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Haloperidol (route of administration) for people with schizophrenia (Protocol)

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TABLE OF CONTENTS

[Intervention Protocol]

Haloperidol (route of administration) for people with schizophrenia

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ABSTRACT

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

To examine the efficacy and safety of the different routes of haloperidol administration for people with schizophrenia.

BACKGROUND

Description of the condition

Schizophrenia is a serious and chronic mental disorder that affects more than 21 million people worldwide and alters how a person thinks, feels, and acts (WHO 2016). The symptoms of schizophrenia are classified into three main categories: positive, negative, and cognitive (NIMH 2016). The positive symptoms include hallucinations and delusions thought to be caused by disturbances in dopaminergic transmissions (Cornblatt 1985; NIMH 2016). The negative symptoms include apathy and social withdrawal, and are thought to be caused by unusual structures in the brain (Cornblatt 1985; NIMH 2016). Finally, the cognitive symptoms of schizophrenia can be defined as poor executive functioning resulting in troubles with working or difficulties in organising tasks throughout the day (Simpson 2010; NIMH 2016).

Schizophrenia has an incidence of 2 to 5 new cases per 10,000 people per year, and a prevalence of 1% of the general population (Jablensky 2000). In addition, due to a wide spectrum of comorbid illnesses and increased risk of suicide (Fuller-Thomson 2016), people with schizophrenia face up to a 50% increase in mortality rates compared with the general population (NICE 2014).

Schizophrenia diagnosis is mainly based on clinical manifestations of symptoms; however, physical tests are principally used to rule out other disorders such as the hallucinations that are associated with other medical conditions including Cushing's disease and brain tumours (APA 2013). The aetiology of schizophrenia appears to be multifactorial, comprising interactions between genetic and environmental factors (WHO 2016).

Schizophrenia usually first appears between the ages of 16 and

30 (NIMH 2016), occurring less frequently in female patients who tend to have a later age of onset than males (WHO 2016). Epidemiological studies show an evenly distributed incidence of schizophrenia among different geographical areas (WHO 1998). There is currently no cure for schizophrenia; however, there are multiple highly effective pharmacological and psychosocial interventions used to manage its symptoms. Furthermore, huge efforts are being spent in research for new and more effective therapies (Miyamoto 2012).

Description of the intervention

Haloperidol is an antipsychotic that belongs to the first generation of antipsychotic drugs. Its discovery in 1958 formed one of the greatest breakthroughs of psychiatry in the last century (Lopez-Munoz 2009). Haloperidol is clinically effective but it causes unpleasant side effects, particularly extrapyramidal and movement disorders. However, it causes few of the other side effects of antipsychotics, such as sedation, orthostatic problems, and weight gain (Tardy 2014).

Haloperidol is available in different forms and is widely prescribed in many countries. The most common route of administration is the oral route (Kaye 2003; Paton 2003). For oral administration, haloperidol is available in the form of tablets and oral concentrate. It is also available as a nasal spray. Haloperidol lactate is a short acting parenteral solution for intramuscular and intravenous administration. Haloperidol decanoate is a long-acting intramuscular preparation.

Patients generally prefer oral haloperidol, a convenient route involving no punctures (Allen 2005). However, cognitive dysfunction - often caused by schizophrenia - coupled with the side effects of haloperidol might cause patients to refuse to adhere to the treatment and this poses an increased risk of poor adherence especially to the oral form because it is usually difficult to quantify patients' compliance to the pills (Quraishi 2000).

The oral route is also relatively slow, reaching peak plasma concentration in 1.7 to 6.1 hours (Kudo 1999), compared to 15 minutes in intranasal and intravenous routes and 37.5 minutes in intramuscular (Miller 2008). Parenteral routes are therefore preferred in acute schizophrenia (Kudo 1999; Allen 2005). Intramuscular haloperidol lactate is used for prompt control of patients with acute agitation, where frequent doses are injected until symptoms are controlled before switching to oral therapy (Kudo 1999).

Another parenteral form, haloperidol decanoate provides slow and prolonged release when administered as a depot intramuscular injection (Altamura 1990), which helps eliminate the problems of non-compliance (Quraishi 2000).

Lately, a new non-invasive intranasal route was introduced for haloperidol, which provides a direct nose-to-central nervous system delivery with no first-pass metabolism, thus a rapid uptake in the brain, enabling its application in psychiatric emergencies when there is no intravenous access (Costantino 2007; El-Setouhy 2016).

How the intervention might work

Pharmacological treatments for schizophrenia target mainly dopamine pathways and receptors, especially D2 receptors, because they play the most important part in the mechanism of psychoses (Miyamoto 2012).

Though the exact pathophysiology of schizophrenia is still poorly understood, dopamine D2 receptor antagonists, such as haloperidol, were found to be of clinical benefit based on moderate-quality evidence (Adams 2013), and this can be justified by the hyperactive dopaminergic signal transmission which is thought to be involved in the aetiology of schizophrenia (Davis 1991). Blockade of D2 receptors causes numerous side effects: the most common are extrapyramidal such as akathisia, dystonia, parkinsonism, rigidity, and tremor (Adams 2013).

Oral haloperidol has a bioavailability of 60% to 70% and a half-life that ranges between 14.5 and 36.7 hours. The half-life for the short-acting intramuscular form is 20.7 hours, and for the intravenous form is 14.1 to 26.2 hours (Kudo 1999). Haloperidol concentrations in the brain tissues are 10 to 30 times higher than its serum concentrations, and its elimination half-life is 6.8 days, which causes the persistence of side effects long after haloperidol withdrawal (Kornhuber 1999**;** Kornhuber 2006). Haloperidol is highly protein bound. Its metabolism occurs in the liver, primarily by CYP3A4, and then it is cleared mainly by glucuronidation (Kudo 1999).

Why it is important to do this review

Schizophrenia is a source of disability for more than 20 million people worldwide (WHO 2016). It often leads to significant dysfunction in social, occupational and educational fields making it hard for people with the condition to maintain marriage or high-level employment (APA 2013). Therefore the search for an effective treatment for this debilitating condition is of extreme value.

Haloperidol is one of the most commonly used interventions to treat schizophrenia. A Cochrane Review provides evidence of its effectiveness in treating schizophrenia (Adams 2013), and despite the discovery of newer antipsychotic drugs, the American Psychiatric Association continues to recommend the use of haloperidol for schizophrenia (Lehman 2004). Furthermore, haloperidol still appears on the World Health Organization (WHO) Model List of Essential Medicines among the medications used to treat psychotic disorders (WHO 2015).

Although haloperidol is an old medication, as with many other antipsychotic drugs its multiple formulations and routes of administration help improve schizophrenia management by enhancing patients' comfort and adherence to the drug; this in turn leads to

improvements in the efficacy and tolerability of treatment as well as patients' quality-of-life (Frijlink 2003). Differences between haloperidol's routes of administration also make some of them better suited for emergency situations and others for long-term use (Kudo 1999; Quraishi 2000; Allen 2005; Costantino 2007). While there is evidence to evaluate differences in pharmacokinetics (Nayak 1987; Miller 2008), dosage equivalence (Vasavan 1986), efficacy (Moller 1982; Quraishi 2000), and occurrence of adverse events (Moller 1982; Quraishi 2000) between the different haloperidol forms, to date there is no robust evidence-base that determines the route of maximum effect and minimal side effects for delivering haloperidol in different clinical scenarios.
This review is important because it aims to systematically investigate these differences and summarise the benefits and drawbacks of each route of administration.

OBJECTIVES

To examine the efficacy and safety of the different routes of haloperidol administration for people with schizophrenia.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all relevant randomised controlled trials. We will include trials that are described as 'double blind' - in which randomisation is implied - in 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 haloperidol, we will only include data if the adjunct treatment is evenly distributed between groups and it is only the route of administration 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 making sure that information is as relevant as possible to the current care of people with schizophrenia, so aim to highlight the current clinical state clearly (acute, early post-acute, 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 (for example, negative symptoms, treatment-resistant illnesses).

Types of interventions

1. Oral Haloperidol

2. Intramuscular Haloperidol

3. Intravenous Haloperidol

4. Intranasal Haloperidol

All the above administered by any dose and any duration.

Types of outcome measures

We aim to divide all outcomes into immediate (less than 7 days), 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. Thereafter we will list other binary outcomes and then those that are continuous.

Primary outcomes

1. Global State

1.1 Clinically important change in global state as defined by each study.
1.2 Relapse, as defined by each study.

2. Quality of life

2.1 Clinically important change in quality of life/satisfaction, as defined by each study.

3. Adverse effects/events

3.1 Clinically important extrapyramidal side effects, as defined by each of the studies.

Secondary outcomes

1. Global state

1.1 Any change in global state, as defined by each study.
1.2 Average endpoint/change score on global state scale.

2. Quality of life

2.1 Any change in quality of life, as defined by each study.
2.2 Average endpoint/change score on quality of life/satisfaction scale.
2.3 Any change in employment status, as defined by each study.

3. Adverse effects/events

3.1 At least one adverse effect/event.
3.2 Average endpoint/change score on general adverse effect scale.
3.3 Clinically important specific adverse effects, such as anticholinergic, antihistamine, endocrinological, cardiovascular, genitourinary, gastrointestinal, neurological, respiratory, abnormal laboratory tests, and any other specific adverse effects.
3.4 Death.

4. Mental state

4.1 General

4.1.1 Clinically important change in general mental state, as defined by each study.
4.1.2 Any change in general mental state, as defined by each study.
4.1.3 Average endpoint/change scores on general mental state scale.

4.2 Specific

4.2.1 Clinically important change in positive symptoms (e.g. delusions, hallucinations) as defined by each study.
4.2.2 Any change in positive symptoms, as defined by each study.
4.2.3 Average endpoint/change scores on positive symptom scale.
4.2.4 Clinically important change in negative symptoms (e.g. affective flattening, alogia, or avolition) as defined by each study
4.2.5 Average endpoint/change scores on negative symptom scale.

5. Cognitive functioning

5.1. Clinically important change in cognitive functioning, as defined by each study.
5.2 Any change in cognitive functioning, as defined by each study.
5.3 Average endpoint/change score in cognitive functioning.

6. Behaviour

6.1 Clinically important change in general behaviour, as defined by each study.
6.2 Any change in general behaviour, as defined by each study.
6.3 Average endpoint/change scores on general behaviour scale.
6.4 Incidence aggression/violence.

7. Social functioning

7.1 Clinically important change in social functioning, as defined by each study.
7.2 Any change in social functioning, as defined by each study.
7.3 Average endpoint/change scores on social functioning scale.

8. Service use

8.1 Hospital admissions.
8.2 Duration of stay in hospital.
8.3 Change in hospital status.

9. Satisfaction with care for either recipients of care or caregivers

9.1 Any change in satisfaction, as defined by each study.
9.2 Average endpoint/change scores on satisfaction scale.

10. Leaving the study early

10.1 For any reason.
10.2 Due to relapse.
10.3 Due to adverse effects.

11. Economic costs

11.1 Costs due to treatment, as defined by each study.
11.2 Savings due to treatment, as defined by each study.

'Summary of findings' table

We will use the GRADE approach to interpret findings (Schünemann 2011); and will use GRADEpro GDT 2015 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 as defined by each study.
2. Quality of life: clinically important change in quality of life/satisfaction, as defined by each study.

3. Adverse effects/events: clinically important extrapyramidal side effects, as defined by each study.
4. Mental state: clinically important change in general mental state, as defined by each study.
5. Cognitive functioning: clinically important change in cognitive functioning, as defined by each study.
6. Behaviour: clinically important change in general behaviour, as defined by each study.
7. Social functioning: clinically important change in social functioning, as defined by each study.

If data are not available for these pre-specified outcomes but are available for ones that are similar, we will present the closest outcome to the pre-specified 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:
Route - Haloperidol 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 (AMED, BIOSIS, CINAHL, ClinicalTrials.Gov, Embase, MEDLINE, PsycINFO, PubMed, WHO ICTRP) and their monthly updates, ProQuest Dissertations and Theses A&I and its quarterly update, Chinese databases (CBM, CNKI, and Wanfang) and their annual updates, handsearches, grey literature, and conference proceedings (see Group's Module). There are 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 any poorly reported study for further information. We will note the outcome of this contact in the 'Included studies' or 'Studies awaiting classification' tables.

Data collection and analysis

Selection of studies

Review authors DK and LZ will independently inspect citations from the searches and identify relevant abstracts; MS and AB 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. SA will then obtain and inspect full reports of the abstracts or reports that meet the review criteria. IH will re-inspect a random 20% of these full reports in order to ensure reliability of selection. Where it is not possible to resolve disagreement by discussion, we will attempt to contact the authors of the study concerned for clarification.

Data extraction and management

1. Extraction

Review authors SA, MS, and AB will extract data from all included studies independently. In addition, to ensure reliability, IH 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 that data only if reviewers independently obtain the same result. If studies are multi-centre, then where possible we will extract data relevant to each centre. We will discuss any disagreement and document our decisions. If necessary, we will attempt to contact authors through an open-ended request in order to obtain missing information or for clarification. IH will help clarify issues regarding any remaining problems and we will document these final decisions.

2. Management

2.1 Forms

We will extract data onto standard, pre-designed, 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; and
c) the instrument should be a global assessment of an area of functioning and not sub-scores which are not, in themselves, validated or shown to be reliable. However there are exceptions: we will include sub-scores from mental state scales measuring positive and negative symptoms of schizophrenia.

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; however, calculation of change needs two assessments (baseline and endpoint) that can be difficult to obtain in unstable and difficult-to-measure conditions such as schizophrenia. We have decided primarily to 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 (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 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 nite number zero, we will subtract the lowest possible value from the mean, and divide this by the standard deviation. If this value is lower than one, it strongly suggests that the data are skewed and we will exclude these data. If this ratio is higher than one but less than two, there is a suggestion that the data are skewed: we will enter these data and test whether their inclusion or exclusion would change the results substantially. 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 2011).
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 SD > (S − S 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

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 make efforts 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 oral haloperidol. 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 DK, LZ, IH will work independently to assess risk of bias by using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess trial quality (Higgins 2011). 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, with the involvement of another member of the review group.

Where inadequate details of randomisation and other characteristics of trials are provided, we will attempt to contact authors of the studies in order 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, we will resolve this by discussion.

We will note the level of risk of bias in both 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. Firstly, authors often fail to account for intra-class 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 seek to contact first authors of studies to obtain intra-class correlation coefficients 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 intra-class correlation coefficient (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 have taken intra-class correlation coefficients 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 washout 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 section 7.7.3.8 (Combining groups) of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). 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 to 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 down-rating 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 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

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 standard deviations (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 2011). When only the SE is reported, SDs are calculated by the formula SD = SE * $\sqrt{}$(n). Chapters 7.7.3 and 16.1.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* present detailed formulae for estimating SDs from P, t or F values, CIs, ranges or other statistics (Higgins 2011). 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 were lost to follow-up

Various methods are available to account for participants who left the trials early or were lost to follow-up. Some trials just 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, i.e. 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 item 'Incomplete outcome data' 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 which 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 Chi^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 Chi^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 Chi² statistic as evidence of substantial heterogeneity (Section 9.5.2 *Cochrane Handbook for Systematic Reviews of Interventions*) (Higgins 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

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 of the *Cochrane Handbook for Systemic reviews of Interventions* (Sterne 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, we will compare outcomes listed in the methods section of the trial report with actually reported results.

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 also described in Section 10 of the *Cochrane Handbook for Systemic 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 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 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 ones. Depending on the direction of effect, these studies can either inflate or deflate the effect size. We choose to use a fixed-effect model for all analyses.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

1.1 Primary outcomes

We do not anticipate any subgroup analyses.

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 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 these for future reviews or versions of this review. We do not anticipate undertaking analyses relating to these.

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 some 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 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 compared with completer data only. If there is a substantial difference, we will report results and discuss them but continue to employ our assumption.

Where assumptions have to be made regarding missing SDs (see Dealing with missing data), we will compare the findings on 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 to the imputed data using the above assumption. If there is a substantial difference, we will report 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 of the 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 use imputed values for ICC in calculating the design effect in cluster randomised trials.

5. Fixed- and random-effects

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

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* *Indicates the major publication for the study*

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SA, LZ, MS, AB: drafted the background.

DK: drafted the methods.

IH: finalized the background and the methods and drafted the outcomes.

AE: provided training, reviewed the whole manuscript, edited it and finalized the outcomes.

All authors revised and finalized the last version of the background and methods of the protocol.

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