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Smoking cessation advice for people with serious mental illness

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Smoking cessation advice for people with serious mental illness (Protocol)

Khanna P, Clifton A, Banks D, Tosh G



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[Intervention Protocol]

Smoking cessation advice for people with serious mental illness

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ABSTRACT

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

To review the effects of smoking cessation advice for people with serious mental illness.

BACKGROUND

Description of the condition

The definition of severe mental illness with the widest consensus is that of the National Institute of Mental Health (NIMH) (Schinnar 1990) and is based on diagnosis, duration and disability (NIMH 1987). People with serious mental illness have conditions such as schizophrenia or bipolar disorder, which over a protracted period of time result in erosion of functioning in day to day life. A European survey put the total population-based annual prevalence of serious mental illness at approximately 2 per 1000 (Ruggeri 2000). People with serious mental illness have a higher morbidity and mortality from chronic diseases than the general population, and this results in a significantly reduced life expectancy (Robson 2007). In schizophrenia, for example, life expectancy is reduced by around 10 years (Newman 1991). Sufferers from serious mental illness have increased rates of cardiovascular disease, infectious diseases (including HIV) (Cournos 2005), non-insulin dependent diabetes, respiratory disease and cancer (Dixon 1999; Robson 2007). Evidence suggests that people with a serious mental illness are heavier, more dependent smokers than in the general population. One study, for example, observed a very high smoking rate of 74% in people with schizophrenia (Meltzer 1996). It is likely that people with serious mental illness smoke more due to a wide range of factors that could include a common aetiology to both smoking and the illness, self medication, smoking to alleviate adverse effects of medications, boredom in the existing environment, and a combinations of these.

Description of the intervention

Smoking cessation advice can take many forms. These are highly divergent and dependent on environmental and socioeconomic factors. Advice is the active provision of preventative information. It has an educative component and is delivered in a gentle non-patronising manner (Stott 1990). Currently, much health promotion and advice exists. Smoking cessation advice could be defined as any verbal or intervention advice about the effects of smoking and smoking cessation from a healthcare professional.

How the intervention might work

Advice may motivate people to seek further support and treatment (Sutherland 2003). Advice from a healthcare professional can have a positive impact on behaviour (Kreuter 2000; Russell 1979). Accordingly, the key to changing behaviour is that the recommended advice given by healthcare practitioners is consistent with the other sources of information encountered by people relating to their particular problem, for example, on stopping smoking (Kreuter 2000). A variety of advice is available for smokers

from healthcare professionals. Routine advice and support to stop smoking should be part of overall healthcare treatment for the general population and for people with serious mental illness. It is critical that health professionals who come into contact with smokers with serious mental illness routinely ask about smoking and advise their patients to stop. Following advice, many smokers with serious mental illness will need further support (Health Development Agency 2004). They should be referred to specialist smoking cessation advisors and key workers, psychiatrists or prescribers and general physicians should be made aware. This is to ensure that attempts at stopping can be monitored and adjustments are made to psychotropic medications, as appropriate (Health Development Agency 2004).

Why it is important to do this review

Globally, tobacco continues to kill nearly 6 million people each year, including more than 600 000 non-smokers who die from exposure to tobacco smoke. Up to half of the world's 1 billion smokers will eventually die of a tobacco-related disease (WHO 2011). Smoking remains the leading cause of preventable morbidity and premature death in the UK. It is estimated that smoking caused an average 86,500 deaths a year between 1998 and 2002 (NICE 2006). Smoking costs the NHS between £1.4 and £1.7 billion a year (DoH 2004) and tobacco consumption is recognised as the UK's single greatest cause of preventable illness and early death, with around 107,000 people dying in 2007 from smoking-related diseases including cancers (Peto 2006). Patients with mental health problems may be less likely to report or seek treatment for their physical symptoms, which often means that doctors may not conduct an appropriate physical assessment (Phelan 2001). Despite a high primary care consultation rate, people with serious mental illness are much less likely than the general population to be offered health promotion interventions such as smoking cessation advice (NHS 2001). People with serious mental illness can spend a large proportion of their low income on smoking thus depriving themselves of a better quality of life by not being able to spend on other things (McDonald 2000). It is estimated that there were at least 200,000 people with schizophrenia in the UK alone and, based on figures of 60% of these smoking an average of 26 cigarettes per day, this group contribute £139 million each year to the government treasury (McCreadie 2000). This is considerably offset by outgoings on healthcare support. Interestingly, a small-scale study by Strathclyde Fire Brigade found that 12% of fires involving care in the community patients over a two year period were due to careless dispersal of smoke materials (Docherty 1999). It is important to undertake this review to facilitate improvements in both the health and safety of people with serious mental illness who smoke and to reduce the overall burden of costs to the smoker and to the taxpayer.

OBJECTIVES

To review the effects of smoking cessation advice for people with serious mental illness.

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 only 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 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 participants by alternate days of the week. Where people are given additional treatments within a smoking cessation advice programme, we will only include data if the adjunct treatment is evenly distributed between groups and it is only the smoking cessation that is randomised.

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 will include trials that involve people with a range of severe mental illnesses if the majority of those randomised have schizophrenia, we will not include trials that only randomise people with bipolar or serious affective disorder. We will not consider substance abuse to be a severe mental disorder in its own right; we feel that studies should remain eligible if they deal with people with dual diagnoses, that is those with severe mental illness plus substance abuse. We will not include studies focusing on dementia, personality disorder and mental retardation as they are not covered by our definition of severe mental illness.

We are interested in making sure that information is as relevant to the current care of people with schizophrenia as possible so we 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

1. Smoking cessation advice

We have found it difficult to find a useful definition of 'advice'. In the context of this review we define 'advice' as preventative information (Greenlund 2002) or counsel (OED) that leaves the recipient to make the final decision. Advice may be directional but not paternalistic in its delivery. We do not consider that programmes of learning and educational or training groups fall into the definition of 'advice'. Advice should have at least a suggestion of: i. an educative component; ii. a preventative aim; and iii. an ethos of self-empowerment. Advice may be directional but not paternalistic in its delivery. We will not consider effects of training programmes as these are the focus of another cochrane review (Tsoi 2010).

2. Standard care

Care in which smoking cessation advice is not specifically emphasised above and beyond the care that would be expected for people suffering from serious mental illness.

Types of outcome measures

For the purposes of this review we will divide outcomes into four time periods: i. immediate (within one week); ii. short term (one week to six months); iii. medium term (six months to one year); and iv. long term (over one year).

Primary outcomes

1. Smoking cessation awareness

1.1 Raised awareness of common problems associated with smoking

2. Smoking behaviour

2.1 Substantial reduction in smoking behaviour

3. Quality of life

3.1 Healthy days

Secondary outcomes

1. Adverse events

1.1 Number of participants with at least one adverse effect

1.2 Clinically important specific adverse effects (withdrawal, irritability, weight gain, reduced appetite, insomnia, anxiety, craving, depression, decreased concentration)

- 1.3 Average endpoint in specific adverse effects
- 1.4 Average change in specific adverse effects
- 1.5 Death - natural or suicide

2. Service use

- 2.1 Hospital admission
- 2.2 Emergency medical treatment
- 2.3 Use of emergency services

3. Financial dependency

- 3.1 Claiming unemployment benefit
- 3.2 Claiming financial assistance because of a physical disability

4. Social

- 4.1 Unemployment
- 4.2 Social Isolation as a result of preventable incapacity
- 4.3 Increased burden to caregivers

5. Economic

- 5.1 Increased costs of health care
- 5.2 Days off sick from work
- 5.3 Contribution to society
- 5.4 Family claiming carers' allowance

6. Leaving the studies early

- 6.1 Any reason
- 6.2 Adverse events
- 6.3 Inefficacy of treatment

7. Quality of life

- 7.1 Loss of independence
- 7.2 Loss of skills in activities of daily living (ADL)
- 7.3 Loss of earnings
- 7.4 Loss of social status

8. Global state

- 8.1 Clinically important change in global state (as defined by individual studies)
- 8.2 Relapse (as defined by the individual studies)

9. Mental state

- 9.1 Clinically important change in general mental state score
- 9.2 Average endpoint general mental score
- 9.3 Average change in general mental state score
- 9.4 Clinically important change in specific symptoms (positive symptoms of schizophrenia, negative symptoms of schizophrenia)
- 9.5 Average endpoint specific symptom score
- 9.6 Average change in specific symptom score

10. Summary of findings table

We will use the GRADE approach to interpret findings (Schünemann 2008) and use GRADE profiler (GRADE Profiler) to import data from RevMan 5 (Review Manager (RevMan)) to create a '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 rated as important to patient care and decision making. We aim to select the following main outcomes for inclusion in the summary of findings table.

1. Smoking cessation.
2. Quality of life - improved to an important extent.
3. Service utilisation outcomes (hospital admission, days in hospital).
4. Economic (increased cost to society).
5. Adverse effect - any important adverse event.

Search methods for identification of studies

Electronic searches

Cochrane Schizophrenia Group Trials Register

We will search the Register using the phrase:
 [(**physical** or **cardio** or **metabolic** or **weight** or **HIV** or **AIDS** or **Tobacc** or **Smok** or **sex** or **medical** or **dental** or **alcohol** or **oral** or **vision** or **sight** or **hearing** or **nutrition** or **advice** or **monitor** in title of REFERENCES) AND (**education** OR **health promot** OR **preventi** OR **motivate** or **advice** or **monitor** in interventions of STUDY)]

This register is compiled by systematic searches of major databases, handsearches and conference proceedings (see [group module](#)).

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

AC and PK will independently inspect citations from the searches and identify relevant abstracts. A random 20% sample will be independently re-inspected by DB 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 AC and PK. Again, a random 20% of reports will be re-inspected by DB, in order to ensure reliable selection. Where it is not possible to resolve any disagreement by discussion, we will attempt to contact the authors of the study for clarification.

Data extraction and management

1. Extraction

Review authors AC and PK will extract data from all included studies. In addition, to ensure reliability DB will independently extract data from a random sample of these studies, comprising 10% of the total. Again, any disagreement will be discussed, the decisions documented and, if necessary, authors of studies will be contacted for clarification. With remaining problems, GT will help clarify issues and the final decisions will be documented. Data presented only in graphs and figures will be extracted whenever possible, but included only if two 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 the data relevant to each component centre separately.

2. Management

2.1 Forms

Data will be extracted onto standard, simple forms.

2.2 Scale-derived data

We will include continuous data from rating scales only if:

- a. the psychometric properties of the measuring instrument have been described in a peer-reviewed journal (Marshall 2000); and
- b. the measuring instrument has not been written or modified by one of the trialists for that particular trial.

Ideally the measuring instrument should either be: i. a self-report; or ii. completed by an independent rater or relative (not the therapist). We realise that this is not often reported clearly; in the '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 the calculation of change needs two assessments (baseline and endpoint), which can be difficult in unstable and difficult to measure conditions such as schizophrenia. We have decided to primarily use endpoint data and only use change data if the former are not available. Endpoint and change data will be combined in the analysis as we will use weighted mean differences (MD) rather than standardised mean differences throughout (Higgins 2011).

2.4 Multiple linear regression data

Many trials in psychiatry report estimates of treatment effects from multiple linear regression models. These models adjust for varying factors such as age, sex, and the baseline measure of the outcome. We will pool treatment estimates from these trials using fixed-effect model (inverse variance) meta-analysis. P values and confidence intervals for treatment effect will be converted to standard errors and entered into RevMan using the generic inverse variance.

2.5 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 started from a positive value (such as the Positive and Negative Syndrome Scale (PANSS) which can have values from 30 to 210) the calculation described above was modified to take the scale starting point into account. In these cases a skew is present if $2SD > (S - S_{min})$, where S is the mean score and S min is the minimum score. Endpoint scores on scales often have a finite start and an endpoint and these rules 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 will be entered into syntheses.

2.6 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 (for example, mean days per month).

2.7 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 into 'clinically improved' or 'not clinically improved' accordingly. It is generally assumed that if there is a 50% reduction in a scale-derived score, such as the Brief Psychiatric Rating Scale (BPRS) (Overall 1962) or the Positive and Negative Syndrome Scale (PANSS) (Kay 1986), this could be considered as a clinically significant response (Leucht 2005; Leucht 2005a). If data based on these thresholds are not available, we will use the primary cut-off presented by the original authors.

2.8 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 smoking cessation advice. Where keeping to this makes it impossible to avoid outcome titles with clumsy double-negatives (for example, '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 AC and PK will work independently to assess risk of bias by using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) to assess trial quality. This set of criteria is based on evidence of associations between an overestimation of effect and high risk of bias of the article, such as due to 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, authors of the studies will be contacted 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 to, again resolution will be made by discussion.

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

Measures of treatment effect

1. Binary data

For binary outcomes we will calculate a standard estimation of the risk ratio (RR) and its 95% confidence interval (CI). It has been shown that RR is more intuitive (Boissel 1999) than odds ratios and that odds ratios tend to be interpreted as RR by clinicians (Deeks 2000).

2. Continuous data

For continuous outcomes we will estimate the mean difference (MD) between groups. We prefer not to calculate effect size measures (standardised mean difference (SMD)). However, if very similar scales are used we will presume there was 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, 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 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 the relevant data are 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 (for example, 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 the 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. Where the additional treatment arms are not relevant, these data will not be used.

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 present 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, data will be presented on a 'once-randomised-always-analyse' basis (an intention-to-treat analysis). Those leaving the study early are all assumed to have the same rates of negative outcome as those who completed, with the exception of the outcome of death and adverse effects. For these outcomes the rate of those who stayed in the study, in that particular arm of the trial, will be used for those who did not. A sensitivity analysis will be undertaken testing how prone the primary outcomes are to change when 'completer' data only 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 completer-only data is reported, we will present and use these.

3.2 Standard deviations

If standard deviations are not reported, we will first try to obtain the missing values from the authors. If not available, where there are missing measures of variance for continuous data but an exact standard error and confidence intervals available for group means, and either the P value or t value is available for differences in mean, we can calculate the variance according to the rules described in

the Cochrane Handbook (Higgins 2011). These state that when only the standard error (SE) is reported, standard deviations (SDs) are calculated by the formula $SD = SE * \text{square root}(n)$. Chapters 7.7.3 and 16.1.3 of the Cochrane Handbook (Higgins 2011) present detailed formula for estimating SDs from P values, t or F values, confidence intervals, ranges or other statistics. If these 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 will nevertheless examine the validity of the imputations in a sensitivity analysis by 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 and indicate that they are the product of LOCF assumptions.

Assessment of heterogeneity

1. Clinical heterogeneity

We will initially consider all included studies, 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 initially consider all included studies, without seeing comparison data, to judge methodological heterogeneity. We will simply inspect all studies for clearly outlying methods which we had not predicted would arise. When such methodological outliers arise these will be fully discussed.

3. Statistical heterogeneity

3.1 Visual inspection

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

3.2 Employing the I^2 statistic

Heterogeneity between studies will be investigated by considering the I^2 statistic method 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: i. magnitude and direction of effects; and ii. strength of evidence for heterogeneity (for example, P value from Chi^2 test or a confidence interval for I^2 statistic). 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 of the Cochrane Handbook) (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

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 (Higgins 2011). We will try to locate protocols of included randomised trials. If the protocol is available, outcomes in the protocol and in the published report will be compared. If the protocol is not available, outcomes listed in the methods section of the trial report will be compared 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 described in Section 10 of the Cochrane Handbook (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 do not plan to 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 on their interpretation.

Data synthesis

We understand that there is no closed argument for preference in the 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. To us, this often seems to be true 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 as 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 have chosen the random-effects model for all analyses. The reader is, however, able to choose to inspect the data using the fixed-model model.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

We anticipate no subgroup analyses.

2. Investigation of heterogeneity

If inconsistency is high, this will be reported. First, we will investigate whether data have been entered correctly. Second, if data are correct, the graph will be visually inspected and studies outside of the company of the rest will be successively removed to see if homogeneity is restored. For this review we have decided that should this occur with data contributing to the summary finding of no more than around 10% of the total weighting, the data will be presented. If not, the data will not be pooled and issues will be discussed. 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 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 descriptions of randomisation, then the data will be employed from these studies.

2. Assumptions for lost binary data

Where assumptions have to be made regarding people lost to follow-up (see Dealing with missing data) we will compare the findings of the primary outcomes when we use our assumption 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 complete data only. A sensitivity analysis will be undertaken 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 judged to be at high risk of bias across one or more of the domains of randomisation (implied as randomised with no further details available), allocation concealment, blinding and outcome reporting for the meta-analysis of the primary outcome. If the exclusion of trials at high risk of bias does not substantially alter the direction of effect or the precision of the effect estimates, then data from these trials will be included in the analysis

4. Imputed values

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

If substantial differences are noted in the direction or precision of effect estimates in any of the sensitivity analyses listed above, we will not pool data from the excluded trials with the other trials contributing to the outcome but will present them separately

5. Fixed 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 alter 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

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Priya Khanna - primary review author, helped write protocol.

Andrew Clifton - helped write protocol.

Graeme Tosh - helped write protocol.

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None known

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