Placebo, usual care and wait-list interventions for all mental health disorders (Protocol)

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**ABSTRACT**

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

Our objectives are to assess the beneficial effects and adverse events of placebos, usual care, and wait-list interventions for all mental health disorders.

There are three research questions: What are the beneficial effects and adverse events of:

1. pharmacological, psychological, and physical placebos versus no-treatment or wait-list interventions;
2. usual care versus no-treatment or wait-list interventions; and
3. wait-list versus no-treatment interventions.

**BACKGROUND**

**Description of the methods being investigated**

Control interventions in randomised clinical trials provide a frame of reference for the experimental interventions that they are compared to and enable estimations of benefits and harms (Higgins 2011; Kazdin 2016; Sibbald 1998). This systematic review will assess the beneficial effects and adverse events of different control interventions in randomised trials that included patients with a mental health disorder. We will include the following as the experimental interventions (usually described as control interventions in the literature - see Table 1): (a) pharmacological placebo, (b)
psychological placebo, (c) physical placebo, (d) usual care, and (e) wait-list. We will include the following comparator interventions: (a) no-treatment and (b) wait-list. When wait-list is the experimental intervention, we will compare it to no-treatment only. We will conduct analyses across all included patient populations and within populations with specific mental health disorders. We are seeking to answer three research questions: what are the beneficial effects and adverse events of (i) different placebo interventions versus no-treatment or wait-list; (ii) usual care versus no-treatment or wait-list; and (iii) wait-list versus no-treatment?

**Pharmacological placebos** are inert substances, usually in pill or liquid form, which do not contain the active ingredients of a given drug treatment. Hróbjartsson and Gøtzsche previously found no clinically important effects of pharmacological, psychological, and physical placebos versus no-treatment and wait-list interventions for various medical conditions (Hróbjartsson 2001; Hróbjartsson 2002; Hróbjartsson 2004; Hróbjartsson 2010). Some criticised their findings for not being well suited to detect placebo effects (Wampold 2010; Wampold 2016), and the placebo phenomenon is difficult to operationalise, despite emerging evidence on its neurobiological and behavioural underpinnings (Enck 2013; Haresnape 2013; Kaptchuk 2015; Meissner 2011a). The optimal design for determining the clinical utility of placebo interventions is arguably randomised trials assessing the effects of placebos versus no-treatment and wait-list (Hróbjartsson 2011; Kaptchuk 2015). This is in part because no-treatment and wait-list comparators control for spontaneous improvement, regression to the mean, and observer-expectancy effects (Kienle 1997).

**Psychological placebos** target the non-specific and shared components of psychological treatments (sometimes labelled ‘common factors’), such as attending sessions, patient expectations, and the therapeutic relationship (Hróbjartsson 2012; Wampold 2010; Wampold 2016). It is methodologically and theoretically difficult to discriminate between psychological placebos and psychological treatments (Borkovec 2005; Hróbjartsson 2012; Mohr 2014), and some have recommended abandoning the term altogether (O’Leary 1978; Wampold 2010; Wampold 2016). However, psychological placebos may be beneficial for differentiating between specific and non-specific factors in active psychological treatments (Mohr 2009). They arguably lead to better participant blinding compared to other control interventions, such as usual care. **Physical placebo** target the inert components of a given physical treatment (such as acupuncture, exercise regimens, or surgery). In a meta-regression model, Hróbjartsson and Gøtzsche found that physical placebos were associated with larger effects than psychological and pharmacological placebos when compared with no-treatment and wait-list interventions (Hróbjartsson 2010). A study on migraine prophylaxis also found that sham acupuncture and sham surgery were associated with higher rates of treatment responders than oral pharmacological placebos (Meissner 2013). The beneficial effects and adverse events of physical placebos for mental health disorders remain unclear.

Usual care reflects locally accepted treatment practices for a given mental health disorder. The intervention is provided either by relevant practitioners and may involve both pharmacological and psychological treatment for people with mental health disorders. Usual care providers are often entrusted to determine patient care independent of the research team (Freedland 2011). The intervention may consequently be subject to large clinical and methodological heterogeneity, little supervision, a mixture of different theoretical approaches, and unclear contents (Comer 2013; Kazdin 2015; Löfholm 2013). However, usual care is arguably a better reflection of routine practice settings than highly controlled psychiatric interventions (Kazdin 2015; Mohr 2014). It may also help to indicate whether psychiatric treatment is favourable over current practice (Mohr 2009). A network meta-analysis found small to medium effects on depressive symptoms in usual care and psychological placebos compared to wait-list, although the quality of evidence was low (Barth 2013). Usual care is sometimes standardised (Bateman 2009; Chanen 2008), which may involve optimising treatment structure, manualisation, the treatment rationale, and model of pathology (Bateman 2017; Cristea 2017; Kongerslev 2015).

Wait-list participants are assessed before and after a given time period, and they only receive treatment after the final assessment. **No-treatment** participants are assessed on repeated occasions, but they are not promised treatment after trial completion (Comer 2013). Some have hypothesised that wait-list participants are more motivated to remain in poor health to receive a desired therapy after trial completion, and that those receiving no-treatment might actively seek out other forms of care during the trial period (Furukawa 2014). Participants in wait-list interventions may therefore be subject to ‘nocebo’ effects (i.e. negative effects from inert interventions) and have worse outcomes relative to no-treatment (Furukawa 2014), but the evidence on this is preliminary (Greville-Harris 2015). Careful monitoring of participants in no-treatment and wait-list interventions is important to ensure toleration of treatment delays and ethical compliance (Comer 2013; Mohr 2009). Hróbjartsson and Gøtzsche found no significant differences between placebos and no-treatment on non-serious adverse events, but the assessment of adverse events was not highly comprehensive (Hróbjartsson 2010). The effects of no-treatment and wait-lists may vary, depending, for example, on sample characteristics (Hesser 2011).

**Why it is important to do this review**

The need to improve mental health treatment is great (Holmes 2018). There is a lack of agreement on the construction of control interventions in psychiatric research and we need empirically informed guidelines to optimise the design of future randomised clinical trials and improve evidence-based practice (Erlen 2015; Freedland 2011; Gold 2018; Kube 2017; Lund 2014; Mohr 2009). By investigating the advantages and disadvantages between all ma-
major control interventions in the field of mental health, this review will provide an empirical basis for such guideline developments. We anticipate that we will include significantly more studies on placebo interventions for mental health disorders than previously reported by Hróbjartsson and Gøtzsche (Hróbjartsson 2001; Hróbjartsson 2004; Hróbjartsson 2010). This will allow for a more comprehensive review of how placebo effects may vary depending on factors such as type of mental health disorder, context of administration, information given to participants, and type of outcome measure (Charlesworth 2017; Fässler 2015; Holmes 2016; Hróbjartsson 2010; Jensen 2017; Rutherford 2014; Walach 2011; Yeung 2017). Placebo interventions are also common in clinical practice despite their unclear clinical utility (Fässler 2010; Howick 2013; Hróbjartsson 2010; Kapchuk 2010), and it is important for participants in randomised trials and practicing health professionals to be better informed on their beneficial effects and adverse events (Blease 2016; Blease 2017; Raieck 2012).

We also need more evidence on the treatment effects of usual care (Rosenberg 2014; Swanson 2014). Usual care arguably emulates care in routine practice better than standardised active psychiatric interventions in randomised clinical trials (Comer 2013; Kazdin 2015). A comprehensive assessment of its benefits and harms may be of significant clinical relevance, and provide novel considerations on the true effectiveness of psychiatric treatments. Moreover, no-treatment and wait-list interventions are common in psychiatric research (Mohr 2014), but, as noted above, they could induce unwanted adverse events in participants (Furukawa 2014). For instance, it is unclear whether participants allocated to waitlists perform worse and experience ‘nocebo’ effects relative to those allocated to no-treatment. By directly comparing wait-list and no-treatment interventions in randomised trials, this review will further explore this relationship. Also, if no-treatment and wait-list participants report significantly more adverse events than other control interventions, the ethical concerns and risks of overestimating the effects of psychiatric interventions in randomised trials should be brought to light (Cunningham 2013; Furukawa 2014).

**OBJECTIVES**

Our objectives are to assess the beneficial effects and adverse events of placebos, usual care, and wait-list interventions for all mental health disorders.

There are three research questions: What are the beneficial effects and adverse events of:

1. pharmacological, psychological, and physical placebos versus no-treatment or wait-list interventions;
2. usual care versus no-treatment or wait-list interventions; and
3. wait-list versus no-treatment interventions?

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

Randomised clinical trials comparing placebo, usual care, or wait-list interventions with either no-treatment or wait-list interventions, will be considered for inclusion. Parallel trials irrespective of language, publication year, and publication type will be eligible. We will only include the first phase of cross-over trials. We will include cluster-randomised trials. In case of non-English language articles, we will seek translation of the relevant sections. Unpublished studies where methods and results can be assessed in written form will be considered eligible.

**Types of data**

All patients in each included trial will be required to have a formal diagnosis of a mental health disorder, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM), First Edition (DSM-I; APA 1952), Second Edition (DSM-II; APA 1968), Third Edition (DSM-III; APA 1980), Third Edition Revised (DSM-III-R; APA 1987), Fourth Edition (DSM-IV; APA 1994), Fourth Edition Text Revision (DSM-IV-TR; APA 2000), and Fifth Edition (DSM-5; APA 2013), or according to the International Classification of Diseases and Related Health Problems (ICD), Sixth Edition (ICD-6; WHO 1949), Seventh Edition (ICD-7; WHO 1955), Eighth Edition (ICD-8; WHO 1967), Ninth Edition (ICD-9; WHO 1975), 10th Edition (ICD-10; WHO 1993), or 11th Edition (ICD-11; WHO 2018). If we retrieve trials published before the introduction of these criteria in 1949, participants will be eligible if they received a formal diagnostic assessment of a mental health disorder by a licensed health professional. We will categorise the different mental health disorders according to the current nomenclature in the DSM-5 (APA 2013). If all participants in a trial have a mental health disorder, but not the same one, we will include it in all the analyses except those on specific mental health disorders (see Types of outcome measures). We will include participants with or without comorbid conditions. Eligible participants will be included irrespective of location, setting, and other demographic variables (including age).

**Types of methods**

**Experimental interventions**
We will define placebo, usual care, and wait-list interventions as any interventions that are clearly labelled or reflect the properties of a placebo, usual care, or wait-list interventions, according to the criteria below (and in Table 1). We anticipate that most of the included interventions will be control interventions in three-group randomised clinical trials, although some might be active interventions. The properties of the interventions deemed experimental for this methodology review are defined as the following (based on the work by Hróbjartsson 2010; Comer 2013; Kazdin 2016).

1. Pharmacological placebo: an intervention that includes an inert substance, typically in the form of a pill or liquid, which does not contain the active ingredients of a given drug.
2. Psychological placebo: an intervention that targets the non-specific or shared components of psychological treatments, such as treatment exposure and human interaction variables, attending sessions, and patient expectations.
3. Physical placebo: an intervention that targets the inert components of a given physical treatment (such as acupuncture, needle injection, exercise regimens, surgery, or electromagnetic stimulation).
4. Usual care: an intervention that reflects locally accepted treatment practices for a given mental health disorder. It is provided either by private or public practitioners and may involve both pharmacological and psychological treatment.
5. Wait-list: an intervention where participants are assessed on repeated occasions, but are promised the “active” intervention after the trial has ended.

Comparator interventions

We will include two comparators: no-treatment and wait-list (see Table 1). When wait-list is the experimental intervention, we will only compare it with no-treatment interventions. We will define these comparator interventions as any interventions that are clearly labelled or reflect the properties of no-treatment and wait-list interventions. The properties of no-treatment interventions are defined as the following (based on the work by Comer 2013):

1. No-treatment: an intervention where participants are assessed on repeated occasions without receiving the active treatment intervention. Unlike wait-list interventions, no-treatment participants are not promised treatment after trial completion.

Description of main comparisons

We will conduct the comparisons on placebo and usual care interventions in the following order.

1. We will first pool no-treatment and wait-list interventions when compared to placebo and usual care interventions.
2. We will then conduct subgroup analyses (see Subgroup analysis and investigation of heterogeneity) between no-treatment and wait-list interventions for all the pooled comparisons from the previous step. If there are significant differences or substantial heterogeneity between the no-treatment and wait-list interventions for a given comparison, we will conduct separate main analyses for these two comparison interventions. However, we will express low confidence in these analyses if they have insufficient statistical power.

Types of outcome measures

Primary outcomes

1. Beneficial effects of placebo, usual care, and wait-list interventions versus no-treatment or wait-list interventions for all mental health disorders.
2. Serious adverse events in placebo, usual care, and wait-list interventions versus no-treatment or wait-list interventions for all mental health disorders and for specific mental health disorders.

Secondary outcomes

1. Beneficial effects of placebo, usual care, and wait-list interventions versus no-treatment or wait-list interventions for specific mental health disorders.
2. Non-serious adverse events in placebo, usual care, and wait-list interventions versus no-treatment or wait-list interventions for all mental health disorders and for specific mental health disorders.

Description of outcome measures

For the first primary outcome only, we will pool pharmacological, psychological, and physical placebos into one placebo estimate. We will also report comparisons of these three placebo interventions for this outcome, and for all other outcomes. We will conduct analyses across all included mental health disorders and within specific mental health disorders. We will group the specific disorders according to the classification in the DSM-5 (APA 2013). We will only calculate the beneficial effects and adverse events on specific mental health disorders when they have been studied in at least three trials that can be combined in a meta-analysis. This is a pragmatic threshold inspired by Hróbjartsson and Götzsche (Hróbjartsson 2010) to reduce spurious positive and negative findings in single trials.

For the outcomes measuring beneficial effects, we will select one outcome from each trial report. We will conduct separate analyses on dichotomous and continuous data (see Measures of the effect of the methods). We will use the following decision hierarchy to select the outcomes measuring effect.

1. We will primarily choose the outcome indicated as the primary outcome in a trial report, for instance the one used for...
the sample size calculation. We will prefer post-treatment data (data from the end of the intervention) over follow-up data.

2. If it is unclear what the primary outcome is in the research report or following author correspondence, we will prefer continuous to dichotomous outcomes.

3. If there are multiple continuous outcomes, we will prefer observer-reported over patient-reported outcomes, and blinded to non-blinded observer-reported outcomes.

Serious adverse events will be defined as any event that leads to death (e.g. suicide), is life-threatening (e.g. suicidality), requires in-patient hospitalisation (e.g. self-harm), prolonged hospitalisation, results in persistent or significant disability, or as any other important event that jeopardises the patient’s life or requires intervention for prevention (ICH 2005). All other adverse events, will be considered non-serious adverse events (ICH 2005). We will conduct separate analyses for specific serious adverse events (e.g. suicide and self-harm). We will combine all non-serious adverse events into a single estimate.

We will extract adverse events from studies as measured by standardised psychometric rating scales, such as the Systematic Assessment for Treatment Emergent Events (SAFTEE) (Levine 1986), laboratory values, or spontaneous reporting. We will also locate adverse events as described in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (ICH 2005). Adverse events in randomised trials generally (Allen 2018) and on psychiatric treatments in particular, can be difficult to detect, and valid instruments to detect them are lacking (Lilienfeld 2007; Linden 2014; Pagsberg 2017; Storebo 2018). However, strategic searches for adverse events using standardised questionnaires seem be becoming more common (Pagsberg 2017; Storebo 2018). Our strategy to locate adverse events in the included studies will therefore be flexible and sensitive. We will correspond with study authors if they do not report data on adverse events.

**Search methods for identification of studies**

**Electronic searches**

We will search the electronic databases and trial registries listed below (Bramer 2017), using the search strategies shown in Appendix 1. The strategy for MEDLINE was used as a template for the other databases and trial registries, with modified syntax and controlled terms as necessary.

**Bibliographic databases**

1. MEDLINE Ovid (1946 to current) (see Appendix 1 for search strategy)
2. PsycINFO Ovid (1806 to current)
3. Embase Ovid (1974 to current)
4. Cochrane Central Register of Controlled Trials (CENTRAL; current issue), in the Cochrane Library.
5. Allied and Complementary Medicine Database (AMED; 1900 to current)
6. Web of Science Core Collection (1900 to current)
7. ProQuest Dissertations and Theses A&I (1743 to current)
8. Sociological Abstracts ProQuest (1952 to current)
9. Google Scholar (https://scholar.google.no/)
10. BIOSIS Previews/Thomson Reuters (1969 to current)
11. Open Grey (1997 to current)

**Clinical trial registries**

2. Clinical Trials (clinicaltrials.gov).
3. EU Clinical Trials Register (www.clinicaltrialregister.eu/ctr-search/search).
4. ISRCTN Registry (www.isrcrn.com).
5. UK Clinical Trials Gateway (www.ukctg.nihr.ac.uk/#popoverSearchDivId).
6. World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; http://www.who.int/trialsearch/)

**Searching other resources**

We will search for other resources at the end of the screening process. We will survey relevant journals such as ACTA Psychiatria Scandinavica, the American Journal of Psychiatry, Biological Psychiatry, the British Journal of Psychiatry, the BMJ, the International Journal of Clinical Psychopharmacology, JAMA Psychiatry, Journal of the American Academy of Child and Adolescent Psychiatry, Journal of Clinical Psychiatry, Journal of Clinical Psychopharmacology, Journal of Psychopharmacology, Lancet Psychiatry, Psychopharmacology, Psychotherapy Research and the Scandinavian Journal of Child and Adolescent Psychiatry and Psychology. We will also review abstracts of key psychiatric conferences given the large proportion of these that do not go on to full publication (Scherer 2018) and ask for relevant unpublished studies from experts in the field. We will trace cross-references from relevant literature.

**Data collection and analysis**

We will conduct this review according to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011), and perform analyses using the latest version of Revman (Review Manager 5). If new versions of the Cochrane Handbook for Systematic Reviews of Interventions are published, we will incorporate the guidance into the conduct of the review.
Selection of studies

Because we expect to retrieve large numbers of records from the electronic literature search, titles and abstracts will be screened only once (divided equally between EF and AT). For quality assurance, an additional author (OJS) will screen a random sample of the retrieved records to check whether there are differences in the included and excluded records between screeners. Two review authors (EF and AT) will independently screen the full-text reports for studies judged to be potentially eligible. They will discuss any disagreements, and an arbiter (OJS) will make the final decision if agreement cannot be reached. Full-text reports will be obtained and assessed for eligibility based on the inclusion criteria (see Criteria for considering studies for this review). Randomised trials in this general topic area that do not fulfil the inclusion criteria will be listed. We will use EPPI Reviewer 4, an online software application for systematic review development, for the screening of abstracts and full-text reports (Thomas 2010). We will include a PRISMA flow diagram to show the flow of included and excludes studies in the full review (Moher 2009).

Data extraction and management

Two review authors (EF and AT) will independently extract data from the included randomised trials. We will resolve disagreements by discussion or use an arbiter (OJS) if necessary. Two authors (EF and AT) will enter data into Review Manager 5. We will request missing information by contacting relevant authors (Young 2011). We will develop a data extraction form to facilitate standardisation of the data extraction process. The forms will include the following items: methods (e.g. study design, study setting, and country), types of participants (e.g. baseline demographics, inclusion and exclusion criteria), description of experimental and comparator interventions and their components (e.g. duration and intensity), outcome measures, and 'Risk of bias' assessment.

Assessment of risk of bias in included studies

All review authors will assess the risk of bias using Cochrane’s ‘Risk of bias’ tool (Higgins 2011). At the time of writing (December 2018), there is an updated version of this tool (Eldridge 2016; Higgins 2017), but, because it is still at the pilot stage, we expect to use the original version. However, we will consider using the updated version if it is finalised before the data extraction phase for this review. For each included trial, the data extractors will independently categorise the ‘Risk of bias’ domains listed below as being low, unclear (uncertain), or high risk of bias, according to the guidelines in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). Potential disagreements will be resolved by discussion, using an arbiter (OJS) if necessary. We will define trials at ‘low risk of bias’ as having low risk of bias on all domains. We will define trials with one or more unclear ‘Risk of bias’ domain as trials at ‘high risk of bias’. We will evaluate the influence of risk of bias on our results (see Sensitivity analysis), due to the risk of overestimating beneficial intervention effects and underestimating adverse events in randomised trials with unclear or inadequate methodological quality (Kjaergard 2001; Lundh 2017; Moher 1998; Savovic 2012; Schulz 1995; Wood 2008). The ‘Risk of bias’ components are the following (based on the work by Higgins 2011).

Random sequence generation

1. Low risk of bias: an adequate method for randomisation sequence generation was used (e.g. computer-generated random numbers or a table of random numbers), or the method was unlikely to introduce selection bias.
2. Unclear risk of bias: there was insufficient information to determine whether the applied randomisation method could introduce selection bias.
3. High risk of bias: the method applied was likely to introduce selection bias.

Allocation concealment

1. Low risk of bias: the method to conceal intervention allocations (e.g. central allocation) was unlikely to bias the results.
2. Unclear risk of bias: there was insufficient information to determine whether the applied method could bias allocation to interventions.
3. High risk of bias: the method applied (e.g. open random allocation schedule) could have biased the allocations to interventions.

Blinding of participants and personnel

1. Low risk of bias: the method of blinding was sufficiently described and blinding was conducted in a satisfactory way.
2. Unclear risk of bias: there was insufficient information to determine whether adequate blinding was used and whether it was likely to bias the effect estimates.
3. High risk of bias: no blinding procedures were used or the blinding procedures were incomplete.

Blinding of outcome assessment

1. Low risk of bias: the method of blinding was described and blinding was conducted in a satisfactory way.
2. Unclear risk of bias: there was insufficient information to determine whether the type of blinding was likely to bias the effect estimates.
3. High risk of bias: no blinding used or incomplete blinding was used.
Incomplete outcome data

1. Low risk of bias: missing data did probably not affect the outcome measures, as all missing data can be considered as missing at random or all data were reported.
2. Unclear risk of bias: there was insufficient information to determine whether missing data, or the method used to handle missing data was likely to bias the effect estimates.
3. High risk of bias: the crude estimate of effects could have been biased given the attrition rates, the reasons for the missing data, or the insufficient methods used to handle missing data.

Selective outcome reporting

1. Low risk of bias: the trial protocol was available and all pre-specified outcomes of interest were reported.
2. Unclear risk of bias: there was insufficient information to determine whether selective outcome reporting could have occurred.
3. High risk of bias: not all of the primary outcomes specified beforehand were reported or participants were excluded after randomisation.

Other sources of bias

1. Low risk of bias: the trial appeared to be free of other sources of bias.
2. Unclear risk of bias: there was insufficient information to determine the extent of other possible sources of bias.
3. High risk of bias: other sources of bias were identified.

Measures of the effect of the methods

Dichotomous data

We will summarise dichotomous data as risk ratios (RR) with 95% confidence intervals (CIs) and Trial Sequential Analysis (TSA)-adjusted CIs (see Subgroup analysis and investigation of heterogeneity).

Continuous data

For continuous data, we will estimate standardised mean differences (SMD). We will use SMD because we anticipate variation in the types of outcome measures. We will calculate SMDs using scores from the end of intervention. When the trials only report change data we will pool these with scores from the end of intervention (da Costa 2013). We will explore whether inclusion of change data will affect the outcomes by performing a sensitivity analysis (see Sensitivity analysis). If the direction of a given scale is opposite to that of most other scales, we will multiply the corresponding mean values by -1.00 to ensure adjusted values. If the trials do not report means and standard deviations but report other values such as t-tests and P values, we will attempt to transform these into standard deviations.

We will use data from means and standard deviations in intention-to-treat (ITT) analyses, as well as replaced missing values, if available. We will otherwise conduct the analyses based on the available data. We will perform all calculations using the latest version of the RevMan software (Review Manager 5).

We will summarise the outcomes measuring adverse events from count data (e.g. spontaneous reporting) as rate ratios with Trial Sequential Analysis (TSA)-adjusted CIs (see Subgroup analysis and investigation of heterogeneity).

Unit of analysis issues

We will exclude all phases of cross-over trials other than the first. We will calculate study estimates on the basis of post-treatment group results. If trials are cluster-randomised, we anticipate appropriate controlling for cluster effects (robust standard errors or hierarchical linear models). If the necessary information is unclear or not available in the trial’s report, we will contact the original authors for further information. If appropriate adjustment strategies are missing, individual participant data will be requested and re-analysed using multilevel models that control for clustering. We will then analyse effect sizes and standard errors in Review Manager 5 and use the generic inverse method (Higgins 2011). The outcome data will then be entered into Review Manager 5, using individuals as the unit of analysis, if there is insufficient information to control for clustering. We will use sensitivity analyses to assess the potential biases of inadequately controlled cluster-randomised trials (Donner 2002) (see Sensitivity analysis).

Dealing with missing data

We will contact study authors for relevant missing data on our primary and secondary outcomes. If the authors do not respond after two attempts to contact them, we will stop communications. If we are not able to obtain missing data, we will use the available data (incomplete data) in the analyses. If data are not reported in a usable way, we will consult a statistician to explore its transformation.

Assessment of heterogeneity

We will evaluate whether heterogeneity is more probably due to clinical (i.e. explainable factors) or unknown factors, by taking into account the number of studies and study characteristics, such as duration, dose, and participants. If there is evidence of substantial heterogeneity, we will discuss the most apparent sources of heterogeneity, and create subgroups based on study characteristics such as study duration, dose, or participants. We will evaluate methodological heterogeneity by comparing trial designs. Assessment of heterogeneity will be carried out for certain com-
 Assessments of reporting biases

Funnel plots will be provided for comparisons with sufficient included studies. Egger's statistical test will be performed for small-study effects (Egger 1997). A visual inspection of funnel plots and Egger's statistical test will not be applied if there are fewer than 10 studies in the meta-analysis, in keeping with the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).

Data synthesis

We will perform statistical analyses according to the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We will apply the inverse variance method to give estimates from studies with less variance (mostly larger studies) more weight. We will use the random-effects model for meta-analysis, because some clinical heterogeneity is expected to be present in most cases. We will use a fixed-effect model as a sensitivity analysis (see Sensitivity analysis). For trials with a high level of statistical heterogeneity, and where the amount of clinical heterogeneity makes it inappropriate to use these trials in meta-analyses, we will provide a narrative description of the trial results. If pooling of data seems feasible, we will pool the included studies' effects and calculate the associated 95% CIs.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses

1. Type of active intervention: i) pharmacological intervention, ii) psychological intervention, iii) physical intervention, or iv) other intervention.
2. Overall risk of bias: i) high risk of bias or ii) low risk of bias.
3. Type of outcome domain: i) blinded observer-reported, ii) non-blinded observer-reported, or iii) patient-reported.
4. Type of comparator intervention: i) wait-list or ii) no-treatment.
5. Awareness of placebo intervention: i) participants were aware that they might receive a placebo, or ii) participants were not aware of such.

6. The trial objective: i) a trial's objective is clearly to assess the effects of placebo, usual care, or wait-list interventions, or ii) no such objectives are stated.
7. Mean age of participants: i) < 18 years, ii) 18 to 50 years, or iii) > 50 years.
8. Duration of intervention: i) three months or above or ii) below three months.
9. Type of usual care: i) pharmacological, ii) psychological, iii) physical, or iv) other.
10. Standardised usual care: i) the usual care intervention was intentionally standardised or manualised, or ii) no standardisation or manualisation.

Meta-regression analyses

Based on the findings from the subgroup analyses, we will consider conducting supplementary meta-regression analyses on continuous outcomes. We will then choose covariates based on relevant subgroup analyses, such as type of intervention, risk of bias, type of outcome domain, mean participant age and duration of interventions.

Diversity-adjusted required information size and Trial Sequential Analysis

Trial Sequential Analysis (TSA) is a methodology that combines a required information size (RIS) calculation for meta-analyses with a threshold for statistical significance (Brok 2009; Thorlund 2009; Wetterlesv 2008; Wetterlesv 2009; Wetterlesv 2017). The TSA enables quantification of the statistical reliability of the data in cumulative meta-analysis, and adjusted P values for sparse data and for repetitive testing on accumulating data (Brok 2008; Brok 2009; Thorlund 2009; Wetterlesv 2008; Wetterlesv 2017). Similar to an a priori sample size estimation in a single randomised trial, a meta-analysis should include a RIS at least as large as the sample size of an adequately powered single trial to reduce the risk of random error. The TSA can calculate the RIS in a meta-analysis and provide an alpha-spending boundary to adjust the significance level for sparse data and repetitive testing (Copenhagen Trial Unit 2018; Wetterlesv 2008; Wetterlesv 2017). This enables one to control for the risk of random error.

Multiple analyses of accumulating data when new trials emerge lead to repeated significance testing and introduces multiplicity issues. Therefore, the use of a conventional naïve P value exacerbates the risk of random errors (Berkey 1996; Thorlund 2011; Wetterlesv 2017). By analysing meta-analyses that do not reach the RIS with trial sequential alpha-spending monitoring boundaries (analogous to interim monitoring boundaries in a single trial), this can be controlled for (Wetterlesv 2008; Wetterlesv 2017).
We will calculate a RIS on the relevant outcomes in this review. If a TSA does not find significant results (no crossing of the alpha-spending boundary and no crossing of the conventional boundary of $P = 0.05$) before the RIS has been reached, several conclusions may be inferred. We will either conclude that more trials are needed to reject or accept an intervention effect used for the calculation of the required sample size, or reject the anticipated effect, if the cumulative Z-curve enters the futility area.

We will calculate the a priori diversity-adjusted required information size (APHRIS), or the number of patients required to detect or reject a specific intervention effect in the meta-analysis. We will also perform a TSA for all the outcomes based on the following a priori assumptions:

- the standard deviation of the primary outcome is 1.0;
- an anticipated intervention effect equal to Hedge's $g$ of 0.5;
- a maximum type I error of 5% ($\alpha$), adjusted according to number of outcomes (Jakobsen 2014);
- a maximum type II error of 10% ($\beta$; equal to a minimum 90% power); and
- a priori anticipated 50% diversity (Brok 2008; Brok 2009; Thorlund 2009; Wetterslev 2008; Wetterslev 2009; Wetterslev 2017).

We will also calculate a post-hoc low bias risk diversity-adjusted required information size (LBHRIS), or the number of patients required to detect or reject a specific intervention effect in the meta-analysis. Lastly, we will perform TSA for the primary outcomes based on the following estimated assumptions:

- the standard deviation of the primary outcome for patients in placebo, usual care, and wait-list interventions in trials at low risk of bias;
- the estimated intervention effect in trials with low risk of bias;
- a maximum type I error of 5% ($\alpha$), adjusted according to number of outcomes (Jakobsen 2014);
- a maximum type II error of 10% ($\beta$; equal to a minimum 90% power); and
- the estimated diversity in the trials included in the meta-analysis (Brok 2008; Brok 2009; Thorlund 2009; Wetterslev 2008; Wetterslev 2009; Wetterslev 2017).

'Summary of findings' tables
The GRADE approach will be used to construct a 'Summary of findings' table to document all review outcomes. GRADE evaluates the quality of a body of evidence based on the confidence that an effect estimate or association reflects the item being assessed. These considerations are based on within-trial risk of bias, directness of evidence, heterogeneity of data, precision of effect estimates and risk of publication bias (Andrews 2013a; Andrews 2013b; Bals hem 2018; Brunetti 2013; Guyatt 2011a; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2011h; Guyatt 2013a; Guyatt 2013b; Mustafa 2013).

When possible, we will use the SMD or the RR for the 'Summary of findings' table, and we will use the TSA as the rating for imprecision (Jakobsen 2014). We will present separate 'Summary of findings' tables for each comparison in the review, and each table will include data from the primary and secondary outcomes, if the data are available (GRADE Working Group 2004).

Sensitivity analysis
Studies contributing to heterogeneity ('outliers') will be removed to evaluate the impact of their statistical heterogeneity on the overall pooled effect estimate. We will remove outliers one by one and assess the impact on the overall outcome.

We will conduct sensitivity analyses to determine whether findings are sensitive to the following decisions made during the review process.

1. Our assessment of the level of clinical heterogeneity.
2. Analytical technique (e.g. fixed-effect and random-effects models).
3. Type of data collection (e.g. different ways to measure adverse events).
4. Imputed data (comparing the analyses with available outcome data with those following the ITT principle).
5. Combination of data in continuous outcomes (end of intervention or change scores).
6. Use of cluster-randomised trials.
7. Impact of non-normally distributed data.

ACKNOWLEDGEMENTS
We thank the Cochrane Methodology Review Group’s editorial team and peer reviewers. We also thank research librarian Trine Kæstel for her valuable guidance on the search strategy.
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Enck 2013

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Ertl 2011

Freedland 2011

Furukawa 2014

Fässler 2010

Fässler 2015

Gold 2018

GRADE Working Group 2004

Greville-Harris 2015
Guyatt 2011a

Guyatt 2011b

Guyatt 2011c

Guyatt 2011d

Guyatt 2011f

Guyatt 2011g

Guyatt 2011h

Guyatt 2013a

Guyatt 2013b

Haresnape 2013

Hesser 2011

Higgins 2003

Higgins 2011

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Holmes 2018

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Kiene 1997

Kjaergard 2001

Kongerslev 2015

Kube 2017

Levine 1986

Lilienfeld 2007

Linden 2014

Lund 2014

Lundh 2017

Löfholm 2013

Meissner 2011a

Meissner 2011b

Meissner 2013

Miranda 2003
Moher 1998

Moher 2009

Moher 2009

Moher 2014

Mustafa 2013

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Pagsberg 2017

Raicek 2012

Review Manager 5 [Computer program]

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WHO 1967

WHO 1975

WHO 1993

WHO 2018

Wood 2008

Yeung 2017

Young 2011

* Indicates the major publication for the study
# ADDITIONAL TABLES

Table 1. Description of experimental interventions

<table>
<thead>
<tr>
<th>Name of intervention</th>
<th>Other common names reported in the literature</th>
<th>Definition</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacological placebo</td>
<td>Pill placebo, placebo tablet, dummy pill</td>
<td>Pharmacological placebos are inert substances, typically in pill or liquid form, which do not contain the active ingredients of a given drug treatment</td>
<td>Participants typically receive a pill containing starch, sugar, or lactose (<a href="#">Double 1993; Meissner 2011b</a>).</td>
</tr>
<tr>
<td>Psychological placebo</td>
<td>Attention placebo, credible placebo, common-factor treatment control, sham intervention, pseudo control</td>
<td>Psychological placebos target the non-specific or shared components of psychological treatments, such as human interaction variables, attending sessions, and patient expectations</td>
<td>In an example from <a href="#">Tan 1986</a>, the psychological placebo participants were exposed to sessions of supportive group counselling, which were thought to represent the non-specific component of the active intervention, which was cognitive behavioural therapy</td>
</tr>
<tr>
<td>Physical placebo</td>
<td>Sham intervention, credible placebo, pseudo control</td>
<td>Physical placebos target the inert components of a given physical treatment (such as acupuncture, needle injection, exercise regimens, surgery, or electromagnetic stimulation)</td>
<td>This could be sham acupuncture where the needles are blunted (<a href="#">Tough 2009</a>), or sham electromagnetic stimulation, where the machine is not turned on or electrodes are attached to inactive sites (<a href="#">Sommer 2006</a>).</td>
</tr>
<tr>
<td>Usual care</td>
<td>Treatment as usual (TAU), standard care, outpatient care, standard practice, support as usual, clinical care, routine care, existing-practice control</td>
<td>Usual care reflects locally accepted treatment practices for a given mental health disorder. It is provided either by private or public practitioners and may involve both pharmacological and psychological treatment</td>
<td>Patients allocated to usual care might receive a large variety of therapies with a theoretical blend of psychodynamic, humanistic and behavioural approaches (<a href="#">Borduin 2009</a>).</td>
</tr>
<tr>
<td>Wait-list</td>
<td>Minimal contact control, delayed treatment</td>
<td>Wait-list participants are assessed on repeated occasions, but are promised the “active” intervention after the trial has ended</td>
<td>In <a href="#">Ertl 2011</a>, participants allocated to the wait-list group were reassessed at baseline and follow-up, and subsequently offered the active treatment, which was narrative exposure therapy</td>
</tr>
<tr>
<td>No-treatment</td>
<td>Minimal contact control</td>
<td>No-treatment participants are assessed on repeated occasions without receiving the active treatment intervention. Unlike wait-list interventions, no-treatment participants are not promised the active intervention (antidepressants or psychotherapy) after trial com-</td>
<td>No-treatment participants in <a href="#">Miranda 2003</a> did not receive any mental-health related treatment, and were not promised the active intervention (antidepressants or psychotherapy) after trial com-</td>
</tr>
</tbody>
</table>
### Table 1. Description of experimental interventions (Continued)

<table>
<thead>
<tr>
<th>“active” intervention after trial completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>A P P E N D I C E S</td>
</tr>
</tbody>
</table>

#### Appendix 1. Search strategy

**Database:** Ovid MEDLINE(R) <1946 to March Week 5 2018>

**Search Strategy:**

1. exp mental disorders/ or exp anxiety disorders/ or exp agoraphobia/ or exp anxiety, separation/ or exp neurocirculatory asthenia/ or exp neurotic disorders/ or exp obsessive-compulsive disorder/ or exp hoarding disorder/ or exp panic disorder/ or exp phobic disorders/ or exp phobia, social/ or exp “bipolar and related disorders”/ or exp bipolar disorder/ or exp “disruptive, impulse control, and conduct disorders”/ or exp fiesetting behavior/ or exp gambling/ or exp trichotillomania/ or exp dissociative disorders/ or exp multiple personality disorder/ or exp elimination disorders/ or exp encephalitis/ or exp enuresis/ or exp “feeding and eating disorders”/ or exp anorexia nervosa/ or exp binge-eating disorder/ or exp bulimia nervosa/ or exp “feeding and eating disorders of childhood”/ or exp female athlete triad syndrome/ or exp food addiction/ or exp night eating syndrome/ or exp pica/ or exp mood disorders/ or exp depressive disorders/ or exp depression, postpartum/ or exp depressive disorder, major/ or exp depressive disorder, treatment-resistant/ or exp dysthymic disorder/ or exp premenstrual dysphoric disorder/ or exp seasonal affective disorder/ or exp cyclothymic disorder/ or exp motor disorders/ or exp neurocognitive disorders/ or exp amnesia/ or exp alcoholic korsakoff syndrome/ or exp amnesia, anterograde/ or exp amnesia, retrograde/ or exp amnesia, transient global/ or exp cognition disorders/ or exp auditory perceptual disorders/ or exp huntington disease/ or exp cognitive dysfunction/ or exp consciousness disorders/ or exp delirium/ or exp emergence delirium/ or exp dementia/ or exp aids dementia complex/ or exp alzheimer disease/ or exp aphasia, primary progressive/ or exp primary progressive nonfluent aphasia/ or exp creutzfeldt-jakob syndrome/ or exp dementia, vascular/ or exp dementia, multi-infarct/ or exp diffuse neurofibrillary tangles with calcification/ or exp frontotemporal lobar degeneration/ or exp frontotemporal dementia/ or exp “pick disease of the brain”/ or exp kluever-bucy syndrome/ or exp lewy body disease/ or exp dyslexia, acquired/ or exp alexia, pure/ or exp neurodevelopmental disorders/ or exp “attention deficit and disruptive behavior disorders”/ or exp attention deficit disorder with hyperactivity/ or exp conduct disorder/ or exp child behavior disorders/ or exp child development disorders, pervasive/ or exp autism spectrum disorder/ or exp asperger syndrome/ or exp autistic disorder/ or exp communication disorders/ or exp childhood-onset fluency disorder/ or exp social communication disorder/ or exp speech sound disorder/ or exp developmental disabilities/ or exp intellectual disability/ or exp learning disorders/ or exp dyscalculia/ or exp dyslexia/ or exp specific learning disorder/ or exp motor skills disorders/ or exp mutism/ or exp reactive attachment disorder/ or exp schizophrenia, childhood/ or exp stereotypic movement disorder/ or exp tic disorders/ or exp paraphilic disorders/ or exp exhibitionism/ or exp “feishism (psychiatric)”/ or exp masochism/ or exp pedophilia/ or exp sadism/ or exp transvestism/ or exp voyeurism/ or exp personality disorders/ or exp antisocial personality disorder/ or exp borderline personality disorder/ or exp compulsive personality disorder/ or exp dependent personality disorder/ or exp histrionic personality disorder/ or exp hysteria/ or exp paranoid personality disorder/ or exp passive-aggressive personality disorder/ or exp schizoid personality disorder/ or exp schizotypal personality disorder/ or exp “schizophrenia spectrum and other psychotic disorders”/ or exp affective disorders, psychotic/ or exp capgras syndrome/ or exp delusional parasitosis/ or exp morgellons disease/ or exp paranoid disorders/ or exp psychotic disorders/ or exp psychoses, substance-induced/ or exp schizophrenia/ or exp schizophrenia, catatonic/ or exp schizophrenia, disorganized/ or exp schizophrenia, paranoid/ or exp shared paranoid disorder/ or exp sexual dysfunctions, psychological/ or exp dyspareunia/ or exp erectile dysfunction/ or exp gender dysphoria/ or exp premature ejaculation/ or exp “sexual and gender disorders”/ or exp vaginismus/ or exp sleep wake disorders/ or exp dyssomnias/ or exp sleep deprivation/ or exp sleep disorders, circadian rhythm/ or exp sleep disorders, intrinsic/ or exp parasomnias/ or exp nocturnal paroxysmal dystonia/ or exp restless legs syndrome/ or exp sleep arousal disorders/ or exp sleep bruxism/ or exp sleep-wake transition disorders/ or exp somatoform disorders/ or exp body dysmorphic disorders/ or exp conversion disorder/ or exp factitious disorders/ or exp munchausen syndrome/ or exp munchausen syndrome by proxy/ or exp hypochondriasis/
or exp neurasthenia/ or exp substance-related disorders/ or exp alcohol-related disorders/ or exp alcohol amnestic disorder/ or exp alcohol withdrawal delirium/ or exp alcoholic intoxication/ or exp alcoholism/ or exp binge drinking/ or exp psychoses, alcoholic/ or exp wernicke encephalopathy/ or exp amphetamine-related disorders/ or exp cocaine-related disorders/ or exp inhalant abuse/ or exp morphine dependence/ or exp opium dependence/ or exp phencyclidine abuse/ or exp substance abuse, intravenous/ or exp substance abuse, oral/ or exp substance withdrawal syndrome/ or exp "tobacco use disorder"/ or exp "trauma and stressor related disorders"/ or exp adjustment disorders/ or exp stress disorders, traumatic/ or exp battered child syndrome/ or exp combat disorders/ or exp psychological trauma/ or exp stress disorders, post-traumatic/ or exp stress disorders, traumatic, acute/
2. exp PLACEBO EFFECT/ or exp Placebos/
3. (control* or compar* or nonspecific or non-specific or un-specific or unspecified or vehicle* or placebo* or credible or pseudo or sham or mock or fake or dumm* or attention or "common factor").ab,hw,kf,ti.
4. (usual or clinic* or standard* or enhance* or routine or outpatient* or convention* or gener* or local* or structur* or manual* or optim*).ab,hw,kf,ti.
5. (care or practi* or management* or treat* or intervention* or contact* or pill* or tablet* or medic* or therap* or surger* or operat*).ab,hw,kf,ti.
6. 4 and 5
7. TAU.ab,hw,kf,ti.
8. exp Waiting Lists/
9. ("no" care or "no" practi* or "no" management* or "no" treat* or "no" intervention* or "no" contact* or "no" pill* or "no" tablet* or "no" medic* or "no" therap* or "no" surger* or "no" operat* or "no" active* or "no" experimental*).ab,hw,kf,ti.
10. (no care or no practi* or no management* or no treat* or no intervention* or no contact* or no pill* or no tablet* or no medic* or no therap* or no surger* or no operat* or no active* or no experimental*).ab,hw,kf,ti.
11. (uncare or unpracti* or unmanagement* or untreat* or unintervention* or uncontact* or unmedic* or untherap* or unsurger* or unoperat* or unactive* or unexperimental*).ab,hw,kf,ti.
12. ("un" care or "un" practi* or "un" management* or "un" treat* or "un" intervention* or "un" contact* or "un" medic* or "un" therap* or "un" surger* or "un" operat* or "un" active* or "un" experimental*).ab,hw,kf,ti.
13. ("minim" care or "minim" practi* or "minim" management* or "minim" treat* or "minim" intervention* or "minim" contact* or "minim" medic* or "minim" therap* or "minim" surger* or "minim" operat* or "minim" active* or "minim" experimental* or "minim" period* or "minim" time*).ab,hw,kf,ti.
14. ("without" care or "without" practi* or "without" management* or "without" treat* or "without" intervention* or "without" contact* or "without" pill* or "without" tablet* or "without" medic* or "without" therap* or "without" surger* or "without" operat* or "without" active* or "without" experimental*).ab,hw,kf,ti.
15. ("delay" care or "delay" practi* or "delay" management* or "delay" treat* or "delay" intervention* or "delay" contact* or "delay" pill* or "delay" tablet* or "delay" medic* or "delay" therap* or "delay" surger* or "delay" operat* or "delay" active* or "delay" experimental* or "delay" list* or "delay" period* or "delay" time*).ab,hw,kf,ti.
16. (await* or wait*).ab,hw,kf,ti.
17. randomi#ed controlled trial.pt.
18. controlled clinical trial.pt.
19. randomi#ed.ab.
20. "placebo" .ab.
21. drug therapy.fs
22. randomly.ab.
23. trial.ab.
24. groups.ab.
25. exp Animals/
26. Humans/
27. 25 not 26
28. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
29. 28 not 27
30. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
31. 2 or 3 or 6
32. 1 and 29 and 30 and 31

Database: PsycINFO <1806 to April Week 1 2018> Search Strategy:
Placebo, usual care and wait-list interventions for all mental health disorders (Protocol)
Copyright © 2019 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
1. exp mental disorders/ or exp adjustment disorders/ or exp affective disorders/ or exp alexithymia/ or exp anxiety disorders/ or exp autism spectrum disorders/ or exp chronic mental illness/ or exp dementia/ or exp dissociative disorders/ or exp eating disorders/ or exp elective mutism/ or exp factitious disorders/ or exp gender identity disorder/ or exp hoarding disorder/ or exp hysteria/ or exp impulse control disorders/ or exp neurosis/ or exp paraphilias/ or exp personality disorders/ or exp pseudodementia/ or exp psychosis/ or exp schizoaffective disorder/ or exp abnormal psychology/ or exp adaptive behavior/ or exp attention deficit disorder/ or exp attention deficit disorder with hyperactivity/ or exp behavior disorders/ or exp borderline states/ or exp brain disorders/ or exp communication disorders/ or exp conduct disorder/ or exp consciousness disturbances/ or exp emotional disturbances/ or exp infantilism/ or exp intellectual development disorder/ or exp learning disorders/ or exp narcissism/ or exp personality processes/ or exp psychiatric patients/ or exp psychiatric symptoms/ or exp psychodiagnosis/ or exp psychopathology/ or exp sexual function disturbances/ or exp sleep disorders/

2. exp PLACEBO/
3. exp OUTPATIENTS/
4. "control* or compar* or nonspecific or non-specific or un-specific or unspecific or vehicle* or placebo* or fals* or credible or pseudo or sham or mock or fake or dummy* or neutral or attention or "common factor*".ab,hw,id,ti.
5. "usual or clinic* or standard* or enhance* or routine or outpatient* or convention* or gener* or local* or structur* or manual* or optim*".ab,hw,id,ti.
6. "(care or practi* or management* or treat* or intervention* or contact* or pill* or tablet* or medic* or therap* or surger* or operat* or period* or time).ab,hw,id,ti.
7. 5 and 6
8. TAU.ab,hw,id,ti.
9. exp Experiment Controls/
10. "(no* care or no* practi* or no* management* or no* treat* or no* intervention* or no* contact* or no* pill* or no* tablet* or no* medic* or no* therap* or no* surger* or no* operat* or no* active* or no* experimental*).ab,hw,id,ti.
11. "(no* care or no* practi* or no* management* or no* treat* or no* intervention* or no* contact* or no* pill* or no* tablet* or no* medic* or no* therap* or no* surger* or no* operat* or no* active* or no* experimental*).ab,hw,id,ti.
12. "(uncare or unpracti* or unmanagement* or ununtreat* or unintervention* or uncontact* or unnedic* or untherap* or unsurger* or unoperat* or unactive* or unexperimental*).ab,hw,id,ti.
13. "(un* care or un* practi* or un* management* or un* treat* or un* intervention* or un* contact* or un* medic* or un* therap* or un* surger* or un* operat* or un* active* or un* experimental*).ab,hw,id,ti.
14. "(minim* care or minim* practi* or minim* management* or minim* treat* or minim* intervention* or minim* contact* or minim* medic* or minim* therap* or minim* surger* or minim* operat* or minim* active* or minim* experimental* or minim* period* or minim* time*).ab,hw,id,ti.
15. "(without care or without practi* or without management* or without treat* or without intervention* or without contact* or without pill* or without tablet* or without medic* or without therap* or without surger* or without operat* or without active* or without experimental*).ab,hw,id,ti.
16. "(delay* care or delay* practi* or delay* management* or delay* treat* or delay* intervention* or delay* contact* or delay* pill* or delay* tablet* or delay* medic* or delay* therap* or delay* surger* or delay* operat* or delay* active* or delay* experimental* or delay* list* or delay* period* or delay* time).ab,hw,id,ti.
17. "(await* or wait*).ab,hw,id,ti.
18. exp Clinical Trials/
19. "(random* adj allocat*).ab.
20. randomi?ed.ab.
21. placebo.ab.
22. "random* .ab.
23. "trial* .ab.
24. "group* .ab.
25. drug therapy.sh.
26. exp Animals/ not Humans/
27. 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
28. 27 not 26
29. 2 or 3 or 4 or 7 or 8
30. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
31. 1 and 28 and 29 and 30
Database: Embase <1974 to 2018 April 09> Search Strategy:

1. exp mental disease/ or exp addiction/ or exp adjustment disorder/ or exp alexithymia/or exp anxiety disorder/ or exp autism/ or exp behavior disorder/ or exp delirium/ or exp dissociative disorder/ or exp emotional disorder/ or exp learning disorder/ or exp memory disorder/ or exp mental deficiency/ or exp mental infantilism/ or exp mental instability/ or exp mood disorder/ or exp neurosis/ or exp organic brain syndrome/ or exp personality disorder/ or exp psychosomatic disorder/ or exp psychotrauma/ or exp schizophrenia spectrum disorder/ or exp stupor/ or exp thought disorder/
2. exp placebo effect/ or exp placebo/
3. exp outpatient care/
4. (control* or compar* or nonspecific or non-specific or un-specific or unspecific or vehicle* or placebo* or credible or pseudo or sham or mock or fake or dummy* or attention or "common factor").ab, hw, kw, ti.
5. (usual or clinic* or standard* or enhance* or routine or outpatient* or convention* or gen* or local* or structur* or manual* or optim*).ab, hw, kw, ti.
6. (care or practi* or management* or treat* or intervention* or contact* or pill* or tablet* or medic* or therap* or surger* or operat* or period* or time).ab, hw, kw, ti.
7. 5 and 6
8. TAU.ab, hw, kw, ti.
9. exp control group/
10. ("no* care" or "no* practi" or "no* management" or "no* treat" or "no* intervention" or "no* contact" or "no* pill" or "no* tablet" or "no* medic" or "no* therap" or "no* surger" or "no* operat" or "no* active" or "no* experimental").ab, hw, kw, ti.
11. (no* care or no* practi* or no* management* or no*treat* or no*intervention* or no*contact* or no*pill* or no*tablet* or no*medic* or no*therap* or no*surger* or no*operat* or no*active* or no*experimental*).ab, hw, kw, ti.
12. (uncare or unpracti* or unmanagement* or untreat* or unintervention* or uncontact* or unnedic* or untherap* or unsurger* or unoperat* or unactive* or unexperimental*).ab, hw, kw, ti.
13. ("un care" or "un practi*" or "un management*" or "un treat" or "un intervention*" or "un contact*" or "un medic*" or "un therap*" or "un surger*" or "un operat*" or "un active*" or "un experimental").ab, hw, kw, ti.
14. ("minim* care" or "minim* practi*" or "minim* management*" or "minim* treat*" or "minim* intervention*" or "minim* contact*" or "minim* medic*" or "minim* therap*" or "minim* surger*" or "minim* operat*" or "minim* active*" or "minim* experimental*" or "minim* period*" or "minim* time").ab, hw, kw, ti.
15. ("without care" or "without practi*" or "without management*" or "without treat" or "without intervention*" or "without contact*" or "without pill" or "without tablet" or "without medic" or "without therap" or "without surger" or "without operat" or "without active*" or "without experimental").ab, hw, kw, ti.
16. ("delay* care" or "delay* practi*" or "delay* management*" or "delay* treat" or "delay* intervention*" or "delay* contact*" or "delay* pill" or "delay* tablet" or "delay* medic*" or "delay* therap*" or "delay* surger" or "delay* operat*" or "delay* active*" or "delay* experimental*" or "delay* list*" or "delay* period*" or "delay* time").ab, hw, kw, ti.
17. (await* or wait*).ab, hw, kw, ti.
18. controlled clinical trial/ or exp clinical trial/ or exp controlled study/ or exp randomized controlled trial/
19. (random* adj allocat*).ab.
20. randomi?ed.ab.
21. placebo.ab.
22. "random* ".ab.
23. "trial* ".ab.
24. drug therapy.fs.
25. exp Animals/ not Humans/
26. 18 or 19 or 20 or 21 or 22 or 23 or 24
27. 26 not 25
28. 2 or 3 or 4 or 7 or 8
29. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
30. 1 and 27 and 28 and 29

Database: Cochrane Central Register of Controlled Trials; current issue:
1. MeSH descriptor: [Mental Disorders] explode all trees
2. MeSH descriptor: [Placebos] explode all trees
3. MeSH descriptor: [Placebo Effect] explode all trees
Placebo, usual care and wait-list interventions for all mental health disorders (Protocol)
14. ("delay* care" or "delay* practi*" or "delay* management*" or "delay* treat*" or "delay* intervention*" or "delay* contact*" or "delay* pill*" or "delay* tablet*" or "delay* medic*" or "delay* therap*" or "delay* surger*" or "delay* operat*" or "delay* active*" or "delay* experimental*" or "delay* list*" or "delay* period*" or "delay* time")
15. (await* or wait*)
16. Randomized or controlled trial* or clinical trial* or placebo* or random* or trial or groups
17. (S2 OR S6 OR S7)
18. (S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15)
19. S1 AND S16 AND S17 AND S18

Database: Web of Science; 1900 to current:
1. TOPIC: (Mental* OR psych* OR Anxi* OR Bipolar OR Conduct disorder* OR Dissociative OR Elimination Disorder* OR Eat* OR Mood* OR Motor Disorder* OR Neuro* OR Paraphilic OR Personality OR Schizophren* OR Sexual Dys* OR Sleep* OR Somatoform* OR Substance* OR Trauma*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
2. TS=((Placebo or control or comparison or vehicle or false or credible or pseudo or sham or mock or dummy or neutral or "standard care" or "usual intervention" or "routine care" or TAU or "treatment as usual" or "usual care" or "standard care" or "standard intervention" or "enhanced care" or "convention* care") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
3. TS=(("waiting list" or wait* or await* or "no*intervention" or "no therapy" or "no*treatment" or "no*care" or "no care" or "no treatment" or "minim*treatment" or "minim*care" or "minim* therapy" or "without care" or "without treatment" or "without intervention" or "without therapy" or "delayed care" or "delayed treatment" or "delayed therapy" or "delayed intervention") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
4. TI=(randomized or randomised or controlled trial* or clinical trial* or placebo* or drug therapy or random* or trial or groups Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
5. #4 AND #3 AND #2 AND #1 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years

Database: ProQuest Dissertations and Theses A&I; 1743 to current:
- ((Mental* OR psych* OR Anxi* OR Bipolar OR Conduct disorder* OR Dissociative OR Elimination Disorder* OR Eat* OR Mood* OR Motor Disorder* OR Neuro* OR paedophilic OR Personality OR Schizophren* OR Sexual Dys* OR Sleep* OR Somatoform* OR Substance* OR Trauma*)
- AND (placebo OR control OR comparison OR vehicle OR false OR credible OR pseudo OR sham OR mock OR dummy OR neutral OR "standard care" OR "usual intervention" OR "routine care" OR TAU OR "treatment as usual" OR "usual care" OR "standard care" OR "standard intervention" OR "enhanced care" OR "convention* care")
- AND (("waiting list" OR wait* OR await* OR "no*intervention" OR "no therapy" OR "no*treatment" OR "no*care" OR "no care" OR "no treatment" OR "minim*treatment" OR "minim*care" OR "minim* therapy" OR "without care" OR "without treatment" OR "without intervention" OR "without therapy" OR "delayed care" OR "delayed treatment" OR "delayed therapy" OR "delayed intervention")
- AND diskw.Exact("PLACEBO" OR "Random" OR "Clinical Trial" OR "Controlled trials" OR "randomised controlled trial" OR "Randomized Controlled Trial")

Database: Sociological Abstracts ProQuest; 1952 to current:
- ((Mental* OR psych* OR Anxi* OR Bipolar OR Conduct disorder* OR Dissociative OR Elimination Disorder* OR Eat* OR Mood* OR Motor Disorder* OR Neuro* OR paedophilic OR Personality OR Schizophren* OR Sexual Dys* OR Sleep* OR Somatoform* OR Substance* OR Trauma*)
- AND ab(placebo OR control OR comparison OR vehicle OR false OR credible OR pseudo OR sham OR mock OR dummy OR neutral OR "standard care" OR "usual intervention" OR "routine care" OR TAU OR "treatment as usual" OR "usual care" OR "standard care" OR "standard intervention" OR "enhanced care" OR "convention* care")
- AND ab(("waiting list" OR wait* OR await* OR "no*intervention" OR "no therapy" OR "no*treatment" OR "no*care" OR "no care" OR "no treatment" OR "minim*treatment" OR "minim*care" OR "minim* therapy" OR "without care" OR "without treatment" OR "without intervention" OR "without therapy" OR "delayed care" OR "delayed treatment" OR "delayed therapy" OR "delayed intervention")
- AND ab("PLACEBO" OR "Random" OR "Clinical Trial" OR "Controlled trials" OR "randomised controlled trial" OR "Randomized Controlled Trial")

Database: Google Scholar; top 200 of relevance according to Bramer 2017:
- Mental| psychiatric | psychological | no treatment | waitlist | placebo | usual care | random | clinical trials
Database: BIOSIS Previews; 1969 to current:
1. TOPIC: (mental disorder*) DocType=All document types; Language=All languages;
2. TOPIC: ("waiting list" or wait* or await* or "no*intervention" or "no*therapy" or "no*treatment" or "no*care" or "no care" or "no treatment" or "minim*treatment" or "minim*care" or "minim*therapy" or "without care" or "without treatment" or "without intervention" or "without therapy" or "delayed treatment" or "delayed therapy" or "delayed intervention") DocType=All document types; Language=All languages;
3. TOPIC: (Placebo or control or comparison or vehicle or false or credible or pseudo or sham or mock or dummy or neutral or "standard care" or "usual intervention" or "routine care" or TAU or "treatment as usual" or "usual care" or "standard care" or "standard intervention" or "enhanced care" or "conventional care") DocType=All document types; Language=All languages;
4. #3 AND #2 AND #1 DocType=All document types; Language=All languages;

Database: Open Grey; 1997 to current
- (mental* OR psych*) AND (placebo OR usual care OR "treatment as usual" OR wait-list OR wait list OR await* OR wait*) AND (no treatment OR wait-list OR wait list OR await OR wait*) AND (random*)

Trial registry: Australian New Zealand Clinical Trials Registry (ANZCTR); www.anzctr.org.au/BasicSearch.aspx
- Search terms: (mental OR psychiatric) AND (placebo OR usual care OR waitlist) AND (no treatment OR waitlist)
- Allocation to treatment: Randomised
- Condition category: Mental health
- Healthy Volunteers: No

Trial registry: Clinical Trials; clinicaltrials.gov
- Condition category: Mental Disorder
- Other terms: (placebo OR usual care OR wait-list)
- Intervention/treatment: No treatment

Trial registry: EU Clinical Trials Register; www.clinicaltrialsregister.eu/ctr-search/search
- (Mental disorder OR psychiatric) AND (placebo OR usual care OR wait-list) AND (no treatment OR wait-list)

Trial registry: ISRCTN; www.isrctn.com
Search 1:
- Condition category: Mental and behavioural disorders
- Interventions: No treatment

Search 2:
- Condition category: Mental and behavioural disorders
- Interventions: Waitlist

Trial registry: UK Clinical Trials Gateway; www.ukctg.nihr.ac.uk/#popoverSearchDivId
- (Mental disorder OR psychiatric) AND (placebo OR usual care OR wait-list) AND (no treatment OR wait-list)

Trial registry: World Health Organization International Clinical Trials Registry Platform (WHO ICTRP); http://apps.who.int/trialsearch/
- Condition: (Mental disorder OR psychiatric)
- Intervention: No treatment OR wait-list
CONTRIBUTIONS OF AUTHORS
All authors contributed to writing this protocol.

DECLARATIONS OF INTEREST
The review authors have no relevant interests to declare.

SOURCES OF SUPPORT

Internal sources
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- The Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark. CG is personally salaried by the institution during the period of this review.

External sources
- No sources of support supplied