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Electroconvulsive therapy for treatment-resistant schizophrenia (Protocol)

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[Intervention Protocol]

Electroconvulsive therapy for treatment-resistant schizophrenia

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A B S T R A C T

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

Our primary objective is to assess the effects (benefits and harms) of ECT for people with treatment-resistant schizophrenia.

Our secondary objectives are to determine whether ECT produces a differential response in people:

- who are treated with unilateral compared to bilateral ECT;

- who have had a long course of ECT (more than 12 sessions) or short course of ECT;

- who are given continuation or maintenance ECT;

- who are diagnosed with well defined treatment resistant schizophrenia as opposed to less rigorously defined treatment-resistant schizophrenia (who would be expected to have a greater affective component to their illness).

B A C K G R O U N D

Description of the condition

Schizophrenia is common mental health condition with an incidence of 15.2 cases per 100,000 per year and a lifetime prevalence of 7.2 cases per 100,000 globally (McGrath 2008). It is a psychotic condition with symptoms comprising of fixed beliefs held on unreasonable grounds (delusions), perceptions without a cause (hallucinations) and disorganised thinking (thought disorder). The course of illness is variable with a minority fully recovering from an initial episode whilst most with have a relapsing remitting course (Harrison 2001). The degree of disability is high with 80% to 90% of people not working (Marwaha 2004). Up to 60% of people with schizophrenia will respond to treatment but it is well-recognised that about 1 in 3 people have an illness that is "treatment resistant" (Meltzer 1997).

Treatment-resistant schizophrenia has not been consistently defined within the literature (Suzuki 2012). In a landmark ran-

domised trial, Kane and colleagues investigated the effects of clozapine compared with chlorpromazine for people with defined treatment resistant illnesses (Kane 1988). In this study treatment-resistant schizophrenia was defined as "at least three periods of treatment with antipsychotics from at least two different classes at adequate doses for an adequate period time with no relief and no period of good functioning over the last five years". The criteria used to define treatment resistance in this study remain some of the most cited in randomised trials concerning people with treatment resistant schizophrenia (Conley 1997), although there is still heterogeneity in the criteria used.

Description of the intervention

Electroconvulsive therapy (ECT) was introduced as a treatment for schizophrenia in 1938 to replace chemically induced seizures (Endler 1988). It involves the induction of a seizure ("fit") by the administration of an electrical stimulus via electrodes usually placed bilaterally on the scalp.

ECT may be modified by the use of anaesthetic agents and muscle relaxants to reduce apprehension and the likelihood of adverse outcomes such as spinal and limb fractures resulting from the convulsions. In the developed world most ECT treatment delivered is modified ECT. Unmodified ECT is still used some parts of the world especially in those that do not have ready access to anaesthetic equipment. There is evidence that the use of ECT in developing countries is higher than in the developed world (Agarwal 1992; Odejide 1987), and also that there is a greater use of unmodified ECT. Possible explanations for this may be that ECT has a perceived greater speed of response and also can be administered inexpensively compared to drug treatments.

It was recognised that ECT was an effective treatment for mood disorders and its use for schizophrenia has declined in the developed world with most patients receiving ECT for depressive disorders (Leiknes 2012). ECT also predates the introduction of neuroleptic and antidepressant medications by more than a decade and there is evidence that its use has declined over time (Thompson 1994).

This may be explained by the fact that ECT is a controversial treatment with concerns about long term side effects such as memory loss (Rose 2003). There is however no conclusive evidence that ECT results in brain damage (Devanand 1994; Dwork 2004; Ende 2000; Weiner 1986). To reduce the risk of cognitive side effects ECT may sometimes be given unilaterally to the non-dominant hemisphere although there is evidence that higher amounts stimulus must be used and that the efficacy is less than for bilateral electrode placement (Sackeim 1993; Sackeim 2000).

There is inconsistency among expert groups about the use of ECT and its indications. The American Psychiatric Association recommends the use of ECT in schizophrenia in the following circumstances: when psychotic symptoms in the present episode have an abrupt or recent onset, when schizophrenia is of the catatonic type or when there is a history of a favourable response to ECT (APA 2008). The Royal College of Psychiatrists says that the treatment of choice for schizophrenia is drug treatment but that ECT can be considered for treatment resistant cases, catatonia and that there is some evidence for ECT's effectiveness in the short term but evidence for sustained benefits in the medium to long term are lacking (Scott 2005). The National Institute for Health and Care Excellence (NICE 2003), however, only recommends ECT for severe depressive illness, a prolonged or severe episode of mania or catatonia (which may also occur in other disorders such as depression).

ECT dosing schedules vary from country to country with ECT often being delivered three times per week in the United States compared to twice a week in the United Kingdom (Scott 2005), although there is considerable variation in practice with small numbers of clinicians in parts of the world administering ECT daily or many times a day until a state of regression is achieved (regressive ECT) (Agarwal 1992). The number of sessions in a course typically varies from four to twelve (Weiner 1994). There is a suggestion that patients with schizophrenia may need 12 to 20 sessions (Kendell 1981). More rarely some patients are also prescribed ECT fortnightly or monthly as 'continuation ECT' or maintenance ECT to prevent relapse (Monroe 1991; Scott 1991). There is evidence that the frequency of ECT influences speed of response and also cognitive adverse effects (Gangadhar 2010).

There is also evidence that the dose of the electrical stimulus also affects the outcome of the treatment with higher doses of electricity being associated with greater efficacy but more cognitive side effects (Sackeim 1993).

Perhaps because of the controversial nature of ECT there are legal restrictions on its administration compared to other treatments in many jurisdictions (Kala 2013; Loo 2010). In the United Kingdom, for example, a patient who has capacity to consent to a medication but is refusing it may be administered that medication if they are subject to the Mental Health Act. Comparitively a patient who has capacity to consent to ECT but is refusing it may not be administered ECT under the Mental Health Act (Mughal 2013). The ethics of research in schizophrenia are also debated given that it can be a condition that affects decision making. Patients with treatment-resistant schizophrenia may be expected to have a severe and enduring illness and might be considered to be more likely to have impairments of decision making and capacity. There is evidence however that with the appropriate interventions in place that patients with schizophrenia are able to perform as well as non-ill controls in assessments of decisional capacity (Carpenter 2000).

How the intervention might work

How ECT works is not well understood. There is empirical evidence from animal models that ECT causes neurogenesis (Madsen 2000) despite the concerns about brain damage and cognitive side effects. Studies from depressed patients (Bocchio-Chiavetto

2006) have shown that ECT causes an increase in brain-derived neurotrophic factor. Studies have shown a potential role for brain-derived neurotrophic factor to be implicated in the development of schizophrenia (Muglia 2003; Nieto 2013). Other putative mechanisms include influencing dopamine and serotonin neurotransmitter activity and immune system modulation (Rosenquist 2014).

Why it is important to do this review

Previous Cochrane reviews of ECT for schizophrenia have not looked specifically at the evidence for ECT in treatment-resistant schizophrenia patients despite this being a clinical dilemma that is a consensus priority for research (Lloyd 2011; Tharyan 2005). Given that ECT remains a controversial treatment it is essential to determine its efficacy as a treatment. This review attempts to assess the current evidence for ECT in specifically for the group of people whose illness has been designated as resistant to treatment.

O B J E C T I V E S

Our primary objective is to assess the effects (benefits and harms) of ECT for people with treatment-resistant schizophrenia.

Our secondary objectives are to determine whether ECT produces a differential response in people:

- who are treated with unilateral compared to bilateral ECT;

- who have had a long course of ECT (more than 12 sessions) or short course of ECT;

- who are given continuation or maintenance ECT;

- who are diagnosed with well defined treatment resistant schizophrenia as opposed to less rigorously defined treatment-resistant schizophrenia (who would be expected to have a greater affective component to their illness).

M E T H O D S

Criteria for considering studies for this review

Types of studies

All relevant randomised controlled trials (RCTs). If a trial is described as 'double blind' but implies randomisation, we will include such trials in a sensitivity analysis (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. Where people are given additional treatments within ECT, we will only include data if the adjunct treatment is evenly distributed between groups and it is only the ECT that is randomised.

Types of participants

We will include people of both sexes, aged 18 years or more, with a diagnosis of treatment-resistant schizophrenia or related disorders (e.g. schizoaffective disorder, schizophreniform disorder), however it is diagnosed. We will conduct a sensitivity analysis by only including people with strictly diagnosed schizophrenia by international standards (International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10), Diagnostic and Statistical Manual of Mental Disorders (DSM) (DSM-III, DSM-IV, DSM-5V), Chinese Classification of Mental Disorders (CCMD) (CCMD-1, CCMD-2, CCMD-3).

Types of interventions

1. Adjunctive use of ECT

ECT is a procedure which involves passing an electrical stimulus through the brain to produce a seizure. It is practice in many countries to administer 'modified' ECT which involves administering a general anaesthetic and muscle relaxant as well as the electrical stimulus. ECT will be normally be delivered as a course over several sessions. We will not exclude studies based on the number and frequency of ECT sessions or whether the ECT was modified or unmodified. We will also not exclude studies where the participants were receiving concurrent pharmacological interventions and other interventions provided that it was only ECT that was being randomised.
We will compare ECT therapy with the following.

"Sham-ECT" or "simulated-ECT":

"sham-ECT" or "simulated-ECT" is where a patient undergoes all the preparations for ECT, often including receiving a general anaesthesia and muscle relaxant but does not receive the electrical stimulus.

Treatment with antipsychotics:

antipsychotic drugs are medications designed to treat psychosis; they are thought to act partly by their dopamine blocking action

but other chemical pathways have also been identified for their action.

Non-pharmacological forms of treatment:

non-pharmacological management of schizophrenia can include but is not limited to interventions such as occupational therapy and psychotherapy.

Placebo/control treatment:

we will include any intervention in this group that is not thought to be an active treatment for schizophrenia.

2. Non-adjunctive use of ECT

ECT may sometimes be the sole treatment that a patient is prescribed. For this comparison we will exclude studies where the participants were prescribed concurrent interventions be they pharmacological or non-pharmacological except where these interventions were part of the process of ECT. We will also include studies where patients received alternative interventions provided these are randomised comparisons with ECT.
We will compare non-adjunctive strategy of ECT with the following:
"sham-ECT" or "simulated-ECT";
treatment with antipsychotics;
non-pharmacological forms of treatment;
placebo/control treatment.

3. Electrode placement

Bilateral ECT versus unilateral ECT

Bilateral ECT is where the electrical stimulus is administered across both hemispheres of the brain. The placement is usually bi-temporal. Unilateral ECT is where the electrical stimulus is administered to the non-dominant hemisphere of the brain. The placement is usually temporoparietal.

4. Duration of course

Course of 6-12 ECT sessions versus course of 12-30 sessions

A session of ECT is where an electrical stimulus is delivered to the brain. A repeat stimulus may be administered in the same session if there was an inadequate seizure. A typical course of ECT for depression would be 6-12 sessions but this is not well defined for schizophrenia. We wish to see if there is evidence that patients with schizophrenia require a longer course of ECT than for depression.

5. Frequency of treatment

ECT administered fortnightly or monthly versus any other treatment

ECT is normally administered at least weekly. In some situations it is given less often and may be called 'maintenance' ECT. We defined 'maintenance' ECT as being delivered either fortnightly or monthly for at least 6 sessions. We will compare 'maintenance' ECT against any other pharmacological or non-pharmacological treatment strategies.

Types of outcome measures

If possible, we will divide all outcomes into short term (less than six weeks), medium term (six weeks to six months) and long term (over six months).

Primary outcomes

1. Response to treatment

Clinically significant response to treatment as defined by the original studies

2. Cognitive functioning

Clinically significant change of cognitive functioning as defined by individual studies

Secondary outcomes

1. Death: suicide or any cause

2. Satisfaction & acceptability of treatment

2.1. Leaving the study early
2.2. Patients reporting adverse events e.g. post-ECT headache

3. Mental state

3.1. Clinically important change in general mental state at short, medium and long term
3.2. Average endpoint general mental state score
3.3. Average change in general mental state scores
3.4. Clinically important change in specific symptoms (positive symptoms of schizophrenia, negative symptoms of schizophrenia) at short, medium and long term
3.5. Average endpoint specific symptom score
3.6. Average change in specific symptom scores

4. General functioning

4.1. Clinically important change in general functioning at short and medium term

4.2. Average endpoint general functioning score

4.3. Average change in general functioning scores

5. Service outcomes

5.1. Number hospitalised

5.2. Number discharged or re-admitted (as defined in individual trials)

6. Adverse events

6.1 General

6.1.1. Any major adverse event

6.1.2. Any reported adverse event

6.1.3. Average endpoint in general adverse event score

6.1.4. Average change in general adverse event score

6.2 Specific

6.2.1. Any major adverse event

6.2.2. Any reported adverse event

6.2.3. Average endpoint in specific adverse event score (e.g. cognitive function)

6.2.4. Average change in specific adverse event score

'Summary of findings' table

We will use the Grading of Recommendations Assessment, Development and Evaluation GRADE) approach to interpret findings (Higgins 2011). We will use GRADEpro to import data from Cochrane's statistical software (Review Manager) in order to create the '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.

- Response to treatment.
- Adverse effects: change of cognitive functioning.
- Acceptability of treatment: leaving the study early.
- Mental state: clinically important change in general mental state as defined by each of the studies.
- General functioning: clinically important change in general functioning as defined by each of the studies.

- Service outcomes: hospitalisation.
- Death

Search methods for identification of studies

Electronic searches

The Trials Search Co-ordinator (TSC) of the Cochrane Schizophrenia Group will search the Group's Study-Based Register of Trials using the following search strategy:

- *Electroconvulsive* in Intervention Field of STUDY.

The Cochrane schizophrenia Group's Register 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 in *Cochrane Library*). There are no language, date, document type, or publication status limitations for inclusion of records into the register.

Searching other resources

We will inspect references of all included studies for further relevant studies. We will also 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 tudies awaiting classification' tables of the full review.

Data collection and analysis

Selection of studies

Two authors (DS, JE) will independently inspect all citations from the searches and identify relevant abstracts. Where disputes arise, we will retrieve the full-text report for further assessment. We will obtain full reports of conference proceedings meeting the review criteria and the two authors (DS, JE) will independently inspect these before adding relevant trials to the review. Where it is not possible to resolve the disagreement we will consult a third review author (CEA). If doubt still remains we will add these trials to the list of those awaiting and we will attempt to contact the authors of the study for clarification.

Data extraction and management

1. Extraction

Two authors (DS, JE) will independently extract data from all included studies. Again, we will discuss any disagreement, document our decisions and, if necessary, we will attempt to contact authors of studies for clarification. With remaining problems we will consult a third author (CEA) to help clarify issues and we will document these final decisions. We will attempt to extract data presented only in graphs and figures whenever possible, but will only include data for which the two authors have independently extracted the same results. We will attempt to contact authors through an open-ended request in order to obtain missing information or for clarification whenever necessary. For multicentre studies, where possible, we will extract data relevant to each component centre separately.

2. Management

2.1 Forms

We will extract data onto pre-standardised data extraction forms.

2.2 Scale-derived data

We will include continuous data from rating scales only if:

- the psychometric properties of the measuring instrument have been described in a peer-reviewed journal (Marshall 2000); and
- 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 a self-report tool or one that was completed by an independent rater or relative (not the therapist). We realise that this is not often reported clearly. Therefore, we will make a note of the description of the measuring instrument in the 'Description of studies' section in the full review.

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. 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 all data before inclusion.

- For change data, we will enter relevant useable change data into analyses, 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 data are skewed or not.
- For endpoint data from small trials (n>200):
  - when a scale starts from the finite number 0, we will subtract the lowest possible value from the mean, and divide this by the standard deviation (SD). If this value is lower than 1, it strongly suggests a skew, and we will exclude the study data. If this ratio was higher than 1 but below 2, there is a suggestion of skew. We will entered the study data and test whether inclusion or exclusion changes the results substantially. Finally, if the ratio is larger than 2, we will include the study data, because skew is less likely (Altman 1996; Higgins 2011);
  - 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 into account the scale starting point. In such cases skew is present if 2 SD > (S - S min), where S is the mean score and S min is the minimum score.
- For endpoint data from larger trials (n<200), we will enter relevant endpoint data from studies of at least 200 participants in the analyses irrespective of the above rules because skewed data pose less of a problem in large studies.

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 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) or the PANSS (Kay 1986; Overall 1962), 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 ECT. Where keeping to this makes it impossible to avoid outcome titles with clumsy double-negatives (e.g. 'Not un-improved') we will report data where the left of the line indicates an unfavourable outcome. We will make a note of this in the relevant graphs.

Assessment of risk of bias in included studies

Two review authors (DS, JE) will work independently to assess risk of bias by using criteria described in the *Cochrane Handbook for Systemic reviews of Interventions* (Higgins 2011). 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 two authors disagree, we will decide on the final rating by consensus, with the involvement of a third author (CEA). 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 as to which category a trial is to be allocated, again, we will resolve by discussion.

We will note the level of risk of bias 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 standard estimation of risk ratios (RRs) and their 95% confidence intervals (CIs). It has been shown that RRs are more intuitive than odds ratios (ORs) and that ORs tend to be interpreted as RRs by clinicians (Boissel 1999; Deeks 2000). The number needed to treat/harm (NNT/ H) statistics with 95% CIs are intuitively attractive to clinicians but can be problematic both in terms of accurate calculation in meta-analyses and interpretation (Hutton 2009). For binary data presented in the 'Summary of findings' tables, where possible, we will calculate illustrative comparative risks.

2. Continuous data

For continuous outcomes we will estimate MDs between groups. We prefer not to calculate effect size measures (i.e. using SMDs). 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 (Divine 1992), whereby P values are spuriously low, CIs 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. We will seek 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). 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 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 of 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 them together and combine them within the two-by-two table. If data are continuous we will combine data following the formula in the *Cochrane Handbook for Systemic 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' tables by down-rating quality. Finally, we will also downgrade quality within the 'Summary of findings' tables should loss be 25-50% 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 (ITT) 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 use these data.

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 (SE) and CIs 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 Systemic reviews of Interventions* (Higgins 2011): When only the SE is reported, SDs are calculated by the formula $SD = SE * \sqrt{n}$. The *Cochrane Handbook for Systemic reviews of Interventions* presents detailed formulae for estimating SDs from P values, 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. We nevertheless will examine the validity of the imputations in a sensitivity analysis excluding 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 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 in the reasons for leaving the studies early between groups is often the core problem in randomised schizophrenia trials. We will therefore not exclude studies based on the statistical approach used. However, we will preferably use the more sophisticated approaches e.g. mixed effects models for repeated measurements or multiple imputation will be preferred 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 clearly outlying people or situations which we had not predicted would arise. When such situations or participant groups arise, we will discuss these in details.

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. we will discuss these in details.

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

We will investigate statistical heterogeneity between studies by considering the I^2 statistic alongside the P value of the Chi^2 test. The I^2 statistics 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 both the magnitude and direction of effects and the strength of evidence for heterogeneity (e.g. P value from Chi^2 test, or CIs for I^2). We will consider an I^2 statistic estimate of greater than or equal to around 50% accompanied by a statistically significant Chi^2 test (P value < 0.1) as evidence of substantial levels of heterogeneity (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 (Higgins 2011). We will attempt 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 plots

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997; 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 the fixed-effect or the 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 the fixed-effect model for all analyses. The reader is, however, able to choose to inspect the data using the random-effects model.

Subgroup analysis and investigation of heterogeneity

1. Secondary objectives

Our secondary objectives are to determine whether ECT produces a differential response in the following subgroups:
- people who were treated with unilateral compared to bilateral ECT;
- people who had had a long course of ECT (more than 12) or short course of ECT;
- people who were given continuation or maintenance ECT;
- people who were diagnosed with well defined treatment resistant schizophrenia as opposed to less rigorously defined treatment resistant schizophrenia.

If the trials directly compared the technique (for example, people are randomised to unilateral or bilateral ECT) then we will present these data within the relevant comparison. However, if, within a comparison, data are reported on subgroups of people (for example, within the unilateral vs bilateral comparison data are presented on those who have a long course as against those who have had a shorter course) then we will report these subgroups. We will do this only for the primary outcomes.

2. Investigation of heterogeneity

We will report relevant findings if heterogeneity was found to be high. Firstly, we will investigate whether data has been entered correctly. Secondly, if data is correct, we will visually inspect the graph(s) and we will remove studies outside of the company of the rest 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 around 10% of the total weighting, we will present the corresponding data. If not, we will not pool data and will instead narratively discuss the 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 are obvious, we will simply state hypotheses regarding these for future reviews or versions of this review. We do not anticipate undertaking future 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 better description of randomisation, then we will use any relevant data 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 assumptions 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 SDs (see Dealing with missing data), we will compare the findings of the primary outcomes when we use our assumptions and when we use data only from people who complete the study to that point. We will undertake 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 we will include data from these trials 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 versus random-effects model

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

6. Diagnostic criteria

We will undertake a sensitivity analysis to assess the effects of excluding trials where patients did not have strictly diagnosed schizophrenia by international standards (ICD-10, DSM-III, DSM-IV, DSM-5, CCMD-1, CCMD-2 or CCMD-3). If there is a substantial difference in our results then we will report these differences and discuss them.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

CONTRIBUTIONS OF AUTHORS

Diarmid Sinclair wrote the protocol.

James Ellison reviewed and drafted parts of the protocol.

Clive Adams reviewed and drafted parts of the protocol.

DECLARATIONS OF INTEREST

Diarmid Sinclair: none known.

James Ellison: none known.

Clive Adams: none known.

SOURCES OF SUPPORT

Internal sources

- University of Nottingham, UK.

The University of Nottingham hosts the Cochrane Schizophrenia Group who helped provide support in conducting the electronic searches, obtaining the studies, administrative and editorial support.

External sources

- No sources of support supplied