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[Intervention Protocol]

Tai chi for schizophrenia

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ABSTRACT

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

To evaluate the effectiveness of Tai Chi plus standard care in treating schizophrenia compared with standard care alone.

BACKGROUND

Description of the condition

Schizophrenia is a chronic, severe and disabling mental illness that typically starts in adolescence or early adulthood (Schultz 2007). Globally, schizophrenia is present in 27 million people (7 per thousand of the population), and affects men and women equally (WHO 2014). Males tend to present with the disease earlier than females (Schultz 2007), and the lifetime prevalence of schizophrenia is around one per cent (Jablensky 1992). Whilst no single cause of schizophrenia had been identified, there are a number of risk factors associated with the illness, and these include environmental, developmental, and genetic factors (Schultz 2007). The greatest risk factor for developing schizophrenia is family history, however, socioeconomic status, maternal infections, season and

location of birth have also been shown to increase risk (Mortensen 1999).

Schizophrenia is characterised by a range of symptoms. These can be divided into three aspects: 'positive' symptoms, such as delusions and hallucinations; 'negative' symptoms, such as social withdrawal, loss of motivation and emotional blunting; and 'abnormalities in cognition' symptoms, such as working memory, attention and information processing deficits (Mueser 2004). These signs and symptoms must be markedly present for one month and supported by indications of social dysfunction at work, school or with interpersonal relationships for at least six months (Schultz 2007), and must not be a result of the effects of a substance, or general medical condition. According to the Global Burden of Disease Study (Horton 2010), schizophrenia accounted for 0.6% of all disability adjusted life years (DALYs), and was attributable to more than 1.2 million DALYs each, ranked as fifth in mental illness and behavioral disorders after depression, anxiety, drug-use

and alcohol-use disorders (Murray 2012).

Description of the intervention

Tai Chi originates from China in the 13th century, as a martial art incorporating physical movements, usually slow and relaxed, with deep breathing (Koh 1981). The principles behind Tai Chi are yin and yang and Qi which underlie Chinese traditional medical theory. Qi can be described as the balanced and free-flowing movement of vital energy throughout the body. If there is a good balance between yin and yang, qi, the body's vital energy, will circulate freely throughout the body. Then the person can maintain his/her health. Otherwise, illness will occur. It is said that practicing Tai Chi could bring about a balance between yin and yang, thus helping the free flow of qi, seeking to promote physical health and peace of mind (NCCAM 2009). Tai Chi is not only a physical exercise, but also a kind of mind-body therapy that can reduce stress, encourage relaxation and enhance psychosocial well-being (Cheng 2003; Motivala 2006).

How the intervention might work

Although the exact mechanism is still unclear, Tai Chi might work in the following ways to treat schizophrenia:

1. Tai Chi is a kind of exercise. A Cochrane meta-analysis showed that exercise therapy was beneficial for schizophrenia through making the patients more physically active and less sedentary (Gorczynski 2010), which are associated with the sufferers' mental health and mortality. Exercise therapy could also relieve some schizophrenic symptoms such as depression and social withdrawal (Faulkner 2005). Tai Chi may benefit people with schizophrenia in the same ways.

2. Tai Chi may help to reduce stress in schizophrenic patients (Wang 2014). Stress is not only an outcome of schizophrenia, but has also been shown to have a role in the development and relapse of schizophrenia. Therefore, Tai Chi could help to treat patients with schizophrenia by decreasing stress.

3. Tai Chi could alleviate depression and anxiety, which are secondary symptoms of schizophrenia, by decreasing neuro-endocrinal stress response (Zhang 2012). It has been shown that Tai Chi could reduce the secretion of corticotropin releasing hormone, which regulates adrenocorticotrophic hormone. This hormone regulates the secretion of cortisol, which releases from the adrenal cortex and has been found to be high in patients with depression (Tsang 2006).

4. Tai Chi could improve abnormalities in cognition through mental concentration during the movements required for the activity (Rogers 2009). The improvement might also be brought about by the nature of the structured cognitive component of Tai Chi that requires movement to be reproduced from a mental

image rather than from preprogrammed memorisation (Brown 1995).

Why it is important to do this review

Antipsychotic drugs are the mainstay of treatment for schizophrenia but usually have adverse effects including extra-pyramidal movement symptoms, weight gain, sedation, sexual dysfunction and metabolic syndrome (Tandon 2010; Van Os 2009). Although antipsychotic medications are effective in treating positive symptoms, their efficacy against negative and cognitive symptoms are not clear. There is a need for adjunct non-pharmacological treatments (Kern 2009). A Cochrane review of exercise therapy demonstrated that it had healthful effects on individuals with schizophrenia, but this review did not include studies of Tai Chi (Gorczynski 2010).

The benefits of Tai Chi to consumers are that it is an inexpensive exercise that can be performed anywhere (i.e. home, park, community hall, etc.). Tai Chi requires no equipment, no registration fees, and can be done alone and without the reliance on interaction from another individual. Although Tai Chi therapy has been used in the treatment of schizophrenia, its efficacy for this illness is yet to be determined. Until good quality evidence is available, it is difficult to know if policy makers should consider this mode of activity as a possible treatment of schizophrenia.

OBJECTIVES

To evaluate the effectiveness of Tai Chi plus standard care in treating schizophrenia compared with standard care alone.

METHODS

Criteria for considering studies for this review

Types of studies

All relevant randomised controlled trials.

If a trial is described as 'double blind' but implies randomisation, we will include such trials in a sensitivity analysis (see [Sensitivity analysis](#)). If their inclusion does not result in a substantive difference, they will remain in the analyses. If their inclusion does result in important, clinically significant but not necessarily statistically significant differences, we will not add the data from these lower quality studies to the results of the better trials, but will present such data within a subcategory.

We will exclude quasi-randomised studies, such as those allocating by alternate days of the week. We will also exclude cross-over studies in which participants receive different treatments sequentially, because of potential carry-over effects from all treatments. Where people are given additional treatments within the group receiving Tai Chi, we will only include data if the adjunct treatment is evenly distributed between groups, and it is only the allocation of Tai Chi that is randomised.

Types of participants

We will consider all people with a diagnosis of schizophrenia. This includes diagnoses made by any means. If trials are found where people with other serious mental illnesses are included we will include them only if over 50% of the participants have schizophrenia. We are interested in making sure that information is as relevant to the current care of people with schizophrenia as possible, so propose to highlight clearly the current clinical state (acute, early post-acute, partial remission, remission) as well as the stage (prodromal, first episode, early illness, persistent) and record as to whether the studies primarily focused on people with particular problems (for example, negative symptoms, treatment-resistant illnesses). We will not exclude trials due to the age, nationality or gender of the participants.

Types of interventions

1. Tai Chi therapy

Participants receiving Tai Chi in addition to standard care. Different forms of Tai Chi (for example, training based on Chen, Yang, Wu, Li, Su and Wudang's style, or exercise programs incorporating principles of Tai Chi philosophy) will be acceptable. Each type of intervention will be analysed as a covariate for primary and secondary outcomes.

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 normally 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. Control group

People receiving standard care, as defined above, for the management of their schizophrenia without Tai Chi intervention. For a study to be included, the Tai Chi therapy intervention and control group have to have a similar duration and approach to standard care.

Types of outcome measures

All outcomes will be divided into short term (less than 6 months), medium term (7 to 12 months) and long term (over 1 year).

Primary outcomes

1. Mental state and behaviour

- 1.1 No clinically important change in general mental state
- 1.2 Average endpoint score in general mental state
- 1.3 Average change scores in general mental state
- 1.4 No clinically important change in general behaviour state
- 1.5 Average endpoint score in general behaviour state
- 1.6 Average change scores in general behaviour state
- 1.7 No clinically important change in specific symptoms (positive symptom of schizophrenia, negative symptoms of schizophrenia, depression, mania)
- 1.8 Average endpoint score in specific symptoms
- 1.9 Average change scores in specific symptoms

2. General functioning

- 2.1 No clinically important change in general functioning
- 2.2 Average endpoint score in general functioning
- 2.3 Average change scores in general functioning
- 2.4 No clinically important change in specific aspects of functioning, such as social or life skills
- 2.5 Average endpoint score in specific aspects of functioning, such as social or life skills
- 2.6 Average change scores in specific aspects of functioning, such as social or life skills

Secondary outcomes

1. Well-being

- 1.1 No clinically important change in well-being
- 1.2 Average endpoint score in well-being
- 1.3 Average change scores in well-being
- 1.4 No clinically important change in specific aspects of well-being
- 1.5 Average endpoint score in specific aspects of well-being
- 1.6 Average change scores in specific aspects of well-being

2. Quality of life

- 2.1 No clinically important change in quality of life
- 2.2 Average endpoint score in quality of life
- 2.3 Average change scores in quality of life
- 2.4 No clinically important change in specific aspects of quality of life
- 2.5 Average endpoint score in specific aspects of quality of life
- 2.6 Average change scores in specific aspects of quality of life

3. Requirement for mental health services

- 3.1 Hospital admission
- 3.2 Time to admission
- 3.3 Other contact with mental health services

4. Satisfaction with treatment

- 4.1 Leaving the studies early
- 4.2 Recipient of care not satisfied with treatment
- 4.3 Recipient of care average endpoint score in satisfaction
- 4.4 Recipient of care average change scores in satisfaction
- 4.5 Carer not satisfied with treatment
- 4.6 Carer average endpoint score in satisfaction
- 4.7 Carer average change scores in satisfaction

5. Physical fitness

- 5.1 No clinically important change in physical fitness
- 5.2 Average endpoint score in physical fitness
- 5.3 Average change scores in physical fitness
- 5.4 No clinically important change in specific aspects of physical fitness
- 5.5 Average endpoint score in specific aspects of physical fitness
- 5.6 Average change scores in specific aspects of physical fitness

6. Adverse effects

- 6.1 Suicide and all causes of mortality
- 6.2 Clinically important general adverse effects
- 6.3 Average endpoint score in general adverse effect
- 6.4 Average change scores in general adverse effect
- 6.5 Clinically important specific adverse effects
- 6.6 Average endpoint score in specific adverse effects
- 6.7 Average change scores in specific adverse effects

7. Costs of care

- 7.1 Direct costs of care
- 7.2 Indirect costs of care

8. 'Summary of findings' table

We will use the GRADE approach to interpret findings ([Schünemann 2008](#)) and will use GRADE profiler ([GRADEPRO](#)) to import data from RevMan 5 ([Review Manager](#)) to create 'Summary of findings' tables. These tables provide outcome-specific information concerning the overall quality 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 rated 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. Mental state and behaviour - improvement or deterioration
2. General functioning - improvement or deterioration
3. Well-being and quality of life

4. Satisfaction with treatment
5. Physical fitness
6. Adverse events
7. Cost of care

Search methods for identification of studies

Electronic searches

1. Cochrane Schizophrenia Group's Trials Register

The Trials Search Coordinator (TSC) will search the Cochrane Schizophrenia Group's Registry of Trials using the following phrase:

("Tai Ji*" or "Tai-Ji*" or Taiji* or "Tai Chi*" or "Tai-Chi*" or "T'ai Chi*" or "T'ai-Chi*") in Title or Abstract of REFERENCE or ("Tai Ji*" or "Tai-Ji*" or Taiji* or "Tai Chi*" or "Tai-Chi*" or "T'ai Chi*" or "T'ai-Chi*") in Intervention of STUDY

The Cochrane Schizophrenia Group's Registry of Trials is compiled by systematic searches of major resources (including AMED, BIOSIS, CINAHL, EMBASE, MEDLINE, PsycINFO, PubMed, and registries of Clinical Trials) and their monthly updates, hand-searches, grey literature, and conference proceedings (see [Group Module](#)). There are no language, date, document type, or publication status limitations of inclusion of records in the Registry.

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.

Data collection and analysis

Selection of studies

YL and LB will independently inspect citations from the searches and identify relevant abstracts. YL and LB will then compare findings to ensure reliability. Where disputes arise, the full report will be acquired for more detailed scrutiny. Full reports of the abstracts meeting the review criteria will be obtained and inspected by YL.

These identified reports will then be re-inspected by LB in order to ensure reliable selection. Where it is not possible to resolve disagreement by discussion, we will attempt to contact the authors of the study for clarification.

Data extraction and management

1. Extraction

Review authors YL and LB will extract data from all included studies independently and compare results of extracted data from all of the studies. Any disagreement will be discussed, decisions documented and, if necessary, authors of studies will be contacted for clarification. Data presented only in graphs and figures will be extracted whenever possible, but included only if two review authors independently have the same result. We will attempt to contact authors through an open-ended request in order to obtain missing information or for clarification whenever necessary. If studies are multi-centre, where possible, we will extract data relevant to each component centre separately.

2. Management

2.1 Forms

We will extract data onto standard, 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); and
- b) the measuring instrument has not been written or modified by one of the trialists for that particular trial.

Ideally the measuring instrument should either be 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. In 'Description of studies' we will note if this is the case or not.

2.3 Endpoint versus change data

There are advantages of both endpoint and change data. Change data can remove a component of between-person variability from the analysis. On the other hand, calculation of change needs two assessments (baseline and endpoint) which can be difficult 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. Endpoint and change

data will be combined in the analysis as we will use mean differences (MD) rather than standardised mean differences (SMDs) throughout the review (Higgins 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 aim to apply the following standards to all data before inclusion:

- a) standard deviations (SDs) and means are reported in the paper or obtainable from the authors;
- b) when a scale starts from the finite number zero, the SD, when multiplied by two, is less than the mean (as otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution (Altman 1996);
- c) if a scale started from a positive value (such as the Positive and Negative Syndrome Scale (PANSS) (Kay 1986) which can have values from 30 to 210), the calculation described above will be modified to take the scale starting point into account. In these cases skew is present if $2 \text{ SD} > (\text{S} - \text{S min})$, where S is the mean score and 'S min' is the minimum score.

Endpoint scores on scales often have a finite start and end point and these rules can be applied. We will present skewed endpoint data from studies of less than 200 participants as 'Other data' within the 'Data and analyses' section, rather than enter such data in analyses. Skewed endpoint data pose less of a problem when looking at means if the sample size is large (>200) and we will enter these into statistical analyses.

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 data are skewed or not. We will present and enter skewed change data into analyses.

2.5 Common measure

To facilitate comparison between trials, we intend 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 Positive and Negative Syndrome Scale (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 therapy. 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. This will be noted in the relevant graphs.

Assessment of risk of bias in included studies

Review authors YL and LB will work independently to assess the risk of bias in included studies by using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) to assess trial quality. This set of criteria is based on evidence of associations between overestimate of effect and high risk of bias of the article such as sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting.

If the raters disagree, the final rating will be made by consensus, with the involvement of another review author. Where inadequate details of randomisation and other characteristics of trials are provided, we will contact authors of the studies in order to obtain further information. Non-concurrence in 'Risk of bias' assessment will be reported, but if disputes arise as to which category a trial is to be allocated, again, we will resolve these by discussion.

The level of risk of bias will be noted in both the text of the review and in the 'Summary of findings' table.

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). It has been shown that RR is more intuitive (Boissel 1999) than odds ratios and that odds ratios tend to be interpreted as RR by clinicians (Deeks 2000). The Number Needed to Treat/Harm (NNT/H) statistic with its confidence intervals is intuitively attractive to clinicians but is problematic both in its accurate calculation in meta-analyses and interpretation (Hutton 2009). For binary data presented in the 'Summary of findings' table/s, where possible, we will calculate illustrative comparative risks.

2. Continuous data

For continuous outcomes will estimate mean difference (MD) between groups. We prefer not to calculate effect size measures (standardised mean difference (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. Firstly, authors often fail to account for intraclass correlation in clustered studies, leading to a 'unit of analysis' error (Divine 1992) whereby P values are spuriously low, confidence intervals unduly narrow and statistical significance overestimated. This causes type I errors (Bland 1997; Gulliford 1999).

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. In subsequent versions of this review we will seek to contact first authors of studies to obtain intraclass correlation coefficients for their clustered data and to adjust for this by using accepted methods (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.

We have sought statistical advice and have been advised that the binary data as 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 intraclass correlation coefficient (ICC) [Design effect = 1+(m-1)*ICC] (Donner 2002). If the ICC is not reported it will be assumed to be 0.1 (Ukoumunne 1999).

If cluster studies have been appropriately analysed taking into account ICCs and relevant data documented in the report, 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. It 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, on entry to the second phase the participants can differ systematically from their initial state 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 effects 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, the additional treatment arms will be presented in comparisons. If

data are binary these will be simply added and combined within the two-by-two table. If data are continuous we will combine data following the formula in section 7.7.3.8 (Combining groups) of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Where the additional treatment arms are not relevant, we will not use 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). Those leaving the study early are all assumed to have the same rates of negative outcome as those who completed, with the exception of the outcome of death and adverse effects. For these outcomes, the rate of those who stay in the study - in that particular arm of the trial - will be used for 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 complete the study to that point are compared to the intention-to-treat analysis using the above assumptions.

3. Continuous

3.1 Attrition

In the case 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, we will reproduce these.

3.2 Standard deviations

If standard deviations (SDs) are not reported, we will first try to obtain the missing values from the authors. If not available, where there are missing measures of variance for continuous data, but an exact standard error and confidence intervals available for group means, and either 'P' value or t' value available for differences

in mean, we can calculate them according to the rules described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011): When only the standard error (SE) is reported, SDs are calculated by the formula $SD = SE * \text{square root } (n)$. Chapters 7.7.3 and 16.1.3 of the *Cochrane Handbook* (Higgins 2011) present detailed formula for estimating SDs from P values, t or F values, confidence intervals, ranges or other statistics. If these formula 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. We nevertheless will examine the validity of the imputations in a sensitivity analysis excluding imputed values.

3.3 Last observation carried forward

We anticipate that in some studies the method of last observation carried forward (LOCF) will be employed within the study report. As with all methods of imputation to deal with missing data, LOCF introduces uncertainty about the reliability of the results (Leucht 2007). Therefore, where LOCF data have been used in the trial, if less than 50% of the data have been assumed, we will present and use these data and indicate that they are the product of LOCF assumptions.

Assessment of heterogeneity

1. Clinical heterogeneity

We will consider all included studies initially, without seeing comparison data, to judge clinical heterogeneity. Different types of Tai Chi might cause heterogeneity. We will simply inspect all studies for clearly outlying people or situations which we had not predicted would arise. When such situations or participant groups arise, these will be fully discussed.

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 which we had not predicted would arise. When such methodological outliers arise these will be fully discussed.

3. Statistical heterogeneity

3.1 Visual inspection

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

3.2 Employing the I^2 statistic

Heterogeneity between studies will be investigated by considering the I^2 method alongside the Chi^2 P value. The I^2 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 i. magnitude and direction of effects and ii. strength of evidence for heterogeneity (e.g. P value from Chi^2 test, or a confidence interval for I^2). An I^2 estimate greater than or equal to around 50%, accompanied by a statistically significant Chi^2 statistic, will be interpreted as evidence of substantial levels of heterogeneity (Section 9.5.2, Higgins 2011). When substantial levels of heterogeneity are found in the primary outcome, we will explore the reasons for heterogeneity (see [Subgroup analysis and investigation of heterogeneity](#)).

Assessment of reporting biases

1. Protocol versus full study

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results. These are described in section 10.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will try to locate protocols of included randomised trials. If the protocol is available, we will compare outcomes in the protocol and in the published report. If the protocol is not available, outcomes listed in the methods section of the trial report will be compared with the results actually reported.

2. Funnel plot

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). These are again described in Section 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). 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 where there are ten or fewer studies, or where all studies are of similar sizes. 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 for use 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. It puts added weight onto small studies which often are the most biased. Depending on the direction of effect these studies can either inflate or deflate the effect size. We choose to use the random-effects model for analyses. The reader is, however, able to choose to inspect the data using the fixed-effect model for analyses.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

1.1 Primary and secondary outcomes

We will perform subgroup analyses according to different types of Tai Chi intervention.

1.2 Clinical state, stage or problem

We propose to undertake this review and provide an overview of the effects of Tai Chi for people with schizophrenia in general. In addition, however, we will try to report data on subgroups of people in the same clinical state, stage and with similar problems.

2. Investigation of heterogeneity

If inconsistency is high, this will be reported. First we will investigate whether data have been entered correctly. Second, if data are correct, the graph will be visually inspected and studies outside of the company of the rest will be successively removed to see if homogeneity is restored. For this review we decided that should this occur with data contributing to the summary finding of no more than around 10% of the total weighting, data will be presented. If not, data will not be pooled and issues will be discussed. 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 are obvious we will simply state hypotheses regarding these for future reviews or versions of this review. We do not anticipate undertaking analyses relating to these.

Sensitivity analysis

1. Implication of randomisation

We aim to include trials in a sensitivity analysis if they are described in some way as to imply randomisation. For the primary outcomes we will include these studies and if there is no substantive difference when the implied randomised studies are added to those with a

better description of randomisation, then all data will be employed from these studies.

2. Assumptions for lost binary data

Where assumptions have to 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/s and when we use data only from people who complete the study to that point. If there is a substantial difference, we will report results and discuss them but will continue to employ our assumption. Where assumptions have to be made regarding missing SD data (see [Dealing with missing data](#)), we will compare the findings of the primary outcomes when we use our assumption/s and when we use data only from people who complete the study to that point. A sensitivity analysis will be undertaken testing how prone results are to change when completer-only data only are compared to the imputed data using the above assumption. If there is a substantial difference, we will report results and discuss them but will continue to employ our assumption.

3. Risk of bias

We will analyse the effects of excluding trials that are judged to be at high risk of bias across one or more of the domains of randomisation (implied as randomised with no further details available), allocation concealment, blinding and outcome reporting for the meta-analysis of the primary outcome. If the exclusion of trials at high risk of bias does not substantially alter the direction of effect or the precision of the effect estimates, then data from these trials will be included in the analysis.

4. Imputed values

We will also undertake a sensitivity analysis to assess the effects of including data from trials where we used imputed values for ICC in calculating the design effect in cluster-randomised trials. If substantial differences are noted in the direction or precision of effect estimates in any of the sensitivity analyses listed above, we will not pool data from the excluded trials with the other trials contributing to the outcome, but will present them separately.

5. Fixed-effect and random-effects models

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

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The search string has been developed by the Trial Search Co-ordinator of the Cochrane Schizophrenia Group and the contact author of this protocol.

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* Indicates the major publication for the study

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DECLARATIONS OF INTEREST

Authors have no known conflicts of interest.

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Author Liu Yan is employed by the hospital, has been allocated time to complete the review.

External sources

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