# Brief family intervention for schizophrenia (Protocol)

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This is a reprint of a Cochrane protocol, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2012, Issue 4

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[Intervention Protocol]

# Brief family intervention for schizophrenia

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**Editorial group:** Cochrane Schizophrenia Group.
**Publication status and date:** New, published in Issue 4, 2012.

**Citation:** Okpokoro U, Adams CE. Brief family intervention for schizophrenia. *Cochrane Database of Systematic Reviews* 2012, Issue 4. Art. No.: CD009802. DOI: 10.1002/14651858.CD009802.



## ABSTRACT

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

To assess the effects of brief family interventions for people with schizophrenia or schizophrenia-like conditions.

## BACKGROUND

### Description of the condition

Schizophrenia is a chronic mental health illness. It is described as a neuropsychiatric and mental disorder characterised by abnormalities in the perception or expression of reality. The emotional, social and cost implications for families and people with schizophrenia are highly detrimental, resulting in impairment of social and vocational functioning in the society at large. Approximately 1% of the world's population will suffer from schizophrenia (Barrowclough 1997). The peak age of onset is typically late adolescence and early adulthood, and a combination of both genetic and environmental factors play roles in its development (Van Os 2009). The symptoms of this illness are often described as 'positive' and 'negative'; positive symptoms are hallucinations, delusions, disordered thought and speech; negative symptoms are lack of normal emotional responses, withdrawal, and blunted affect. The course of the illness and management is largely influenced by the predominance of either positive and negative symptoms (Hirsch 2003).

### Description of the intervention

The objectives of psychosocial family interventions are varied. These include:

1. improving the capabilities of relatives to anticipate and solve problems;
2. achieving significant change in relatives' behaviour and belief systems;
3. supporting relatives to set and maintain suitable limits and still keep to some degree of separation as appropriate;
4. minimising emotions of anger and guilt felt by the relatives;
5. minimising negative family environment (that is, damping emotional tension in the family by diminishing relatives' burden and psychological stress);
6. building a therapeutic coalition with caregivers of the person with schizophrenia; and
7. encouraging understanding of limitations to patient performance (Pitschel-Walz 2004).

A mental health professional educates the person with schizophrenia and their family members about the illness. They create an alliance in planning treatment and provide mutual support and understanding of the disease. Family intervention furnishes rela-

tives with insight into signs and symptoms that serve as an alert to imminent acute episodes so that strategies may be employed directed towards averting relapse. There have been various psychosocial programmes designed over the years, such as counselling groups for family members, family therapy in a single or multiple family settings, psychoeducational groups for relatives, group therapy for family members and educational lectures for family members (Pitschel-Walz 2004). Many of these are delivered by skilled, specifically trained mental health professionals, who work with the families every two weeks or so, across considerable time periods, such as one year.

### How the intervention might work

The probability of the affected member relapsing is greater when the family is over-involved, hostile, critical and dissatisfied - a concept known as 'expressed emotions'. The apparent connection between expressed emotion and relapse was demonstrated some time ago. In 1962 Brown and co-workers highlighted the connection between expressed emotions and schizophrenia in families (Brown 1962) and this has since been corroborated by others (Kuipers 1988; Vaughn 1986). This concept of expressed emotions substantiates the relevance of psycho-educational work with family members who care for people with schizophrenia (Pitschel-Walz 2004)

Designs of interventions focus on diminishing the level of environmental stimuli and expressed emotion through education, training and therapy. Mental health service providers have anticipated knowledgeable family members acting as cohorts in therapy (Böker 1992; Lefley 1990) which, in turn, might positively impact on patients' compliance with medication (Corrigan 1990; Kissling 1994).

### Why it is important to do this review

Psychosocial family interventions for people with schizophrenia has been tested in trials and results indicate some positive effects. There is evidence attesting to diminished rate of relapse in people receiving standard length psychosocial family interventions (Pharoah 2006). Studies of brief versions of family therapy will be specifically omitted from this review. There is also some evidence that these particular psychosocial interventions may improve functioning and family well-being.

Short-term psychoeducational programmes which have less content have also been shown to have the potential of imparting basic information and equipping families caring for relatives with schizophrenia with new strategies. These brief educational programmes have been shown to be successful in diminishing distress for these families as a result of better knowledge (Abramowitz 1989; Smith 1987). There is considerable investment in longer forms of family psychosocial interventions as against a shorter approach. Guidelines recommending family intervention do not specify which approach to adopt (NICE 2009). There is potential for considerable savings if the efficacy of shorter and longer approaches are compared.

## OBJECTIVES

To assess the effects of brief family interventions for people with schizophrenia or schizophrenia-like conditions.

## 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. Where people are given additional treatments such as standard drug treatment, we will include data if the adjunct treatment is evenly distributed between groups.

#### Types of participants

Adults, however defined, with schizophrenia or related disorders, including schizophreniform disorder, schizoaffective disorder and delusional disorder - again, by any means of diagnosis.

We are interested in making sure that information is as relevant to the current care of people with schizophrenia as possible so propose to clearly highlight the current clinical state (acute, early post-acute, partial remission, remission) as well as the stage (prodromal, first episode, early illness, persistent) and as to whether the studies primarily focused on people with particular problems (for example, negative symptoms, treatment-resistant illnesses).

#### Types of interventions

Any intervention described as 'family intervention' for people with schizophrenia of brief duration (five sessions or less or, where the

number of sessions is not stated but less than three months duration).

Compared with:

1. any intervention described as 'family intervention' for people with schizophrenia of longer duration;
2. any other non-family psycho-social or educational package of brief duration;
3. any other non-family psycho-social or educational package of longer duration; or
4. standard care.

## Types of outcome measures

We propose to divide our outcomes into short-term (1 month), medium-term (3 months) and long-term (6 months - 1 year).

### Primary outcomes

**1. Service utilisation**

1.1 Hospital admission

**2. Clinical global response**

2.1 Relapse

### Secondary outcomes

**1. Service utilisation**

1.2 Days in hospital

**2. Clinical global response**

2.2 Global state - improved
2.3 Average change or endpoint score in global state
2.4 Leaving the study early
2.5 Compliance with medication

**3. Mental state and behaviour**

3.1 Positive symptoms (delusions, hallucinations, disordered thinking)
3.2 Negative symptoms (avolition, poor self-care, blunted affect)
3.3 Average change or endpoint score

**4. Social functioning**

4.1 Average change or endpoint scores
4.2 Social impairment
4.3 Employment status (employed/unemployed)
4.4 Work related activities
4.5 Unable to live independently
4.6 Imprisonment

**5. Family outcome**

5.1 Average score/change in family burden
5.2 Patient and family coping abilities
5.3 Understanding of the family member with schizophrenia
5.4 Family care and maltreatment of the person with schizophrenia
5.5 Expressed emotion
5.6 Quality of life/satisfaction with care for either recipients of care or their carers

**6. Adverse events/effects**

6.1 Suicide and all causes of mortality
6.2 Other adverse events/effects

**6. Economic outcomes**

6.1 Cost of care

### Summary of findings table

We will use the GRADE approach to interpret findings ( Schünemann 2008) and use GRADEPRO to import data from 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 that we will 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. Service utilisation**

1.1 Hospital admission
1.2 Days in hospital

**2. Clinical global response**

2.1 Relapse
2.2 Clinical global response
2.3 Compliance with medication

**3. Quality of life/satisfaction with care for either recipients of care or their carers**

**4. Economic outcomes**

4.1 Cost of care

## Search methods for identification of studies

### Electronic searches

#### Cochrane Schizophrenia Group Trials Register

The register will be searched using the phrase:
[*family* in interventions of STUDY]
This register is compiled by systematic searches of major databases, handsearches and conference proceedings.

### Searching other resources

#### 1. Reference searching

We will inspect references of all identified 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

Review author OU will independently inspect citations from the searches and identify relevant abstracts. A random 20% sample will be independently re-inspected by CEA 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 OU. Again, a random 20% of reports will be re-inspected by CEA 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 author OU will extract data from all included studies. In addition, to ensure reliability, CEA will independently extract data from a random sample of these studies, comprising 10% of the total. Again, any disagreement will be discussed, decisions documented and, if necessary, we will contact the authors of studies for clarification. With any remaining problems CEA will help clarify issues and these final decisions will be documented. We will extract data presented only in graphs and figures whenever possible, but we will include the data only if both review authors independently have the same result. Attempts will be made 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:

1. the psychometric properties of the measuring instrument have been described in a peer-reviewed journal (Marshall 2000); and
2. 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 primarily to 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 (SMD) throughout (Higgins 2011, Chapter 9.4.5.2 ).

### 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 and means are reported in the paper or obtainable from the authors;
b) when a scale starts from the finite number zero, the standard deviation, 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 starts from a positive value (such as Positive and Negative Syndrome Scale (PANSS) which can have values from 30 to 210), we will modify the calculation described above to take the scale starting point into account. In these cases skew is present if 2 SD > (S-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 above can be applied. 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. Skewed data from studies of less than 200 participants will be entered in additional tables rather than into an analysis. Skewed data pose less of a problem when looking at means if the sample size is large and skewed data from studies with over 200 participnats will be entered into syntheses.

### 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, efforts will be made 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 2005; Leucht 2005a). 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 brief family therapy. Where keeping to this makes it impossible to avoid outcome titles with clumsy double-negatives (e.g. 'Not improved') 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

Again review author OU will work independently to assess risk of bias by using criteria described in the *Cochrane Handbook for Systemic 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 member of the review group. Where inadequate details of randomisation and other characteristics of trials are provided, we will contact the authors of the studies in order to obtain further information. Non-concurrence in quality assessment will be reported, but if disputes arise as to which category a trial is to be allocated, again, resolution will be made 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 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).

#### 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 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, 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 intra-class 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 intra-class 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 intra-class correlation coefficients 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, 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 Systemic reviews of Interventions*. Where the additional treatment arms are not relevant, these data will not be reproduced.

### 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 was less than 50%, we will mark such data with (*) to indicate that such a result may well be prone to bias.

#### 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 outcomes 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 present and use such 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 confidence intervals available for group means, and either a '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 * square root (n). Chapters 7.7.3 and 16.1.3 of the *Cochrane Handbook for Systemic reviews of Interventions* (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 these data but 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. 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

We will investigate heterogeneity between studies 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 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 10.1 of the *Cochrane Handbook for Systemic 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, we will compare outcomes listed in the methods section of the trial report with actual 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 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 10 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 ones. Depending on the direction of effect, these studies can either inflate or deflate the effect size. We choose random-effects model for all analyses. The reader will, however, be able to choose to inspect the data using the fixed-effect model.

### Subgroup analysis and investigation of heterogeneity

#### 1. Subgroup analyses - only primary outcomes

#### 1.1 Clinical state, stage or problem

We propose to undertake this review and provide an overview of the effects of brief family interventions 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, we will visually inspect the graph and 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, 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 better description of randomisation, then we will use all 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 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/s.

Where assumptions have to be made regarding missing SDs 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/s. If there is a substantial difference, we will report these results and discuss them but will continue to employ our assumption/s.

#### 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 use 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

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 the greater weights assigned to larger trials with greater event rates, altered the significance of the results compared to the more evenly distributed weights in the random-effects model.

## ACKNOWLEDGEMENTS

The Cochrane Schizophrenia Group Editorial Base in Nottingham produces and maintains standard text for use in the Methods section of their reviews. We have used this text as the basis of what appears here and adapted it as required.

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* *Indicates the major publication for the study*

## HISTORY

Protocol first published: Issue 4, 2012

## CONTRIBUTIONS OF AUTHORS

Okpokoro Uzuazomaro - instigated and wrote the protocol.

Clive E Adams - helped with the protocol.

## DECLARATIONS OF INTEREST

Okpokoro Uzuazomaro - none.

Clive E Adams - none.

## SOURCES OF SUPPORT

### Internal sources

- The University of Nottingham, UK.
- Institute of Mental Health, Nottingham, UK.

### External sources

- No sources of support supplied