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[Intervention Protocol]

Psychoeducation for the parents of people with severe mental illness

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ABSTRACT

Objectives

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

To assess the effects (benefits and harms) of psychoeducation specifically for parents of people with SMI.

BACKGROUND

Description of the condition

Severe mental illness (SMI) can be very disabling with a chronic and relapsing course. SMI has been described as a mental disorder that needs treatment for at least two years, and which causes dysfunction comparable to a score of ≤ 50 on the Global Assessment of Functioning (GAF) test (Parabiaghi 2006). However, there is no consensus on the definition of SMI (Conejo 2014). It is agreed that a certain degree of dysfunction is necessary to define the presence of SMI, but there is no full agreement about the inclusion of different dimensions, such as the presence of a particular mental disorder, the need for family and social support, the use of healthcare services, or the duration of the illness (Conejo 2014). International taxonomies and classifications, like the *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition (DSM-5) (APA 2013), do not include SMI as a differentiated mental disorder, yet the World Health Organization (WHO) considers schizophrenia (and other psychotic disorders), bipolar disorder, and moderate or severe depression as examples of SMI (Cohen 2017). Thus, these or similar disorders are often included within the concept of SMI when the duration of the illness is at least two years, and particularly, if disability results in difficulties involving social and occupational functioning (Liberman 2008).

Schizophrenia

Schizophrenia is an SMI characterised by a chronic course of disturbances in thoughts and behaviour, which involves cognitive, behavioural and emotional symptoms. Schizophrenia usually begins between the ages of 20 and 30, earlier in men than in women, and its associated symptoms and dysfunctions last a lifetime, decreasing in intensity over the years (APA 2013). The principal symptoms of psychosis are usually described as 'positive symptoms', like hallucinations and delusions, and 'negative symptoms', such as poverty of speech, emotional apathy and self-neglect (APA 2013; NICE 2014). Cognitive dysfunction in schizophrenia is frequent and affects attention, working memory, verbal learning and memory, and executive functions (Sharma 2003). It is usual to refer to schizophrenia under the general term of psychosis, which includes schizophrenia and other disorders like schizoaffective disorder, schizophreniform disorder and delusional disorder (NICE 2014).

According to the Global Burden of Disease (GBD) studies, the lifetime prevalence of schizophrenia is estimated to be 0.28% (Charlson 2018). Schizophrenia and other psychotic disorders present gender differences in the age of onset: mean age of 18 to 25 years for men and 25 to 35 years for women (Ochoa 2012).

Bipolar disorders

Bipolar disorders are a group of mood disorders characterised by periods of depressed or elevated/irritable mood that last for weeks or months (APA 2013). Bipolar disorder, also known as manic-depressive illness, is a chronic and disabling disorder characterised by episodes of mania or hypomania (abnormally elevated mood or irritability) and episodes of depressed mood (NICE 2018a). DSM-5 classification of mental disorders include several types of bipolar disorder: 1) bipolar I disorder occurs when a manic episode is followed or preceded by a hypomanic or major depressive episode; 2) bipolar II disorder occurs when the person experiences a present or past hypomanic episode and a major depressive episode (not including symptoms that are a sure consequence of a medical condition); 3) cyclothymic disorder occurs when, for at least two years, a person experiences numerous periods with hypomanic symptoms and depressive symptoms that do not meet the criteria for a hypomanic episode or a major depressive episode, respectively; 4) substance/medication-induced bipolar and related disorder occurs when there is a persistent disorder in mood, induced after drug intake; 5) bipolar and related disorder due to another medical condition occurs when there is a persistent disorder in the mood as a consequence of a pathophysiological condition (APA 2013). Estimates of the lifetime prevalence of bipolar I and II disorders vary (NICE 2018a). The prevalence of bipolar I and II disorders in the USA is about 1% and 0.4%, respectively (Merikangas 2007; Merikangas 2012).

Cyclothymic disorder and those bipolar and related disorders induced by substance/medication, or by medical conditions, do not represent a dysfunction severe enough to be considered SMI, since SMI requires a score of ≤ 50 on the GAF (APA 2013; Parabiaghi 2006).

Depression

Depression is a mood disorder characterised by the presence of depressed mood and loss of pleasure in most activities (NICE 2018b). The severity of depression is determined by the number and severity of symptoms, and by the degree of functional impairment. To be considered an SMI, the severity of the depression symptoms must be moderate to high (NICE 2018b). The course of depression and its response to the treatment depend on a wide range of biological, psychological and social factors, such as the presence of a physical condition or another chronic disease (NICE 2015). Depression often has a remitting and relapsing course, and symptoms may persist between episodes, thus it can be considered as a chronic illness. The lifetime prevalence of depression is estimated to be from 31% to 47% of the population (Bernard 2017; Ghaemmohamadi 2018; Mitchell 2017; Ojagbemi 2017; Tung 2018). Moreover, depression is considered to be one of the main specific causes of disability-adjusted life-years (GBD 2015 DALYs and HALE 2016).

The care provided by families and carers is important for people with SMI (Chien 2013). The primary carer of a person with SMI is usually a parent, most often the mother (Caqueo-Urizar 2006; Geriani 2015). This responsibility supposes a daily burden, which can cause many physical, psychological and social problems (Bauer 2012). Parents of people with SMI are at high risk for mental health morbidity as a result of being a carer (Lasebikan 2013), such as increased levels of stress, depression, and anxiety (Bauer 2012). Therefore, this role poses a significant risk to the psychological, physical, and social well-being of the parents (Bauer 2012; Catalano 2018; Lasebikan 2013; Sajadi 2017). Also related to being a carer, family caregivers could be considered as hidden patients experiencing their own physical and mental disorders (Sajadi 2017). Many symptoms have been reported, such as anxiety, insomnia, depression, as well as physical symptoms such as headache or muscle aches (Bauer 2012).

On the other hand, there is some evidence that carers do find benefit from a sense of self-worth in their caring role (Bauer 2012). However, lack of knowledge about the SMI, treatments, or symptoms, or doubt about the person with SMI's ability to manage themselves autonomously, often increases discomfort or anxiety in the carers (Saunders 2013). As a consequence, this affects their

ability to care and, consequently, the well-being of the person with SMI (Knafl 2015; Sajadi 2017), as there is an association between the well-being of the carer and outcomes for the person with SMI in terms of prevention of relapses, quality of life and recovery (Knafl 2015).

Description of the intervention

Psychoeducation can be defined as an intervention that involves professionals as education providers for people with SMI and their carers, including immediate family members (in particular parents) and other relatives, about symptoms, treatments, care and prognosis of mental illness (Bauml 2006; Raymond 2017). Psychoeducation may reduce relapse and readmission, encourage medication compliance, and reduce length of hospital stay in individuals with schizophrenia (Xia 2011).

The characteristics of psychoeducational interventions vary. The length of each psychoeducational programme could vary from one-day interventions to one-year programmes, but the time for a successful intervention is estimated to be from two to six months (Sin 2013). The duration of each session can also vary, but it usually ranges from 60 to 90 minutes (Lyman 2014; Sin 2013). A psychoeducational intervention can be provided individually or in groups. Interventions are commonly delivered in a face-to-face format, although online or mixed model formats (online and face-to-face) have gained interest recently and are used more frequently (Sin 2017).

Psychoeducational interventions for family carers of people with SMI are commonly delivered by educational programmes informing about the mental illness and its management (Sin 2017). The main objectives are to bring support and resources to the carers of individuals with SMI, to promote their well-being, reduce stress and burden, and to improve family well-being (Sin 2013). Transferring knowledge about mental health issues as a core component, those programmes go beyond their educational element to also teach skill-building strategies, like coping and problem solving (Lyman 2014). Most of the psychoeducational interventions for family carers have multiple components in common, such as knowledge of the illness, coping strategies, problem solving and peer support, making use of cognitive behavioural, systematic or dyadic techniques (Lyman 2014; Sin 2013). Psychoeducational programmes should be provided by a trained professional whose aim is to promote decision making in a collaborative environment between professionals, people with SMI, and family members (Raymond 2017).

How the intervention might work

Psychoeducation may engage the family with healthcare services and professionals, thereby helping them to build a better system of knowledge and coping strategies, improving their understanding of the illness, and reducing their distress and worries (Harvey 2018). According to literature, increased knowledge commonly correlates to improved self-perception of coping skills, self-efficacy and well-being (Raymond 2017; Sin 2013). Moreover, several studies have shown positive effects on families and people with SMI receiving psychoeducation, gaining empowerment, increasing a positive perception of peer support and even reducing relapse and rehospitalisation (Katsuki 2018; Petrakis 2017; Timmerby 2016). Finally, psychoeducation may be part of an initial form of more complex interventions, like family psychotherapeutical interventions, that could be beneficial for a longer period of time (Raymond 2017; Sin 2013).

Why it is important to do this review

A Cochrane Review providing a rigorous and up-to-date assessment of the effects of psychoeducational interventions specifically for parents of people with SMI is needed. To our knowledge, there are no systematic reviews on this topic. There is a Cochrane Review of the effects of psychoeducational interventions specifically for the siblings of people with SMI (Sin 2015). However, we consider that the parents' role is different and requires a specific evaluation. Current research suggests that the roles of parents and other family carers differ, as it is usually the parents who are the primary carers, and other relatives are not as involved with statutory health or social services (Sin 2012). Thus, it is important to determine the effectiveness of psychoeducation focused on the parents of people with SMI. On the other hand, there are different psychoeducation programmes available to support carers of people with SMI, which makes it difficult to know the best modality or strategy of psychoeducation to apply to parents (Sin 2013; Sin 2017). Also, parents often underline the scarce assistance they receive from mental health professionals (Bauer 2012; Saunders 2013), which may suggest there is room for improving their mental health if they receive effective interventions.

OBJECTIVES

To assess the effects (benefits and harms) of psychoeducation specifically for parents of people with SMI.

METHODS

Criteria for considering studies for this review

Types of studies

We will consider all relevant randomised controlled trials (RCTs). We will include RCTs meeting our inclusion criteria and reporting data, useable either for the qualitative or quantitative synthesis. Thus, we will not exclude otherwise eligible studies without our review outcome data. If randomisation is not explicitly mentioned, but the trials are described as 'double-blind', we will include them, assuming that randomisation is implied. We will assess the impact of this decision by excluding these trials in a sensitivity analysis. We will exclude quasi-randomised studies, such as those that allocate intervention by alternate days of the week. Where people are given additional treatments as well as the psychoeducational intervention, we will only include data if the adjunct treatment is evenly distributed between groups and it is only the psychoeducational intervention that is randomised. We will include studies irrespective of their publication status. Thus, we will consider unpublished data.

Types of participants

Participants of interest are the parents of people with SMI, treated in any setting.

- Parent: we will define parents to incorporate modern society family structures. Thus, by parents, we will consider biological parents, adoptive parents, or step-parents.
- SMI: SMI is a serious mental disorder that needs treatment for at least two years, and that causes dysfunction comparable to a

score of ≤ 50 on the GAF (Parabiaghi 2006) (see more details in Description of the condition). In practical terms, we will include trials where the participants have the following diagnoses: schizophrenia or related disorders (including schizophreniform disorder, schizoaffective disorder and delusional disorder), bipolar disorder, and depression with psychotic features.

- Age of the people with SMI: we will include trials with participants of any age.
- Setting: we will exclude trials in which the parents of people with SMI receive the intervention together with the individuals with SMI.

Studies with mixed populations, that is, also including other relatives of people with SMI, such as siblings (Sin 2015), or people with non-severe mental disorders, such as non-psychotic depression, will only be eligible if ≥ 80% of the participants fulfil all the review inclusion criteria.

Types of interventions

1. Intervention: psychoeducational intervention

We will consider any psychoeducational intervention delivered face-to-face, targeting the parents of people with SMI. However, as suggested in another Cochrane Review (Sin 2015), psychoeducation for the management of crisis during the SMI will not be eligible because it is a different review question that warrants another review.

1.1. Definition of psychoeducational intervention

We will define a psychoeducational intervention as in previous Cochrane Reviews (Sin 2015; Xia 2011): a programme involving interaction between information providers and service users or carers, or both, in either an individual or group format. A psychoeducational intervention must fulfil the following criteria.

- There is an educational element that instils knowledge or information on the illness condition and its management.
- The educational element is significant within the design and prominent in terms of time duration within the overall content/duration of the multimodal interventions (comprising at least 50% of the total duration based on the programme's manual content).
- The educational intervention is led by a professional, such as a doctor, nurse, psychologist, occupational therapist, or social worker. However, co-facilitation by a lay person is acceptable.

We will consider any psychoeducational intervention, irrespective of its duration. In line with previous reviews (Sin 2015; Xia 2011), we will define the intervention duration as 'brief' (10 sessions or less; or where the number of sessions is not stated but they are delivered over a 10-week period, or less) or 'standard' (more than 10 sessions, or where the number of sessions is not stated but they are delivered over a period longer than 10 weeks). Besides these categories, we will admit sessions of any duration.

1.2. Target groups of the psychoeducational intervention: parents of people with SMI

To be eligible, the target participants of the psychoeducational intervention must be the parents of a person with SMI (as defined in Types of participants). We will admit psychoeducational interventions that also include other participants, such as other immediate family members, relatives or the service users, if data specific to the effect of the intervention for the parents are published or obtainable from the study authors. Interventions that include both parents and individuals with SMI will not be eligible (but will be detailed in the table of excluded studies).

1.3. Format: face-to-face

We will include interventions delivered face-to-face. Thus, we will exclude online or mixed (online and face-to-face) formats to deliver the psychoeducational interventions.

1.4. Co-interventions

We will only include studies in which additional interventions are provided if all the co-interventions are evenly distributed between groups and psychoeducation is the only intervention different between the intervention and the control group. Examples of co-interventions are pharmacological treatments for depression or other non-pharmacological interventions, such as psychotherapy.

1.5. Non-psychoeducational interventions

We will not consider the following interventions as psychoeducational interventions, and will therefore exclude them.

- Bibliotherapy, that is, a brief intervention that focuses purely on the provision of didactic education or health information using textual or video materials solely. Bibliotherapy does not include interactions between the professional facilitator and the participants (NICE 2010).
- Mutual support groups that, from the outset, are facilitated solely by lay persons, wider family members or parents.

2. Comparator

We will consider studies with any of the following comparators.

2.1. Inactive comparator

- No intervention
- Placebo
- Sham intervention: a procedure or device that appears to be the same as the actual procedure or device being studied but does not contain active processes or components (Clinical Trials 2021).
- Waiting list
- Usual or standard care: the normal level of psychiatric care/services provided in the geographical area for parents where the trial was carried out. We will assume that the services provided for parents of service users, in most circumstances, are minimal and most often include signposting to information and voluntary services for carers/families (Sin 2012; Smith 2009).

2.2. Active intervention targeting the parents of people with SMI

- Pharmacological interventions
- Non-pharmacological interventions other than psychoeducation, such as counselling, cognitive behavioural therapy, or family therapy

We will exclude studies comparing different types of psychoeducational interventions. We will also exclude studies comparing the same psychoeducational intervention but with different modes of delivery. For example, a psychoeducational intervention delivered by doctors as compared to delivered

by nurses, or delivered in groups versus individually, or a psychoeducational intervention consisting of more than five sessions versus five or less.

Types of outcome measures

We aim to divide all outcomes into short term (≤ 3 months), medium term (> 3 months and ≤ 6 months) and long term (> 6 months).

We generally prefer binary (e.g. improved/not improved) outcomes, because they are easier to interpret. We will also analyse continuous outcomes, but will present them after the binary outcomes. For valid scales please see Data extraction and management. For outcomes such as 'clinically important change' or 'any change' we will use the definition used by each of the trials.

Primary outcomes

1. Psychosocial well-being

1.1. Clinically important change in psychosocial well-being in the short term (≤ 3 months)

2. Quality of life

2.1. Clinically important change in quality of life in the short term (≤ 3 months)

3. Adverse events

3.1. At least one adverse event in the short term (≤ 3 months)

Secondary outcomes

1. Psychosocial well-being

1.1. Clinically important change in psychosocial well-being in the medium (> 3 months and ≤ 6 months) and long term (> 6 months)

1.2. Any change in psychosocial well-being in the short (≤ 3 months), medium (> 3 months and ≤ 6 months) and long term (> 6 months)

1.3. Average endpoint score on a psychosocial well-being scale in the short (≤ 3 months), medium (> 3 months and ≤ 6 months) and long term (> 6 months)

2. Quality of life

2.1. Clinically important change in quality of life in the medium (> 3 months and ≤ 6 months) and long term (> 6 months)

2.2. Any change in quality of life in the short (≤ 3 months), medium (> 3 months and ≤ 6 months) and long term (> 6 months)

2.3. Average endpoint score on a quality of life scale in the short (≤ 3 months), medium (> 3 months and ≤ 6 months) and long term (> 6 months)

3. Anxiety

3.1. Clinically important change in anxiety in the short (≤ 3 months), medium (> 3 months and ≤ 6 months) and long term (> 6 months)

3.2. Any change in anxiety in the short (≤ 3 months), medium (> 3 months and ≤ 6 months) and long term (> 6 months)

3.3. Average endpoint score on an anxiety scale in the short (≤ 3 months), medium (> 3 months and ≤ 6 months) and long term (> 6 months)

4. Satisfaction with the care of children

4.1. Clinically important change in satisfaction with the care of children in the short (≤ 3 months), medium (> 3 months and ≤ 6 months) and long term (> 6 months)

4.2. Any change in satisfaction with the care of children in the short (≤ 3 months), medium (> 3 months and ≤ 6 months) and long term (> 6 months)

4.3. Average endpoint score on a satisfaction scale with the care of children in the short (≤ 3 months), medium (> 3 months and ≤ 6 months) and long term (> 6 months)

6. Adverse events

6.1. At least one adverse event in the medium (> 3 months and ≤ 6 months) and long term (> 6 months)

Search methods for identification of studies

The search strategy will include electronic searches and additional strategies to retrieve as many relevant publications as possible. We will not apply any language restriction within the limits of the search.

Electronic searches

We will perform two separate searches.

1. The Information Specialists of Cochrane Schizophrenia Group (CSzG) will search CSzG's Study-Based Register of Trials using the following search strategy:

(*Parent* in Intervention Field) AND (*Parent* in Participants Field) of STUDY

In such a study-based register, searching the major concept retrieves all the synonyms and relevant studies. This is because the studies have already been organised, based on their interventions, and linked to the relevant topics (Shokraneh 2017). This allows rapid and accurate searches that reduce waste in the next steps of systematic reviewing (Shokraneh 2019).

Following the methods from Cochrane (Lefebvre 2021), the Information Specialist compiles this register from systematic searches of major resources and their monthly updates (unless otherwise specified).

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library
- MEDLINE
- Embase
- Allied and Complementary Medicine (AMED)
- BIOSIS
- Cumulative Index to Nursing and Allied Health Literature (CINAHL)
- PsycINFO
- PubMed
- US National Institute of Health Ongoing Trials Register (ClinicalTrials.gov)
- World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp)
- ProQuest Dissertations and Theses A&I and its quarterly update

- Chinese databases (Chinese Biomedical Literature Database, China Knowledge Resource Integrated Database, and Wanfang) and their annual updates

The register also includes handsearches and conference proceedings (see Group's website). It does not place any limitations on language, date, document type or publication status.

2. The Information Specialist of the Cochrane Common Mental Disorders (CCMD) Group will search the following databases and trial registers using relevant keywords, subject headings (controlled vocabularies) and search syntax, appropriate to each resource:

- Cochrane Common Mental Disorders Controlled Trials Register (CCMDCTR; all available years);
- Cochrane Central Register of Controlled Trials (CENTRAL; current issue) in the Cochrane Library;
- Ovid MEDLINE (1946 onwards; search strategy Appendix 1);
- Ovid Embase (1974 onwards);
- Ovid PsycINFO (1806 onwards);
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov/; all available years);
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/; all available years).

Searching other resources

1. Reference searching

We will inspect references of all included studies for further relevant studies. We will also perform forward snowballing of the included or other relevant studies and consult PubPeer for comments on the included studies (pubpeer.com).

2. Personal contact

We will contact the first author of each included study for information regarding unpublished trials. We will note the outcome of this contact in the 'Included studies' or 'Studies awaiting classification' tables.

Data collection and analysis

Selection of studies

At least two review authors (ACM, ALAE, DMM, DC, FJCM, MGS, PMH) will independently inspect citations from the searches and identify relevant abstracts. Where disputes arise, we will acquire the full report for more detailed scrutiny. At least two review authors (ACM, ALAE, DMM, DC, FJCM, MGS, PMH) will then obtain and independently inspect full reports of the abstracts or reports meeting the review criteria. Where it is not possible to resolve disagreement by discussion, we will discuss with the senior author of the team (JLA) to resolve it. If disagreement exists following discussion with the third review author, we will attempt to contact the authors of the study concerned for clarification. We will document all decisions. We will implement the selection process with Covidence software (Covidence 2021).

Data extraction and management

1. Extraction

At least two review authors (DC, ES, ACM, PMH) will independently extract data from all included studies. We will attempt to extract data presented only in graphs and figures whenever possible, but will only include it if two reviewer authors independently obtain the same result. We will discuss any disagreement. Where it is not possible to resolve disagreements by discussion, we will discuss with JLA. We will document all decisions. If necessary, we will attempt to contact authors through an open-ended request in order to obtain missing information or for clarification. JLA will help clarify issues regarding any remaining problems, and we will document these final decisions.

2. Management

2.1 Forms

We will extract data onto standard, predesigned, simple forms in Covidence software (Covidence 2021).

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);
- the measuring instrument has not been written or modified by one of the trialists for that particular trial; and
- the instrument is a global assessment of an area of functioning and not subscores which are not, in themselves, validated or shown to be reliable. However, we will include subscores of scales if these were validated or if these were predefined in a scale such as the positive symptom, negative symptom and general symptom scores of the Positive and Negative Syndrome Scale (PANSS; Kay 1986).

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, however, that this is not often reported clearly.

2.3 Endpoint versus change data

There are advantages to both endpoint and change data: change data can remove a component of between-person variability from the analysis; however, calculation of change needs two assessments (baseline and endpoint) that can be difficult to obtain in unstable and difficult to measure conditions such as schizophrenia. We have decided primarily to use endpoint data, and only use change data if the former are not available. If necessary, we will combine endpoint and change data in the analysis. This procedure is possible when using mean differences (MDs) (Deeks 2021) and also when using standardised mean differences (SMDs). Although theoretically, the combination of change and endpoint data when SMDs are used can be problematic, meta-epidemiological research has shown that on average no major over- or underestimations can be expected (da Costa 2013).

2.4 Skewed data

Continuous data on clinical and social outcomes are often not normally distributed (the distribution of the outcomes is asymmetrical, and the data are said to be skewed). To avoid the pitfall of applying parametric tests to non-parametric data, we

will apply the following check to relevant continuous data before inclusion.

For endpoint data from studies including fewer than 200 participants, we will calculate the observed mean minus the lowest possible value of the scale and divide this by the standard deviation (SD) (Higgins 2021a). For example, in a scale that has possible lowest values higher than zero (such as the Positive and Negative Syndrome Scale (PANSS), which can have values from 30 to 210 (Kay 1986)), we will subtract the minimum score (in this case 30) from the observed mean and then divide by the SD. In a scale that has zero as the minimum possible score, we will divide the observed mean by the SD. For this calculation, we will check the original publication of the scales referenced in the studies, in order to understand if they can have the lowest possible score different from zero, and if the adjustment described above is needed or not. If the ratio obtained is lower than one, it strongly suggests that the data are skewed. If it is higher than one but less than two, there is a suggestion that the data are skewed; if the ratio is larger than two it is less likely that they are skewed (Altman 1996; Higgins 2021a).

Studies with fewer than 200 participants and a suggestion of skewness (ratio < 2), will be included in the main analysis. We will exclude them in a sensitivity analysis to check if this has an impact on the main analysis results (see Sensitivity analysis for further details). If this is the case, we will exclude these studies from the main analysis and present their data using the 'Other data' format in the data and analyses tables.

We will enter all relevant data from studies with at least 200 participants in the main analysis irrespective of the above rules because skewed data pose less of a problem in large studies. We will also enter all relevant change data, as when continuous data are presented on a scale that includes a possibility of negative values (such as change-from-baseline measures) it is difficult to tell whether or not data are skewed.

2.5 Common measurement

To facilitate comparison between trials, we aim, where relevant, to convert variables that can be reported in different metrics, such as days in hospital (mean days per year, per week, or per month) to a common metric (e.g. mean days per month).

2.6 Conversion of continuous to binary

Where possible, we will make efforts to convert outcome measures to dichotomous data. This can be done by identifying cut-off points on rating scales and dividing participants accordingly into 'clinically improved' or 'not clinically improved'. It is generally assumed that if there is a 50% reduction in a scale-derived score, such as the Brief Psychiatric Rating Scale (BPRS) (Overall 1962), or the PANSS (Kay 1986), which corresponds to 'much improved' according to the clinical global impressions (CGI) of raters (Guy 1976), this could be considered as a clinically significant response (Leucht 2005a; Leucht 2005b), in particular for people who are acutely ill. However, we assume that most participants included in the studies would not have acute problems. For these, even small improvements may be meaningful, such as at least a 20% reduction of the BPRS or PANSS, which corresponds to 'minimally improved' on the CGI (Leucht 2005a; Leucht 2005b). Therefore, we chose these cut-offs as the primary ones. If data based on these thresholds are not available, we will use the primary cut-off presented by the original authors, because the exact cut-off is not as important in a meta-analysis using risk ratios (RRs) or odds ratios (ORs) as effect sizes (Furukawa 2011).

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 the psychoeducational intervention. Where keeping to this makes it impossible to avoid outcome titles with clumsy double-negatives (e.g. 'not unimproved'), we will report data where the left of the line indicates an unfavourable outcome and note this in the relevant graphs.

Assessment of risk of bias in included studies

Review authors JLA and DC will work independently to assess risk of bias (RoB) by using the RoB 2 tool and referring to the criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021b; Sterne 2019).

This set of criteria is based on judgement of the following domains.

- Bias arising from the randomisation process
- Bias due to deviations from intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

For each domain, we will rate the available 'signalling questions' in order to reach a judgement (high, some concerns, low) following the tool algorithms implemented in the RoB 2 Excel tool (Higgins 2021c).

RoB 2 generally allows studies to be addressed from two angles: 1) the effect of assignment to the interventions at baseline, regardless of whether the interventions were received as intended - the 'intention-to-treat effect'; and 2) adherence to the interventions - the 'per-protocol effect' (Higgins 2021b). For potential benefits, we aim to assess the 'intention-to-treat effect'. For potential harms, we will assess the 'per-protocol effect' (Higgins 2021c; Piaggio 2006).

We will evaluate the outcomes presented in the summary of findings tables (see below) with the RoB 2 tool.

For cluster-randomised trials, we will use the version of the RoB 2 tool for cluster-RCTs (Eldridge 2021). For cross-over trials, since we will only use data from the first phase (see Measures of treatment effect), we will use RoB 2 for parallel RCTs.

If the raters disagree, we will make the final rating by consensus. 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 risk of bias assessment, but if disputes arise regarding the category to which a trial is to be allocated, we will resolve this by discussion.

We will note the level of risk of bias in both the text of the review, the relevant forest plots, figures to describe the risk of bias across studies, and the summary of findings table(s). We will analyse the effects of excluding trials that are at overall high risk of bias for the meta-analysis of the primary outcomes.

Measures of treatment effect

1. Binary data

For binary outcomes, we will calculate a standard estimation of the RR and its 95% confidence interval (CI), as it has been shown that RRs are more intuitive than ORs (Boissel 1999); and that ORs tend to be interpreted as RRs by clinicians (Deeks 2000). Although the number needed to treat for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH), with their CIs, are intuitively attractive to clinicians, they are problematic to calculate and interpret in meta-analyses (Hutton 2009). For binary data presented in the summary of findings table(s) we will, where possible, calculate illustrative comparative risks and the absolute risk difference (RD) for relevant basal risk scenarios.

2. Continuous data

For continuous outcomes, we will estimate the MD between groups, in particular when natural units (such as days, kilograms, etc.) are used. We prefer not to calculate effect size measures (SMD). However, if scales of very considerable similarity are used, we will presume there is a small difference in measurement, and we will calculate SMD. It should be noted that SMD can be transformed to MD by using the formula MD = SMD x SD of the scale of interest (Higgins 2021d).

Unit of analysis issues

1. Cluster-randomised trials

Studies increasingly employ 'cluster randomisation' (such as randomisation by clinician or practice), but analysis and pooling of clustered data pose problems. Authors often fail to account for intraclass correlation in clustered studies, leading to a unit of analysis error whereby P values are spuriously low, CIs unduly narrow and statistical significance overestimated (Divine 1992). This causes type I errors (Bland 1997; Gulliford 1999).

Where clustering has been incorporated into the analysis of primary studies, we will present these data as if from a non-cluster-randomised study, but adjust for the clustering effect.

Where clustering is not accounted for in primary studies, we will present data in a table, with an asterisk (*) 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 will adjust for this by using accepted methods (Gulliford 1999).

We have sought statistical advice and have been advised that the binary data from cluster-randomised trials presented in a report should be divided by a 'design effect'. This is calculated using the mean number of participants per cluster (m) and the ICC: thus design effect = 1 + (m − 1) * ICC (Donner 2002). If the ICC is not reported we will assume it to be 0.1 (Ukoumunne 1999).

If cluster-randomised trials have been appropriately analysed and taken ICCs and relevant data documented in the report into account, synthesis with studies allocated at the individual level will be possible using the generic inverse variance technique.

2. Cross-over trials

A major concern about cross-over trials is the carry-over effect. This occurs if an effect (e.g. pharmacological, physiological or psychological) of the treatment in the first phase is carried over to the second phase. As a consequence, participants can differ significantly from their initial state at entry to the second phase, despite a washout phase. For the same reason, cross-over trials are not appropriate if the condition of interest is unstable (Elbourne 2002). As both carry-over and unstable conditions are very likely in our review outcomes, we will only use data from the first phase of cross-over studies.

3. Studies with multiple treatment groups

Where a study involves more than two treatment arms, if relevant, we will present the additional treatment arms in comparisons. If data are binary, we will simply add these and combine within the two-by-two table. If data are continuous, we will combine data following the formula in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021e), as implemented in the RevMan calculator (RevMan Web 2021). Where additional treatment arms are not relevant, we will not reproduce these data.

Dealing with missing data

1. Dealing with missing participant data and overall loss of credibility

To deal with missing participant data we will follow established guidance (Akl 2013; Akl 2016; Ebrahim 2013; Ebrahim 2014; Guyatt 2017). We will address selective outcome reporting and publication bias elsewhere. We will consider two main groups of missing data: 'premature end of follow-up' (PEFU) and 'missing participant data' (MPD). We will focus on MPD. PEFU, which is specific to a participant, refers to the cessation of following up of a specific participant before the planned end of study follow-up. On the other hand, MPD is specific to the outcome, and refers to the participant randomised in a trial for whom outcome data are not available for the reviewer, and therefore cannot be analysed for a specific effect estimate. Thus, PEFU could result in MPD for a number of outcomes, but not for outcomes measured before the participant was lost to follow-up (Akl 2016).

Various methods are available in trials to account for MPD. By preference, we will use available case analysis (ACA) and assess the impact of MPD in the item 'missing outcome data' of RoB 2.

We will also assess bias arising from the exclusion of participants from the analysis for reasons other than missing outcome data. We will assess this aspect under the domain of bias due to deviations from the intended intervention, rather than bias due to missing outcome data (Higgins 2021f). Appendix 2 provides definitions for the following key concepts: intention-to-treat (ITT) analysis, per-protocol (PP) analysis, ACA, as-treated analysis (ATA), and naive PP analysis. For potential benefits, the effect of interest for this review is the effect of assignment to the interventions at baseline, regardless of whether the interventions are received and adhered to during the follow-up. Thus, we plan to apply an ITT analysis first. If this is not possible because the outcome is not measured in all the randomised participants, we will try to apply the ACA in the ITT population. When the ITT principle is not possible, we will prefer the PP analysis instead of an ATA (Higgins 2021f). For potential harms, we will attempt to perform a PP analysis in the first place.

ITT analysis may not be appropriate for harms, as it is wrong to attribute harms to a treatment that somebody did not receive, and because ITT analysis tends to bias the results towards no difference (Higgins 2021f; Piaggio 2006).

We will follow the next process to deal with MPD and exclusions from the analysis.

Step 1. Handling postrandomisation exclusions for whom data were available

First, we will try to identify postrandomisation exclusions: participants excluded from the analysis but for whom the outcome was measured, e.g. due to a PP analysis. Second, we plan to reanalyse these exclusions according to our preferred analysis approach (ITT analysis for potential benefits and PP analysis for potential harms). We will look for the information in the trial reports or contact the trialists for clarification. We will consider postrandomisation exclusions to judge the risk of bias due to deviations from the intended intervention.

Step 2. Determining MPD per study outcome effect estimate

We will follow the Akl 2016 guidance to define MPD. We will classify MPD as follows: a) participant 'lost to follow-up' (LTFU): a participant with whom researchers lose contact and thus cannot complete planned data collection efforts (CONSORT glossary 2021); and b) participant that was not LTFU, but for whom the results of a test were not available (Akl 2013). We will extract the proportions of randomised participants with MPD (with reasons) by outcome and by randomised group.

Step 3. Accounting for MPD for each outcome effect estimate at the study level

Analysis approach

For each study and effect estimate with MPD, we will attempt to use the ACA based on the ITT principle, that is, we plan to analyse the participants providing outcome data according to the group to which they were randomised. If possible, we will 'reinclude' avoidable exclusions made by the authors.

Assessing risk of bias due to missing outcome data

For each outcome effect estimate, we will assess the risk of bias due to missing outcome data (see Assessment of risk of bias in included studies). We will estimate one 'plausible worst-case' scenario with plausible assumptions on the MPD to challenge the statistical significance of the results of the primary analysis (Akl 2013; Ebrahim 2013). If the direction or the statistical significance of the effect estimate change under this scenario, we will conclude that MPD is associated with high risk of bias due to missing outcome data for the effect estimate in that study. See assumptions for the 'plausible worst-case' scenario in Sensitivity analysis.

Step 4. Approaches to account for MPD for each outcome effect estimate at the meta-analysis level

Analysis approach at the meta-analysis level

For each meta-analysis, we will consider the data provided by the studies with an ACA of the ITT population. Although at some degree of MPD data lose credibility (Xia 2009), we will meta-analyse the studies independently of their risk of bias due to missing outcome data.

Assessing the risk of bias due to missing outcome data for each outcome estimate across studies

For the meta-analyses of the primary outcomes, we plan to conduct a sensitivity analysis to address the robustness of the results associated with MPD according to GRADE guidance (Guyatt 2017). See Sensitivity analysis.

2. Dealing with missing summary data in each study

If SDs are not reported, we will try to obtain the missing values from the authors. If these are not available, where there are missing measures of variance for continuous data, but an exact standard error (SE) and CIs are available for group means, and either the P value or t value are available for differences in mean, we can calculate SDs according to the rules described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021d). When only the SE is reported, SDs are calculated by the formula SD = SE * √(n). The *Cochrane Handbook for Systematic Reviews of Interventions* presents detailed formulae for estimating SDs from P, t or F values, CIs, ranges or other statistics (Higgins 2021d). If these formulae do not apply, we will calculate the SDs according to a validated imputation method which is based on the SDs of the other included studies (Furukawa 2006). Although some of these imputation strategies can introduce error, the alternative would be to exclude a given study's outcome and thus to lose information. Nevertheless, we will examine the validity of the imputations in a sensitivity analysis that excludes studies with imputed values.

3. Dealing with missing study-level characteristics

If study-level characteristics (e.g. factors for subgroup analysis) are not reported, we will try to obtain this information from the primary authors. If, finally, we cannot obtain the information, we will record this in the data extraction template.

Assessment of heterogeneity

1. Clinical heterogeneity

We will consider all included studies initially, without seeing comparison data, to judge clinical heterogeneity. We will simply inspect all studies for participants who are clearly outliers or situations that we had not predicted would arise and, where found, discuss such situations or participant groups.

2. Methodological heterogeneity

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

3. Statistical heterogeneity

3.1 Visual inspection

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

3.2 Employing the I^2 statistic

We will investigate heterogeneity between studies by considering the I^2 statistic alongside the Chi^2 P value. The I^2 statistic describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) (Deeks 2021; Higgins 2003). The importance of the observed value of I^2

depends on the magnitude and direction of effects as well as the strength of evidence for heterogeneity (e.g. P value from Chi^2 test, or a CI for I^2). We will interpret an I^2 estimate ≥ 50% and accompanied by a statistically significant Chi^2 statistic as evidence of substantial heterogeneity (Deeks 2021). When substantial levels of heterogeneity are found in the primary outcome, we will explore reasons for heterogeneity (Subgroup analysis and investigation of heterogeneity).

3.3 Employing the 95% prediction interval

The 95% prediction interval (PI) will be our main source of information to judge statistical heterogeneity. The 95% PIs are useful for expressing the amount of between-study variation in a meta-analysis, as they specify the predicted range of possible true intervention effects in an absolute scale (Borenstein 2019; Deeks 2021). This information is not provided by the I^2 statistic (Borenstein 2017).

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997; Higgins 2021f).

1. Protocol versus full study

We will try to locate protocols of included randomised trials. If the protocol is available, we will compare outcomes in the protocol and in the published report. If the protocol is not available, we will compare outcomes listed in the methods section of the trial report with actually reported results. If details from ClinicalTrials.gov and the WHO registry (ICTRP) are available, they will be included in the search results, so we can use these to compare the differences between planned methods and published results.

2. Funnel plot

We are aware that funnel plots may be useful in investigating reporting biases, but they have limited power to detect small-study effects. We will not use funnel plots for outcomes where there are ≤ 10 studies, or where all studies are of similar size. In other cases, where funnel plots are possible, we will seek statistical advice in their interpretation.

Data synthesis

We plan to perform a meta-analysis only if participants, interventions, comparisons and outcomes are sufficiently similar to ensure a clinically meaningful answer (Higgins 2021a). Based on our understanding of the sampling frame of the studies from the literature, we choose to use the random-effects model for meta-analysis. This model assumes that the studies in the analysis are representative of different, yet comparable, intervention effects, and that the results of the meta-analysis will be generalised to those effects (Borenstein 2019). Thus, the random-effects model allows for taking into account differences between studies, even if there is no statistically significant heterogeneity, and discussing not only the mean effect size, but also the dispersion in effect size across studies (Borenstein 2019).

For each meta-analysis we will calculate the central estimate, i.e. the RR, MD or SMD; the 95% CI and the 95% PI. We will use RevMan Web 2021 to perform the analyses, and Comprehensive Meta-Analysis to calculate the PIs (CMA Prediction Intervals 2021).

We will conduct syntheses of the following comparisons, targeting parents of people with SMI.

- Psychoeducation compared with inactive interventions (no intervention, placebo, sham intervention, usual or standard care)
- Psychoeducation compared with any pharmacological active intervention
- Psychoeducation compared with other non-pharmacological active intervention

Subgroup analysis and investigation of heterogeneity

We will try to explain heterogeneity in the results by checking data entry or by performing predefined subgroup analyses.

1. Subgroup analyses

We will undertake subgroup analyses only for primary outcomes to minimise the risk of multiple comparisons. We will perform subgroup analysis independently of the statistical heterogeneity detected. We will attempt to determine if there are similar benefits/effects from the interventions according to the following factors.

1. Number of episodes per individual with SMI: individuals with a first episode of psychosis versus individuals with more than one episode
2. Duration of the SMI: service users with an SMI of long duration (mean or median ≥ 10 years) versus short duration (< 10 years)
3. Duration of the psychoeducational intervention: interventions with brief duration (≤ 10 sessions or where the number of sessions is not stated, but the intervention is delivered within 10 weeks or less) versus interventions with longer duration (> 10 sessions or where the number of sessions is not stated, but the intervention is delivered in > 10 weeks).
4. Intervention format: individual (i.e. one information provider seeing one parent) versus group format (two parents involved in the sessions.

2. Management of inconsistency (unexplained relevant heterogeneity)

If we detect relevant statistical heterogeneity, but it cannot be explained (by incorrect data entry or by subgroup analyses), we will still pool the data. However, we will downgrade the overall certainty of evidence due to inconsistency.

Sensitivity analysis

Where possible, we will perform sensitivity analyses for the primary outcomes. If there are substantial differences in the direction or precision of effect estimates in any sensitivity analysis, we will maintain the main analyses without excluding any study and discuss these findings in the discussion. The only exception for this approach will be sensitivity analyses of skewed data (see below).

1. Implication of randomisation: we will exclude trials that are described as double-blind, but where randomisation is not explicitly mentioned.
2. Assumptions for missing data: we will repeat the analyses in a 'plausible worst-case' scenario. If the results of the primary meta-analysis are robust to these assumptions, we will not downgrade certainty in the evidence for risk of bias due to MPD (Guyatt 2017). For binary outcomes measuring benefits, such

as a clinically important change in psychosocial well-being, we will assume in the control group a relative incidence (RI) of 1 between those participants with missing data (MPD) and those who were followed up (FU) ($RI_{MPD/FU}$ = 1): the event incidence among those with MPD (I_{MPD}) is equal to the event incidence among those without MPD (I_{FU}). Concerning the experimental arm, we will assume $RI_{MPD/FU}$ = 0.75, that is, I_{MPD} is 0.75 times I_{FU}. For binary outcomes measuring harms, such as adverse events, we will assume $RI_{MPD/FU}$ = 1 in the control group, and $RI_{MPD/FU}$ = 1.50 in the experimental arm. We may change these thresholds if we find convincing justification. For continuous outcomes, we will impute mean values from other included studies and the SD from the median SDs of the control arms (Guyatt 2017). For included studies with different measurement instruments for the same construct, we will convert all scores to SMD or to the units of a selected reference instrument (Guyatt 2017).

3. Missing outcome data: we will exclude studies at a high risk of bias due to missing outcome data.
4. Risk of bias: we will exclude trials that are at an overall high risk of bias (see Assessment of risk of bias in included studies).
5. Imputed values: we will exclude trials where we use imputed values for ICC in calculating the design effect in cluster-randomised trials, or where SDs were imputed.
6. Skewed data: we will perform a sensitivity analysis excluding studies with less than 200 participants for which there is a suggestion of skewness (mean/SD ratio < 2 - see Data extraction and management). If this changes the results in comparison with the main analysis (from significantly favouring the intervention to significantly favouring the control, or vice-versa), we will also exclude these studies from the main analysis and present their data using the 'Other data' format in the data and analyses tables.

Summary of findings and assessment of the certainty of the evidence

We will use the GRADE approach to interpret findings (Schünemann 2021); and will use GRADEpro GDT (GRADEpro GDT) to export data from our review (from RevMan Web 2021) to create summary of findings tables. These tables provide outcome-specific information concerning the overall certainty of evidence from each included study in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on all outcomes we rate as important to patient care and decision-making. We will feed the overall RoB 2 judgements into the GRADE assessment. We aim to select the following main outcomes for inclusion in the summary of findings tables.

- Clinically important change in psychosocial well-being in the short term (≤ 3 months)
- Average endpoint score on a psychosocial well-being scale in the short term (≤ 3 months)
- Clinically important change in quality of life in the short term (≤ 3 months)
- Average endpoint score on a quality of life scale in the short term (≤ 3 months)
- Clinically important change in psychosocial well-being in the medium term (> 3 months and ≤ 6 months)
- Clinically important change in quality of life in the medium term (> 3 months and ≤ 6 months)
- At least one adverse event in the short term (≤ 3 months)

If data are not available for these prespecified outcomes, but are available for ones that are similar, we will present the closest outcome to the prespecified one in the table, but take this into account when grading the finding.

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The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Irene Bighelli, Technical University of Munich
- Managing Editor (provided editorial guidance to authors, edited the article, conducted editorial policy checks): Hui Wu, Technical University of Munich
- Contact Editor: Javier Ortiz-Orendain, Mayo Clinic
- Copy Editor (copy-editing and production): Clare Dooley, Cochrane, Andrea Takeda
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APPENDICES

Appendix 1. Search strategy

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to April 12, 2022>

Search Strategy:

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1 Bipolar Disorder/ (43493)

2 Cyclothymic Disorder/ (765)

3 exp Schizophrenia/ (111646)

4 Mental Disorders/ (172825)

5 Mania/ (255)

6 ((bipolar adj3 (affective or depress* or disorder* or episode* or mood or psychosis or spectrum or state or states)) or cyclothymi* or schizophreni* or severe mental illness*).ti,ab,id,kf,kw. (170086)

7 (affective psycho* or mania or manic or hypermani* or hypomani* or rapid cycling).ti,ab,id,kf,kw. (23397)

8 or/1-7 (362029)

9 Depressive Psychosis.mp. (807)

10 Depression/ (139546)

11 Depressive Disorder/ (74642)

12 Adjustment Disorders/ (4285)

13 Depressive Disorder, Major/ (35189)

14 Anxiety Disorders/ (38434)

15 (depress* or (affective adj2 disorder*)).ti,ab,id,kf,kw. (531751)

16 or/10-15 (591767)

17 Psychotic Disorders/ (50057)

18 Affective Disorders, Psychotic/ (2308)

19 Delusions/ (7983)

20 (delusion* or psychotic or psychosis or psychoses).ti,ab,kf,kw. (84617)

21 or/17-20 (103291)

22 and/16,21 (24664)

23 or/8-9,22 (370741)

24 (psychoeducat* or psycho-educat*).mp. (7793)

25 educat*.ti. (173219)

26 ((health or psyc* or mental) adj3 (educat* or train* or knowledge or literacy or literate)).mp. (288673)

27 or/24-26 (426216)

28 and/23,27 (10102)

29 (parent* or mother* or father* or guardian? or significant other? or carer? or family or families).mp. (1872723)

30 and/28-29 (2752)

31 (RCT or "at random" or (random* adj3 (administ* or allocat* or assign* or class* or cluster or crossover or cross-over or control* or determine* or divide* or division or distribut* or expose* or fashion or number* or place* or pragmatic or quasi or recruit* or split or subsitut* or treat*))).ti,ab,id,kf,kw. (655613)

32 (randomi#ed or randomi#ation or randomi#ing).ti,ab,id,kf,hw. (1006627)

33 randomised controlled trial.pt,sh. (564457)

34 controlled clinical trial.pt,sh. (94812)

35 (control* and (trial or study or group?) and (waitlist* or wait* list* or ((treatment or care) adj2 usual))).ti,ab,id,kf,kw. (26399)

36 ((single or double or triple or treble) adj2 (blind* or mask* or dummy)).ti,ab,id,kf,kw. (188823)

37 placebo.sh,ti. or (placebo adj3 (control or group?)).ti,ab,id,kf,kw. (87508)

38 or/31-37 (1271349)

39 and/30,38 (457)

Appendix 2. Glossary

As-treated analysis (ATA)	Approach to per-protocol (PP) analysis that analyses the participants according to the intervention that they actually received, rather than according to their randomised intervention (Akl 2013; Higgins 2021b).
Available case analysis (ACA)	Available case analysis (ACA) is an intention-to-treat (ITT) analysis that excludes participants with missing outcome data. Thus, ACA includes data on only those whose results are known, using as a denominator the total number of people who had data recorded for the particular outcome in question (Higgins 2011). ACA may be biased, depending on the missing data mechanism and the amount of missing participant data. ACA is also called 'complete case analysis (CCA)' or 'modified intention-to-treat (mITT)' analysis; the phrase 'mITT' is used in different ways (Abraha 2010). It may refer to an analysis that excludes participants who did not receive a specified minimum amount of the intended intervention. Our use of the term refers to missing data rather than to adherence to the intervention.
Intention-to-treat (ITT) analysis	Analysis strategy that meets all the following principles (Fergusson 2002; Higgins 2021b; Meinert 2012; Piantadosi 2005). 1. To include all randomised participants in the analysis (and thus to measure outcome data on all participants). 2. To analyse the participants in the arm to which they were randomised, regardless of the intervention they actually received, whether the interventions were implemented as intended, and the adherence to the intervention. The advantage of ITT analysis is that it allows for determining the effect of the assignment to the intervention. This ensures that the benefits of randomisation – that the two intervention groups should be similar with respect to measured and unmeasured prognostic factors – are maintained (Higgins 2021b).
Naive per-protocol analysis	Approach to PP analysis that restricts the analysis to participants who adhered to their assigned intervention (Higgins 2021b).
Per-protocol (PP) analysis	Analysis that excludes participants who did not receive the intended intervention in accordance with the protocol (Higgins 2021b).

CONTRIBUTIONS OF AUTHORS

All authors prepared the protocol.

- Guarantor of the review: DC
- Conceiving the review: DC
- Designing the review: DC, JLA
- Co-ordinating the review: DC, JLA
- Designing search strategies: NA, JLA, DC
- Providing a methodological perspective: JLA, AM
- Providing a clinical perspective: DC, FJCM, MGS, ACM, PMH, AAE, DMM, PMH
- Providing a policy perspective: all
- Providing a consumer perspective: none
- Writing the protocol: DC, JLA; supported by all
- Editing the protocol: DC, JLA
- Providing general advice on the review: all

DECLARATIONS OF INTEREST

- DC: none known
- JLA: none known
- FJCM: none known
- MGS: none known
- PMH: none known
- AM: none known
- AAE: none known
- NAD: none known
- DMM: none known
- ACM: none known

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