological, physiological, or psychological) of the treatment in the first phase is carried over to the second phase. As a consequence, participants can differ significantly from their initial state at entry to the second phase, despite a wash-out phase. For the same reason cross-over trials are not appropriate if the condition of interest is unstable (Elbourne 2002). As both carry-over and unstable conditions are very likely in severe mental illness, we will only use data from the first phase of cross-over studies.

3. Studies with multiple treatment groups

Where a study involves more than two treatment arms, if relevant, we will present the additional treatment arms in comparisons. If data are binary, we will simply add these and combine within the two-by-two table. If data are continuous, we will

combine data following the formula in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). Where additional treatment arms are not relevant, we will not reproduce these data.

Dealing with missing data

1. Overall loss of credibility

At some degree of loss of follow-up, data must lose credibility (Xia 2009). We choose that, for any particular outcome, should more than 50% of data be unaccounted for, we will not reproduce these data or use them within analyses. If, however, more than 50% of those in one arm of a study are lost, but the total loss is less than 50%, we will address this within the 'Summary of findings' table/s by downgrading quality. Finally, we will also downgrade quality within the 'Summary of findings' table/s should the loss be 25% to 50% in total.

2. Binary

In the case where attrition for a binary outcome is between 0% and 50% and where these data are not clearly described, we will present data on a 'once-randomised-always-analyse' basis (an intention-to-treat analysis (ITT)). Those participants leaving the study early are all assumed to have the same rates of negative outcome as those who completed the study. We will use the rate of those who stay in the study - in that particular arm of the trial - and apply this also to those who did not. We will undertake a sensitivity analysis testing how prone the primary outcomes are to change when data only from people who completed the study to that point are compared to the ITT analysis using the above assumptions.

3. Continuous

3.1 Attrition

We will use data where attrition for a continuous outcome is between 0% and 50%, and data only from people who complete the study to that point are reported.

3.2 Standard deviations

If SDs are not reported, we will try to obtain the missing values from the authors. If these are not available, where there are missing measures of variance for continuous data, but an exact standard error (SE) and CIs available for group means, and either P value or t value available for differences in mean, we can calculate SDs according to the rules described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). When only the SE is reported, SDs are calculated using the formula $SD = SE * \sqrt{n}$. The *Cochrane Handbook for Systematic Reviews of Interventions* presents detailed formulae for estimating SDs from P, t or F values, CIs, ranges, or other statistics (Higgins 2011a). If these formulae do not apply, we will calculate the SDs according to a validated imputation method which is based on the SDs of the other included studies (Furukawa 2006). Although some of these imputation strategies can introduce error, the alternative would be to exclude a given study's outcome and thus to lose information. Nevertheless, we will examine the validity of the imputations in a sensitivity analysis that excludes imputed values.

3.3 Assumptions about participants who left the trials early or who were lost to follow-up

Various methods are available to account for participants who left the trials early or who were lost to follow-up. Some trials only

present the results of study completers; others use the method of last observation carried forward (LOCF); while more recently, methods such as multiple imputation or mixed-effects models for repeated measurements (MMRM) have become more of a standard. While the latter methods seem to be somewhat better than LOCF (Leon 2006), we feel that the high percentage of participants leaving the studies early and differences between groups in their reasons for doing so is often the core problem in randomised schizophrenia trials. We will therefore not exclude studies based on the statistical approach used. However, by preference we will use the more sophisticated approaches, that is we will prefer to use MMRM or multiple imputation to LOCF, and we will only present completer analyses if some kind of ITT data are not available at all. Moreover, we will address this issue in the 'incomplete outcome data' item of the 'Risk of bias' tool.

Assessment of heterogeneity

1. Clinical heterogeneity

We will consider all included studies initially, without seeing comparison data, to judge clinical heterogeneity. We will simply inspect all studies for participants who are clearly outliers or situations that we had not predicted would arise and, where found, discuss such situations or participant groups.

2. Methodological heterogeneity

We will consider all included studies initially, without seeing comparison data, to judge methodological heterogeneity. We will simply inspect all studies for clearly outlying methods that we had not predicted would arise and discuss any such methodological outliers.

3. Statistical heterogeneity

3.1 Visual inspection

We will inspect graphs visually to investigate the possibility of statistical heterogeneity.

3.2 Employing the I^2 statistic

We will investigate heterogeneity between studies by considering the I^2 statistic alongside the χ^2 P value. The I^2 statistic provides an estimate of the percentage of inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of I^2 depends on the magnitude and direction of effects as well as the strength of evidence for heterogeneity (e.g. P value from χ^2 test, or a confidence interval for I^2). We will interpret an I^2 estimate greater than or equal to 50% and accompanied by a statistically significant χ^2 statistic as evidence of substantial heterogeneity, per Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). When substantial levels of heterogeneity are found in the primary outcome, we will explore reasons for heterogeneity ([Subgroup analysis and investigation of heterogeneity](#)).

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). These are described in Section 10.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2011).

1. Protocol versus full study

We will attempt to locate protocols of the included trials. If the protocol for a given study is available, we will compare the outcomes in the protocol with those in the published report. If the protocol is not available, we will compare the outcomes listed in the methods section of the trial report with the actually reported results.

2. Funnel plot

We are aware that funnel plots may be useful in investigating reporting biases but are of limited power to detect small-study effects. We will not use funnel plots for outcomes for which there are 10 or fewer studies, or where all studies are of similar size. In other cases, where funnel plots are possible, we will seek statistical advice in their interpretation.

Data synthesis

We understand that there is no closed argument for preference of fixed-effect or random-effects models. The random-effects method incorporates an assumption that the different studies are estimating different, yet related, intervention effects. This often seems to be true to us, and the random-effects model takes into account differences between studies, even if there is no statistically significant heterogeneity. There is, however, a disadvantage to the random-effects model, in that it puts added weight onto small studies, which are often the most biased ones. Depending on the direction of effect, these studies can either inflate or deflate the effect size. We choose to use the fixed-effect model for all analyses.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

1.1 Primary outcomes

We do not anticipate a need for any subgroup analysis.

2. Investigation of heterogeneity

We will report if inconsistency is high. Firstly, we will investigate whether data have been entered correctly. Secondly, if data are correct, we will inspect the graph visually and remove outlying studies successively to see if homogeneity is restored. For this review we have decided that should this occur with data contributing to the summary finding of no more than 10% of the total weighting, we will present data. If not, we will not pool these data and will discuss any issues. We know of no supporting research for this 10% cut-off, but are investigating the use of prediction intervals as an alternative to this unsatisfactory state.

When unanticipated clinical or methodological heterogeneity is obvious, we will simply state hypotheses regarding this for future reviews or versions of this review. We do not anticipate undertaking analyses relating to this.

Sensitivity analysis

If there are substantial differences in the direction or precision of effect estimates in any of the sensitivity analyses listed below, we will not add data from the lower-quality studies to the results of the higher-quality trials, but will present these data within a subcategory. If their inclusion does not result in a substantive difference, they will remain in the analyses.

1. Implication of randomisation

If trials are described in such a way as to imply randomisation, for the primary outcomes, we will pool data from the implied trials with trials that are randomised.

2. Assumptions for lost binary data

Where assumptions must be made regarding people lost to follow-up (see [Dealing with missing data](#)), we will compare the findings of the primary outcomes when we use our assumption compared with completer data only. If there is a substantial difference, we will report the results and discuss them but continue to employ our assumption.

Where assumptions must be made regarding missing SDs (see [Dealing with missing data](#)), we will compare the findings of the primary outcomes when we use our assumption compared with completer data only. We will undertake a sensitivity analysis testing how prone results are to change when completer data only are compared with imputed data using the above assumption. If there is a substantial difference, we will report the results and discuss them but continue to employ our assumption.

3. Risk of bias

We will analyse the effects of excluding trials that are at high risk of bias across one or more 'Risk of bias' domains (see [Assessment of risk of bias in included studies](#)) for the meta-analysis of the primary outcome.

4. Imputed values

We will also undertake a sensitivity analysis to assess the effects of including data from trials where we have used imputed values for ICC in calculating the design effect in cluster-randomised trials.

5. Fixed-effect and random-effects

We will synthesise data using the fixed-effect model; however, we will also synthesise data for the primary outcome using the random-effects model to evaluate whether this alters the significance of the results.

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Jing Li: no known conflicts of interest.

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