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## Effectiveness of the Management of Major Depressive Episodes/Disorder in Adults with Chronic Diseases: A Protocol for Systematic Review and Meta-Analysis

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**TITLE**

Effectiveness of the Management of Major Depressive Episodes/Disorder in Adults with Chronic Diseases: A Protocol for Systematic Review and Meta-Analysis

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**KEYWORDS**

Depressive Disorder; Chronic Disease; Disease Management; Systematic Review; Study Protocol

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## ABSTRACT

### INTRODUCTION

Depression is a global-scale public health problem, and a significant association has been established between depression and chronic diseases. The growing comorbidity of chronic and mental diseases pose a challenge to health care systems. We aim to assess the effectiveness of the management of Major Depressive Episodes/Disorder in adults with chronic diseases.

### METHODS AND ANALYSIS

We will conduct a systematic review and meta-analysis of randomized clinical trials on treatments for Major Depressive Episodes/Disorder in adults who suffer from chronic diseases. Two databases MEDLINE and Cochrane, and the reference lists of the included articles, will be searched for studies either in English or Spanish with published results within the 2005-2015 period. Studies must fulfil the following conditions: i) participants aged 18 years or older, diagnosed as having a Major Depressive Episode/Disorder according to standardized criteria and comorbid physical diseases; ii) interventions (be it pharmacological, psychological, psychosocial, or a combination) must be compared to control conditions (other “active” intervention, treatment as usual, waiting list, or placebo); iii) and must report reduction in depressive symptoms after treatment, response to treatment, remission of Major Depressive Episodes/Disorder, and/or significant improvement in quality of life. Data extraction, risk of bias evaluation, results summarization, and quality of the evidence (GRADE), will be performed as recommended by the Cochrane Collaboration. A qualitative synthesis and a random effects meta-analysis will be carried out. Effect sizes will be calculated (relative risk and Cohen’s d),  $I^2$  and Q statistics will be employed to study heterogeneity, and publication bias analysis will be performed. Subgroup analyses and meta-regression will be carried out.

### DISSEMINATION

Results are expected to be published in specialized peer-reviewed journals.

### REGISTRATION

The protocol for systematic review and meta-analysis was submitted in the International Prospective Register of Systematic Reviews (PROSPERO) on January 11 2016, under record number CRD42016029166.

### STRENGTHS AND LIMITATIONS OF THIS STUDY

- The PRISMA-P checklist was used for the publication of this protocol.
- A more stringent definition of depression will be employed (standardized diagnostic criteria).
- The Cochrane Handbook for Systematic Reviews of Interventions was used to assist the design of this systematic review.

- Subgroup analyses and meta-regression will be carried out to assess possible sources of heterogeneity.

### **AMENDMENTS**

If any changes are introduced to the protocol after its publication, they will be included in this section. These changes will not be incorporated into the text of the protocol.

For peer review only

## INTRODUCTION

Depression is a global-scale public health problem due to its frequency, associated disabilities, and recurrence. At the start of the present decade, it was estimated that the world prevalence of major depressive disorder had reached 4.4%,<sup>[1]</sup> thus establishing itself as the main cause of years lived with disability (YLD), explaining 8.2% of the total YLDs in 2010.<sup>[2]</sup>

The lack of timely treatment for unipolar depression is a predictor of poorer response, lower likelihood of remission, higher recurrence, and greater risk of chronicity.<sup>[3]</sup> This situation, in addition to inconsistencies in the management of the disease in real contexts and the insufficient resources assigned to mental health,<sup>[4-5]</sup> amplify the impact of depression as a public health problem.

In addition, a significant association has been established globally between depression and chronic diseases such as asthma, angina, and diabetes,<sup>[6]</sup> which illustrates the complex interaction between mental diseases –especially depression– and other health conditions, thus highlighting the notion that there can be no health without mental health,<sup>[7]</sup> and stressing the need to develop responsive health services.<sup>[8]</sup>

It has also been documented that depression is a risk factor for chronic diseases,<sup>[9-11]</sup> and that it significantly worsens the health<sup>[6,12-13]</sup> and the prognosis of its sufferers,<sup>[14-19]</sup> which results in a greater usage rate of health care services<sup>[20]</sup> and low treatment adherence;<sup>[21]</sup> likewise, poor health<sup>[22]</sup> and the presence of chronic diseases are risk factors for depression.<sup>[11, 22-23]</sup>

The strong link between depression and chronic diseases signals the presence of complex underlying biological mechanisms.<sup>[24]</sup> Recent evidence strongly supports this notion: clear links have been observed between such pathologies, in the form of deregulations in the activity of the hypothalamic-pituitary-adrenal axis (HPA),<sup>[25-26]</sup> a rise in metabolic stress,<sup>[27-28]</sup> increased cellular ageing,<sup>[29]</sup> and an alteration of innate inflammatory response.<sup>[30-33]</sup>

These shared biological pathways and lifestyle-associated factors may be the basis of morbimortality and disability in sufferers of these diseases,<sup>[16]</sup> rather than the specific mechanisms of each health condition, which stresses the need to approach these problems in an integrated fashion.<sup>[34]</sup> In this context, timely treatment for depression has been shown to have a major impact on the control of chronic diseases<sup>[35]</sup> and on the reduction of health care costs.<sup>[36-37]</sup>

The global health situation, characterized by a tendency towards ageing populations, along with a higher prevalence of chronic diseases and their increased degree of associated disability,<sup>[38]</sup> pose a challenge to health care systems, which will also need to deal with a greater number of mental patients.<sup>[39]</sup> In this context, the search for effective treatments for depression in people with chronic diseases gains relevance.

The most recent efforts made to summarize this evidence have been mainly limited by their use of studies that include subjects classed as depressed according to either validated questionnaires or standardized diagnostic criteria,<sup>[40-44]</sup> which constitutes a potential source of heterogeneity, and by their focus on depression in specific chronic diseases<sup>[40-42,44]</sup> or on a single type of approach, such as psychoactive drugs.<sup>[43,45]</sup> In view of the aforementioned, the present systematic

review is intended to assess the effectiveness of the management of Major Depressive Episodes/Disorder in adults with chronic diseases.

## OBJECTIVES

The objective of this systematic review is to assess the effectiveness of the available treatments for Major Depressive Episodes/Disorder in adults who suffer from chronic diseases. In order to do this, the present systematic review and meta-analysis seek to answer the following questions:

1. Which treatments are effective in reducing depressive symptoms in adults with Major Depressive Episodes/Disorder and chronic diseases?
2. Which treatments for Major Depressive Episodes/Disorder in adults with chronic diseases are effective in achieving a response?
3. Which treatments are effective in achieving the remission of Major Depressive Episodes/Disorder in adults with chronic diseases?
4. Which treatments are effective in attaining a significant improvement in the quality of life of adults with Major Depressive Episodes/Disorder and chronic diseases?

## METHODS AND ANALYSIS

The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist[46] was used for the publication of the protocol of the present systematic review and meta-analysis.

## STUDY ELEGIBILITY CRITERIA

### Participants

1. Participant characteristics  
Adults, aged 18 years or older, with no distinction of sex or ethnicity, diagnosed with Major Depressive Episodes/Disorder and one (or more) comorbid chronic physical disease(s).
2. Diagnosis of Major Depression  
The review will only include studies whose participants were diagnosed with Major Depressive Episodes/Disorder using the following standardized criteria: ICD-9,[47] ICD-10,[48] DSM-III,[49] DSM-IV,[50] or DSM-5.[51] The diagnosis must have been provided by a qualified individual, either a psychiatrist or another suitably trained health professional.
3. Comorbidities  
Comorbid physical diseases are not the main concern of this review; however, they must be diagnosed using well-established standardized criteria applied by qualified health professionals.  
Patients with one or more of the following conditions will be included: diabetes, cancer, cardiovascular diseases, chronic respiratory diseases, HIV infection, and rheumatic diseases, among others.

### Interventions

1. Pharmacological treatment  
Involving the use of tricyclic antidepressants (for example, amitriptyline), selective serotonin re-uptake inhibitors (for example, fluoxetine),

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2  
3 monoamine oxidase inhibitors (for example, phenelzine), serotonin and  
4 norepinephrine reuptake inhibitors (for example, venlafaxine), non classified  
5 antidepressants (for example, bupropion), and/or any new antidepressant  
6 agents.[52]

7  
8 2. Psychological therapy

9 Any standardized treatment method with a well-defined psychotherapeutic  
10 content in which a collaborative bond is established between a patient and a  
11 provider (a psychologist or a suitably trained health professional), aimed at  
12 reducing the gravity of the symptoms of Major Depressive Episode/Disorder  
13 and attaining a better level of functioning.[53]

14 Treatments can be intended for individuals, families, or groups, in either a  
15 face-to-face or distance format, through the use of information and  
16 communication technologies.

17 These include behavioural, cognitive, humanistic, psychoanalytic,  
18 psychodynamic, and/or integrative types of psychotherapy.

19  
20  
21 3. Psychosocial interventions

22 Treatments intended to supply help, education, or orientation to patients  
23 concerning Major Depression Episode/Disorder. These can include  
24 psychoeducational strategies, self-help groups, psychosocial rehabilitation  
25 strategies, support for reintegration to society or the workplace, and  
26 monitoring, among others.[54]

27  
28 4. Any combination of points 1, 2, and 3.

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30  
31 **Comparators**

- 32 1. Comparison between one or more treatments labelled "interventions" by the  
33 researchers and which are consistent with the previous section  
34 ("interventions").[55]
- 35 2. Treatment as usual/standard treatment for the management of the disease,  
36 established according to current norms or according to the criterion of the  
37 clinician at the relevant level of health care, conducted naturalistically.[55]
- 38 3. Waiting list in which patients are temporarily assigned to the *treatment as*  
39 *usual/standard treatment* condition until treatment and follow-up have been  
40 completed for those in the intervention group.[55]
- 41 4. Placebo: any control condition defined by the researchers as lacking an  
42 active component.[55]
- 43  
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46 **Outcomes**

47 Studies must specify the following outcomes: reduction in depressive symptoms  
48 after treatment, response to treatment, remission of Major Depressive  
49 Episodes/Disorder, and significant improvement in quality of life.

50 Further details are included in the section "Outcomes and prioritisation".

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53 **Study design**

54 Randomized clinical trials, systematic reviews, or meta-analyses published in the  
55 databases defined for the searches.

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58 **Context**

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There is no restriction of setting; that is, patients can come from the primary, secondary, or tertiary health care levels, from any health care system, and from any country. The population included must be receiving treatment at a health care facility.

#### REPORT ELIGIBILITY CRITERIA

Studies must have been published in English or Spanish. Publications must have an abstract available which includes its results. Study protocols will be excluded. Studies must have been published within the last 10 years, from 30/08/2005 to 30/08/2015.

#### INFORMATION SOURCES

The databases defined as information sources were MEDLINE and Cochrane. The search strategy for both sources is described in the relevant section. In addition, the researchers reviewed the reference lists of the articles included in order to facilitate the identification of relevant studies.

#### SEARCH STRATEGY

Table 1 includes the search strategies for each information source.

<b>Table 1. Search Strategies</b>	
MEDLINE	<pre> ((((("Depression/drug therapy"[Mesh] OR "Depression/nursing"[Mesh] OR "Depression/psychology"[Mesh] OR "Depression/rehabilitation"[Mesh] OR "Depression/therapy"[Mesh]) OR ("Depressive Disorder/diet therapy"[Mesh] OR "Depressive Disorder/drug therapy"[Mesh] OR "Depressive Disorder/nursing"[Mesh] OR "Depressive Disorder/psychology"[Mesh] OR "Depressive Disorder/rehabilitation"[Mesh] OR "Depressive Disorder/therapy"[Mesh])) OR ("depression care"[Title/Abstract] OR ((((("depression/nursing"[Title/Abstract] OR "depression/psychology"[Title/Abstract]) OR "depression/therapy"[Title/Abstract]) OR "antidepressant"[Title/Abstract]) OR "depression treatment"[Title/Abstract]) OR "depression psychotherapy"[Title/Abstract]) OR "depression counseling"[Title/Abstract]) OR "depression therapy"[Title/Abstract]) OR "depression management"[Title/Abstract]))) AND </pre>



	<pre> (((((((chronic disease[Title/Abstract] OR "chronic disease"[Title/Abstract]) OR "chronic disease"[MeSH Terms]) OR ("diabetes"[Title/Abstract] OR "diabetes mellitus"[MeSH Terms])) OR ((((((Chronic Respiratory Diseases[Title] OR "Chronic respiratory disease"[Title/Abstract]) OR "Chronic respiratory diseases"[Title/Abstract]) OR "Asthma"[Title/Abstract]) OR Chronic Obstructive Pulmonary Disease[Title/Abstract]) OR "Pulmonary Disease, Chronic Obstructive"[Mesh]) OR "Chronic Obstructive Pulmonary Disease"[Title/Abstract])) OR (("Neoplasms"[Mesh] OR "Neoplasms"[Title/Abstract]) OR "Cancer"[Title/Abstract])) OR ((Cardiovascular Diseases[Title/Abstract] OR "Cardiovascular Diseases"[Mesh]) OR "Cardiovascular Diseases"[Title/Abstract])) OR "HIV Infections"[Mesh] OR "Rheumatic Diseases"[Mesh])))) AND (("comorbid"[Title/Abstract] OR "comorbidity"[Title/Abstract]) OR "comorbidities"[Title/Abstract]) OR "comorbidity"[MeSH Terms])) AND ((Randomized Controlled Trial[ptyp] OR Meta-Analysis[ptyp] OR systematic[sb]) AND hasabstract[text] AND "2005/08/30"[PDat] : "2015/08/27"[PDat] AND (English[lang] OR Spanish[lang])) </pre>
Cochrane	<pre> "depression" AND "chronic" AND "disease" AND "treatment" in Title, Abstract, Keywords , Publication Year from 2005 to 2015 in Trials' </pre>

## STUDY RECORDS

All the records yielded by the database search will be compiled and duplicates will be removed. Two authors (DA and PM) will review all the titles and abstracts independently and in duplicate to assess the eligibility of the publications. The results of this phase will be discussed within the group (AC, DA, and PM), which will make it possible to estimate the degree of agreement reached. AC will provide his assistance to solve any disagreements that may arise.

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2  
3 Publications selected after reviewing their title and abstract, and those whose  
4 inclusion is in doubt, will be evaluated in full by three of the authors (AC, DA, and  
5 PM). Disagreements will be solved through discussion and with the assistance of a  
6 fourth author (GR) whenever necessary.

7  
8 Multiple publications of a single study will be grouped together to avoid repeating  
9 the same data. This is how the final list of studies included in the review will be  
10 defined.

11 To extract data from the studies selected, and to present their characteristics, the  
12 format recommended in the Cochrane Handbook for Systematic Reviews of  
13 Interventions will be used.[56]

14 To follow this format, a piloting process will be conducted which will make it  
15 possible to estimate the degree of agreement reached. Three studies will be  
16 randomly selected and the authors (AC, DA, and PM), independently and in  
17 duplicate, will extract information from them. The results obtained will be compared  
18 within the group, disagreements will be resolved through discussion, and the  
19 consensual criteria for extracting information will be refined.

20 After this piloting process, the authors (AC, DA, and PM) will divide the studies  
21 among themselves to extract data independently and will meet periodically to  
22 evaluate the fidelity of the process. The assistance provided by a fourth author  
23 (GR), will be used to solve substantial disagreements and to randomly evaluate the  
24 correspondence between the data reported by the studies and those extracted for  
25 the review.  
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### 30 DATA ITEMS

31 Using the extraction format specified in the previous section,[56] the data included  
32 will concern: the study (author, year), details about its design and the duration of  
33 the follow-up process, participant characteristics (setting, sex, age, type of chronic  
34 disease [if specified], Major Depressive Episode/Disorder, gravity of the symptoms  
35 [if specified], and any specific characteristics of the sample which are relevant to  
36 the clinical trial), intervention specifications (active and control groups), and the  
37 main results of the study which are relevant to the review.  
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### 41 OUTCOMES AND PRIORITISATION

#### 42 **Primary outcomes**

- 43 1. Effectiveness in the reduction of depressive symptoms  
44 Significant differences between the intervention and control groups in terms  
45 of depressive symptomatology after treatment, measured using validated  
46 questionnaires for depression: the Beck Depression Inventory,[57] the  
47 Hamilton Depression Rating Scale,[58] the Patient Health  
48 Questionnaire,[59] or the Montgomery-Åsberg Depression Scale,[60] among  
49 others.  
50 Timing: not specified. At least two follow-up measures.
- 51 2. Treatment response  
52 A change of over 50% in depression scores on validated questionnaires,  
53 compared with baseline scores.  
54 Timing: not specified. At least two follow-up measures.
- 55 3. Remission of Major Depressive Episodes/Disorder  
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Absence of clinical depression after treatment completion, according to depression scores on validated questionnaires.

Timing: not specified. At least two follow-up measures.

### Secondary outcomes

1. Significant improvement in quality of life, evaluated through validated instruments, such as the SF-36 Health Survey[61] or the WHO Quality of Life-BREF instrument (WHOQOL-BREF).[62]

Timing: not specified. At least two follow-up measures.

### RISK OF BIAS - INDIVIDUAL STUDIES

Risk of bias will be assessed with the Cochrane Risk of Bias Tool, as per the Cochrane Handbook for Systematic Reviews of Interventions.[56] This tool includes an assessment of six well-defined bias sources: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Each of these sources is associated with specific criteria for classifying the risk of bias as high, low, or unclear.

Usually, in randomized clinical trials of psychological interventions, it is not possible to blind the participants and providers.[63] Even though this aspect will be considered and discussed as a plausible source of bias, it will not be prioritised in the evaluation compared to other potential sources of bias in studies of psychological interventions.

The same piloting process used for extracting data from the studies included will be carried out. AC, DA, and PM will participate directly, while GR will supervise the process, providing her assistance to solve substantial disagreements and to randomly evaluate the fidelity of the data extracted vis-à-vis the original material. No studies will be excluded from later analyses, regardless of the assessment of their risk of bias; however, this issue will be taken into account when discussing the effects of the studies on treatment effectiveness outcomes.

### DATA SYNTHESIS

In this stage, all the authors (AC, DA, GR, PM, PV) will work together.

A qualitative synthesis of all the studies included will be conducted in order to provide an overview of the effectiveness of treatments for Major Depressive Episodes/Disorder in adults with comorbid chronic diseases.

A meta-analytic methodology will be applied, including a random effects model of the studies with relatively similar characteristics, since it is assumed that multiple sources of heterogeneity will exist (the studies are not identical).[64]

As effect size measures, in each of the selected studies, relative risk (RR) will be calculated for dichotomous outcomes, while the standardized mean difference (SMD) (Cohen's d) between treatment groups will be calculated for continuous data.[65]

In general, the treatments described in the intervention section will be compared with the control condition selected for each study in order to assess their effect on the primary and secondary outcome measures relevant to the present review.

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3 Heterogeneity between randomized clinical trials will be studied by visually  
4 inspecting the resulting forest plots and by employing the  $I^2$  and Q statistics.[66]  
5 Results will be summarized using the Summary of Findings table recommended in  
6 the Cochrane Handbook for Systematic Reviews of Interventions.[56] This table will  
7 include:  
8

- 9  
10 a. Reduction in depressive symptoms achieved by the treatments,  
11 reported as a continuous outcome measure.  
12 b. Response to treatments for Major Depressive Episodes/Disorder,  
13 reported as a dichotomous outcome measure.  
14 c. Remission of Major Depressive Episodes/Disorder achieved by the  
15 treatments, reported as a dichotomous outcome measure.  
16 d. Significant improvement in the quality of life of adults with Major  
17 Depressive Episodes/Disorder and chronic diseases achieved by the  
18 treatments, reported as a dichotomous outcome measure.  
19

20 Subgroup analyses will be conducted by: type of chronic condition, treatment type,  
21 and setting.

22 In addition, a meta-regression will be carried out. In order to do this, the sample will  
23 be stratified according to the initial severity of the Major Depressive  
24 Episodes/Disorder, which will make it possible to assess the potential differential  
25 effect of a treatment in connection with the severity of the disorder.  
26  
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#### 28 META-BIAS(ES)

29 Funnel plots and Egger's test will be used to assess potential publication  
30 biases.[67]  
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#### 33 CONFIDENCE IN CUMULATIVE EVIDENCE

34 After presenting this summary of findings, the quality of the whole set of tests for  
35 each individual result will be assessed using the GRADE approach, as  
36 recommended in the Cochrane Handbook for Systematic Reviews of  
37 Interventions.[56] This approach considers the following aspects: within-study risk  
38 of bias, directness of evidence, heterogeneity, precision of effect estimates, and  
39 risk of publication bias. This approach specifies four levels of quality (high,  
40 moderate, low, and very low).  
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#### 43 DISSEMINATION

44 Results are expected to be published in specialized peer-reviewed journals  
45 (preferred topics: Mental Health, Psychology, Psychiatry, and/or Systematic  
46 Reviews).  
47  
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### 15 **AUTHORS' CONTRIBUTIONS**

16 GR is in charge of the review, of supervising the process, and of providing her  
17 expert opinion on the subject. DA, AC, and PM made contributions to the  
18 development of the selection criteria and the search strategy, and will be tasked  
19 with extracting the data and evaluating the risk of bias. PV provided his statistical  
20 and clinical expertise and will help to supervise the process. All the authors  
21 contributed equally to the study design, and edited, modified, and approved the  
22 final version of the manuscript.  
23  
24

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34 Both financial backers are not involved in any other aspect of the project.  
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38 All authors have completed the ICMJE uniform disclosure form. The authors have  
39 no competing interests to disclose.  
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# BMJ Open

## Effectiveness of the Management of Major Depressive Episodes/Disorder in Adults with Comorbid Chronic Physical Diseases: A protocol for systematic review and meta-analysis

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**TITLE**

Effectiveness of the Management of Major Depressive Episodes/Disorder in Adults with Comorbid Chronic Physical Diseases: A protocol for systematic review and meta-analysis

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## ABSTRACT

### INTRODUCTION

Depression is a global-scale public health problem, and a significant association has been established between depression and chronic physical diseases. This growing comorbidity pose a challenge to health care systems. We aim to assess the effectiveness of the management of Major Depressive Episodes/Disorder in adults with comorbid chronic physical diseases.

### METHODS AND ANALYSIS

We will conduct a systematic review and meta-analysis of randomized clinical trials. Two databases MEDLINE and Cochrane Library (Cochrane Database for Systematic Reviews and CENTRAL), and the reference lists of the included articles, will be searched for studies either in English or Spanish with published results within the 2005-2015 period. Studies must fulfil the following conditions: i) participants aged 18 years or older, diagnosed as having a Major Depressive Episode/Disorder according to standardized criteria and chronic physical diseases; ii) interventions (be it pharmacological, psychological, psychosocial, or a combination) must be compared to control conditions (other “active” intervention, treatment as usual, waiting list, or placebo); iii) and must report reduction in depressive symptoms after treatment, response to treatment, remission of Major Depressive Episodes/Disorder, and significant improvement in quality of life. Data extraction, risk of bias evaluation, results summarization, and quality of the evidence (GRADE), will be performed as recommended by the Cochrane Collaboration. A qualitative synthesis and a random effects meta-analysis will be carried out. Effect sizes will be calculated (relative risk and Cohen’s d),  $I^2$  and Q statistics will be employed to study heterogeneity, and publication bias analysis will be performed. Subgroup analyses and meta-regression will be carried out.

### DISSEMINATION

Results are expected to be published in specialized peer-reviewed journals.

### REGISTRATION

The protocol for systematic review and meta-analysis was submitted in the International Prospective Register of Systematic Reviews (PROSPERO) on January 11 2016, under record number CRD42016029166.

### STRENGTHS AND LIMITATIONS OF THIS STUDY

- The PRISMA-P checklist was used for the publication of this protocol.
- A more stringent definition of depression will be employed (standardized diagnostic criteria).
- The Cochrane Handbook for Systematic Reviews of Interventions was used to assist the design of this systematic review.

- Subgroup analyses and meta-regression will be carried out to assess possible sources of heterogeneity.

### AMENDMENTS

If any changes are introduced to the protocol after its publication, they will be included in this section. These changes will not be incorporated into the text of the protocol.

For peer review only

## INTRODUCTION

Depression is a global-scale public health problem due to its frequency, associated disabilities, and recurrence. At the start of the present decade, it was estimated that the world prevalence of major depressive disorder had reached 4.4%,<sup>[1]</sup> thus establishing itself as the main cause of years lived with disability (YLD), explaining 8.2% of the total YLDs in 2010.<sup>[2]</sup>

The lack of timely treatment for unipolar depression is a predictor of poorer response, lower likelihood of remission, higher recurrence, and greater risk of chronicity.<sup>[3]</sup> This situation, in addition to inconsistencies in the management of the disease in real contexts and the insufficient resources assigned to mental health,<sup>[4-5]</sup> amplify the impact of depression as a public health problem.

In addition, a significant association has been established globally between depression and chronic diseases such as asthma, angina, and diabetes,<sup>[6]</sup> which illustrates the complex interaction between mental diseases –especially depression– and other health conditions, thus highlighting the notion that there can be no health without mental health,<sup>[7]</sup> and stressing the need to develop responsive health services.<sup>[8]</sup>

It has also been documented that depression is a risk factor for chronic physical diseases,<sup>[9-11]</sup> and that it significantly worsens the health<sup>[6,12-13]</sup> and the prognosis of its sufferers,<sup>[14-19]</sup> which results in a greater usage rate of health care services<sup>[20]</sup> and low treatment adherence;<sup>[21]</sup> likewise, poor health<sup>[22]</sup> and the presence of chronic diseases are risk factors for depression.<sup>[11, 22-23]</sup>

The strong link between depression and chronic physical diseases signals the presence of complex underlying biological mechanisms.<sup>[24]</sup> Recent evidence strongly supports this notion: clear links have been observed between such pathologies, in the form of deregulations in the activity of the hypothalamic-pituitary-adrenal axis (HPA),<sup>[25-26]</sup> a rise in metabolic stress,<sup>[27-28]</sup> increased cellular ageing,<sup>[29]</sup> and an alteration of innate inflammatory response.<sup>[30-33]</sup> These shared biological pathways and lifestyle-associated factors may be the basis of morbimortality and disability in sufferers of these diseases,<sup>[16]</sup> rather than the specific mechanisms of each health condition, which stresses the need to approach these problems in an integrated fashion.<sup>[34]</sup> In this context, timely treatment for depression has been shown to have a major impact on the control of chronic diseases<sup>[35]</sup> and on the reduction of health care costs.<sup>[36-37]</sup>

The global health situation, characterized by a tendency towards ageing populations, along with a higher prevalence of chronic diseases and their increased degree of associated disability,<sup>[38]</sup> pose a challenge to health care systems, which will also need to deal with a greater number of mental patients.<sup>[39]</sup> In this context, the search for effective treatments for depression in people with comorbid chronic physical diseases gains relevance.

The most recent efforts made to summarize this evidence have been mainly limited by their use of studies that include subjects classed as depressed according to either validated questionnaires or standardized diagnostic criteria,<sup>[40-44]</sup> which constitutes a potential source of heterogeneity, and by their focus on depression in specific chronic diseases<sup>[40-42,44]</sup> or on a single type of therapeutic approach, such as psychoactive drugs.<sup>[43,45]</sup> In view of the aforementioned, the present systematic review is intended to assess the effectiveness of the management of

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2  
3 Major Depressive Episodes/Disorder in adults with comorbid chronic physical  
4 diseases.  
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## 6 7 OBJECTIVES

8 The objective of this systematic review is to assess the effectiveness of the  
9 available treatments for Major Depressive Episodes/Disorder in adults who suffer  
10 from chronic physical diseases. In order to do this, the present systematic review  
11 and meta-analysis seek to answer the following questions:  
12

- 13 1. Which treatments are effective in reducing depressive symptoms in adults  
14 with Major Depressive Episodes/Disorder and comorbid chronic physical  
15 diseases?
- 16 2. Which treatments for Major Depressive Episodes/Disorder in adults with  
17 comorbid chronic physical diseases are effective in achieving a response?  
18
- 19 3. Which treatments are effective in achieving the remission of Major  
20 Depressive Episodes/Disorder in adults with comorbid chronic physical  
21 diseases?  
22
- 23 4. Which treatments are effective in attaining a significant improvement in the  
24 quality of life of adults with Major Depressive Episodes/Disorder and  
25 comorbid chronic physical diseases?  
26

## 27 METHODS AND ANALYSIS

28 The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols  
29 (PRISMA-P) checklist[46] was used for the publication of the protocol of the  
30 present systematic review and meta-analysis.  
31

## 32 STUDY ELEGIBILITY CRITERIA

### 33 Participants

- 34 1. Participant characteristics  
35 Adults, aged 18 years or older, with no distinction of sex or ethnicity,  
36 diagnosed with Major Depressive Episodes/Disorder and one (or more)  
37 comorbid chronic physical disease(s).  
38
- 39 2. Diagnosis of Major Depression  
40 The review will only include studies whose participants were diagnosed with  
41 Major Depressive Episodes/Disorder using the following standardized  
42 criteria: ICD-9,[47] ICD-10,[48] DSM-III,[49] DSM-IV,[50] or DSM-5.[51] The  
43 diagnosis must have been provided by a qualified individual, either a  
44 psychiatrist or another suitably trained health professional.  
45
- 46 3. Comorbidities  
47 Comorbid physical diseases are not the main concern of this review;  
48 however, they must be diagnosed using well-established standardized  
49 criteria applied by qualified health professionals.  
50 Patients with one or more of the following conditions will be included:  
51 diabetes, cancer, cardiovascular diseases, chronic respiratory diseases, HIV  
52 infection, rheumatic diseases, and gastrointestinal disease.  
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### 56 Interventions

- 57 1. Pharmacological treatment  
58  
59  
60

Involving the use of tricyclic antidepressants (for example, amitriptyline), selective serotonin re-uptake inhibitors (for example, fluoxetine), monoamine oxidase inhibitors (for example, phenelzine), serotonin and norepinephrine reuptake inhibitors (for example, venlafaxine), non classified antidepressants (for example, bupropion), and/or any new antidepressant agents.[52]

## 2. Psychological therapy

Any standardized treatment method with a well-defined psychotherapeutic content in which a collaborative bond is established between a patient and a provider (a psychologist or a suitably trained health professional), aimed at reducing the gravity of the symptoms of Major Depressive Episode/Disorder and attaining a better level of functioning.[53]

Treatments can be intended for individuals, families, or groups, in either a face-to-face or distance format, through the use of information and communication technologies.

Examples of psychological therapies that may be included are: behavioural, cognitive, interpersonal, among others.

## 3. Psychosocial interventions

Treatments intended to supply help, education, or orientation to patients concerning Major Depression Episode/Disorder. These can include psychoeducational strategies, self-help groups, psychosocial rehabilitation strategies, support for reintegration to society or the workplace, and monitoring, among others.[54]

## 4. Any combination of points 1, 2, and 3.

### Comparators

1. Comparison between one or more treatments labelled "interventions" by the researchers and which are consistent with the previous section ("interventions").[55]
2. Treatment as usual/standard treatment for the management of the disease, established according to current norms or according to the criterion of the clinician at the relevant level of health care, conducted naturalistically.[55]
3. Waiting list in which patients are temporarily assigned to the *treatment as usual/standard treatment* condition until treatment and follow-up have been completed for those in the intervention group.[55]
4. Placebo: any control condition defined by the researchers as lacking an active component.[55]

### Outcomes

Studies must specify the following outcomes: reduction in depressive symptoms after treatment, response to treatment, remission of Major Depressive Episodes/Disorder, and significant improvement in quality of life.

Further details are included in the section "Outcomes and prioritisation".

### Study design

Randomized clinical trials, systematic reviews, or meta-analyses published in the databases defined for the searches.



## Context

There is no restriction of setting; that is, patients can come from the primary, secondary, or tertiary health care levels, from any health care system, and from any country. The population included must be receiving treatment at a health care facility.

## REPORT ELIGIBILITY CRITERIA

Studies must have been published in English or Spanish. Publications must have an abstract available which includes its results. Study protocols will be excluded. Studies must have been published within the last 10 years, from 30/08/2005 to 30/08/2015.

## INFORMATION SOURCES

The databases defined as information sources were MEDLINE and Cochrane Library (Cochrane Database for Systematic Reviews and CENTRAL). The search strategy for both sources is described in the relevant section.

In addition, the researchers reviewed the reference lists of the articles included in order to facilitate the identification of relevant studies.

## SEARCH STRATEGY

Table 1 includes the search strategies for each information source.

**Table 1. Search Strategies**

MEDLINE	<ol style="list-style-type: none"> <li>1. Depression[Mesh] OR (depress*[Title/Abstract] AND care[Title/Abstract] AND manag*[Title/Abstract]) OR (depress*[Title/Abstract] AND (therapy[Title/Abstract] OR treatment[Title/Abstract] OR psychotherapy[Title/Abstract] OR counseling[Title/Abstract] OR antidepress*[Title/Abstract])</li> <li>2. Chronic Disease[Mesh] OR Diabetes Mellitus[Mesh] OR Chronic Obstructive Pulmonary Disease[Mesh] OR Chronic Respiratory Disease[Title/Abstract] OR Ashtma[Title/Abstract] OR Neoplasms[Mesh] OR Cancer[Title/Abstract] OR Cardiovascular Diseases[Mesh] OR HIV Infections[Mesh] OR Rheumatic Diseases[Mesh] OR Gastrointestinal Diseases[Mesh]</li> <li>3. Randomized Controlled Trial[Publication type] OR Controlled Clinical Trial[Publication Type] OR Random Allocation[Mesh] OR Placebos[Mesh] OR Control Groups[Mesh] OR Clinical Trials As A Topic[Mesh] OR Meta-Analysis[Publication Type] OR Systematic Review[Title/Abstract]</li> <li>4. #1 AND #2 AND #3</li> </ol>
Cochrane Library*	<ol style="list-style-type: none"> <li>1. [mh "Depression"] OR [mh "Depressive Disorder"] OR ((depress*:ti,ab) AND (care OR manag*):ti,ab) OR ((depress*:ti,ab) AND (therapy OR treatment OR psychotherapy OR counseling OR antidepress*):ti,ab)</li> </ol>

- |  |   |
|--|---|
|  | <p>2. [mh "Chronic Disease"] OR [mh "Diabetes Mellitus"] OR [mh "Chronic Obstructive Pulmonary Disease"] OR ("Chronic Respiratory Disease":ti,ab) OR (Asthma:ti,ab) OR [mh Neoplasms] OR (Cancer:ti,ab) OR [mh "Cardiovascular Diseases"] OR [mh "HIV Infections"] OR [mh "Rheumatic Diseases"] OR [mh "Gastrointestinal Diseases"]</p> <p>3. #1 AND #2</p> |
|--|---|

## STUDY RECORDS

All the records yielded by the database search will be compiled and duplicates will be removed. Two authors (DA and PM) will review all the titles and abstracts independently and in duplicate to assess the eligibility of the publications. The results of this phase will be discussed within the group (AC, DA, and PM), which will make it possible to estimate the degree of agreement reached. AC will provide his assistance to solve any disagreements that may arise.

Publications selected after reviewing their title and abstract, and those whose inclusion is in doubt, will be evaluated in full by three of the authors (AC, DA, and PM). Disagreements will be solved through discussion and with the assistance of a fourth author (GR) whenever necessary.

Multiple publications of a single study will be grouped together to avoid repeating the same data. This is how the final list of studies included in the review will be defined.

To extract data from the studies selected, and to present their characteristics, the format recommended in the Cochrane Handbook for Systematic Reviews of Interventions will be used.[56]

To follow this format, a piloting process will be conducted which will make it possible to estimate the degree of agreement reached. Three studies will be randomly selected and the authors (AC, DA, and PM), independently and in duplicate, will extract information from them. The results obtained will be compared within the group, disagreements will be resolved through discussion, and the consensual criteria for extracting information will be refined.

After this piloting process, the authors (AC, DA, and PM) will divide the studies among themselves to extract data independently and will meet periodically to evaluate the fidelity of the process. The assistance provided by a fourth author (GR), will be used to solve substantial disagreements and to randomly evaluate the correspondence between the data reported by the studies and those extracted for the review.

## DATA ITEMS

Using the extraction format specified in the previous section,[56] the data included will concern: the study (author, year), details about its design and the duration of the follow-up process, participant characteristics (setting, sex, age, type of chronic physical diseases [if specified], Major Depressive Episode/Disorder, gravity of the symptoms [if specified], and any specific characteristics of the sample which are relevant to the clinical trial), intervention specifications (active and control groups), and the main results of the study which are relevant to the review.

## OUTCOMES AND PRIORITISATION

### Primary outcomes

1. Effectiveness in the reduction of depressive symptoms  
Significant differences between the intervention and control groups in terms of depressive symptomatology after treatment, measured using validated questionnaires for depression: the Beck Depression Inventory,[57] the Hamilton Depression Rating Scale,[58] the Patient Health Questionnaire,[59] or the Montgomery-Åsberg Depression Scale,[60] among others.  
Timing: not specified. At least two follow-up measures.
2. Treatment response  
According to standard definition,[61] a change of over 50% in depression scores on validated questionnaires, compared with baseline scores.  
Timing: not specified. At least two follow-up measures.
3. Remission of Major Depressive Episodes/Disorder  
Absence of clinical depression after treatment completion, according to depression scores on validated questionnaires.  
Timing: not specified. At least two follow-up measures.

### Secondary outcomes

1. Significant improvement in quality of life, evaluated through validated instruments, such as the SF-36 Health Survey[62] or the WHO Quality of Life-BREF instrument (WHOQOL-BREF).[63]  
Timing: not specified. At least two follow-up measures.

## RISK OF BIAS - INDIVIDUAL STUDIES

Risk of bias will be assessed with the Cochrane Risk of Bias Tool, as per the Cochrane Handbook for Systematic Reviews of Interventions.[56] This tool includes an assessment of six well-defined bias sources: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Each of these sources is associated with specific criteria for classifying the risk of bias as high, low, or unclear.

Usually, in randomized clinical trials of psychological interventions, it is not possible to blind the participants and providers.[64] Even though this aspect will be considered and discussed as a plausible source of bias, it will not be prioritised in the evaluation compared to other potential sources of bias in studies of psychological interventions.

The same piloting process used for extracting data from the studies included will be carried out. AC, DA, and PM will participate directly, while GR will supervise the process, providing her assistance to solve substantial disagreements and to randomly evaluate the fidelity of the data extracted vis-à-vis the original material. No studies will be excluded from later analyses, regardless of the assessment of their risk of bias; however, this issue will be taken into account when discussing the effects of the studies on treatment effectiveness outcomes.

## DATA SYNTHESIS

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3 In this stage, all the authors (AC, DA, GR, PM, PV) will work together.

4 A qualitative synthesis of all the studies included will be conducted in order to  
5 provide an overview of the effectiveness of treatments for Major Depressive  
6 Episodes/Disorder in adults with chronic physical diseases.

7 A meta-analytic methodology will be applied, including a random effects model of  
8 the studies with relatively similar characteristics, since it is assumed that multiple  
9 sources of heterogeneity will exist (the studies are not identical).[65]

10 As effect size measures, in each of the selected studies, relative risk (RR) will be  
11 calculated for dichotomous outcomes, while the standardized mean difference  
12 (SMD) (Cohen's d) between treatment groups will be calculated for continuous  
13 data.[66]

14 In general, the treatments described in the intervention section will be compared  
15 with the control condition selected for each study in order to assess their effect on  
16 the primary and secondary outcome measures relevant to the present review.

17 Heterogeneity between randomized clinical trials will be studied by visually  
18 inspecting the resulting forest plots and by employing the  $I^2$  and Q statistics.[67]

19 Results will be summarized using the Summary of Findings table recommended in  
20 the Cochrane Handbook for Systematic Reviews of Interventions.[56] This table will  
21 include:

- 22 a. Reduction in depressive symptoms achieved by the treatments,  
23 reported as a continuous outcome measure.
- 24 b. Response to treatments for Major Depressive Episodes/Disorder,  
25 reported as a dichotomous outcome measure.
- 26 c. Remission of Major Depressive Episodes/Disorder achieved by the  
27 treatments, reported as a dichotomous outcome measure.
- 28 d. Significant improvement in the quality of life of adults with Major  
29 Depressive Episodes/Disorder and chronic physical diseases  
30 achieved by the treatments, reported as a continuous outcome  
31 measure.

32 Subgroup analyses will be conducted by: ethnicity, setting, type of physical chronic  
33 condition, psychiatric comorbidities, and treatment type.

34 In addition, a meta-regression will be carried out. In order to do this, the sample will  
35 be stratified according to the initial severity of the Major Depressive  
36 Episodes/Disorder, which will make it possible to assess the potential differential  
37 effect of a treatment in connection with the severity of the disorder.

#### 38 META-BIAS(ES)

39 Funnel plots and Egger's test will be used to assess potential publication  
40 biases.[68]

#### 41 CONFIDENCE IN CUMULATIVE EVIDENCE

42 After presenting this summary of findings, the quality of the whole set of tests for  
43 each individual result will be assessed using the GRADE approach, as  
44 recommended in the Cochrane Handbook for Systematic Reviews of  
45 Interventions.[56] This approach considers the following aspects: within-study risk  
46 of bias, directness of evidence, heterogeneity, precision of effect estimates, and  
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3 risk of publication bias. This approach specifies four levels of quality (high,  
4 moderate, low, and very low).  
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### 7 **DISSEMINATION**

8 Results are expected to be published in specialized peer-reviewed journals  
9 (preferred topics: Mental Health, Psychology, Psychiatry, and/or Systematic  
10 Reviews) and dissemination activities will be targeted to all the health-care  
11 providers.  
12

### 13 **CONTRIBUTORSHIP STATEMENT**

14 GR is in charge of the review, of supervising the process, and of providing her  
15 expert opinion on the subject. DA, AC, and PM made contributions to the  
16 development of the selection criteria and the search strategy, and will be tasked  
17 with extracting the data and evaluating the risk of bias. PV provided his statistical  
18 and clinical expertise and will help to supervise the process. All the authors  
19 contributed equally to the study design, and edited, modified, and approved the  
20 final version of the manuscript.  
21  
22

### 23 **COMPETING INTERESTS**

24 All authors have completed the ICMJE uniform disclosure form. The authors have  
25 no competing interests to disclose.  
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36 Information Technology Innovation Centre for Social Applications (CITIAPS).  
37 Financial backers are not involved in any other aspect of the project.  
38  
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### 41 **DATA SHARING STATEMENT**

42 No additional data available.  
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**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol\***

Section and topic	Item No	Checklist item
<b>ADMINISTRATIVE INFORMATION</b>		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
<b>INTRODUCTION</b>		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
<b>METHODS</b>		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

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4	Selection process	11b State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
5	Data collection process	11c Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
6		
7	Data items	12 List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
8		
9		
10	Outcomes and prioritization	13 List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
11		
12	Risk of bias in individual studies	14 Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
13		
14	Data synthesis	15a Describe criteria under which study data will be quantitatively synthesised
15		15b If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$ , Kendall's $\tau$ )
16		15c Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
17		15d If quantitative synthesis is not appropriate, describe the type of summary planned
18		
19	Meta-bias(es)	16 Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
20	Confidence in cumulative evidence	17 Describe how the strength of the body of evidence will be assessed (such as GRADE)
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22 **\* It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important**  
 23 **clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the**  
 24 **PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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 27 *From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and*  
 28 *meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.*

# BMJ Open

## Effectiveness of the Management of Major Depressive Episodes/Disorder in Adults with Comorbid Chronic Physical Diseases: A protocol for a systematic review and meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-011249.R2
Article Type:	Protocol
Date Submitted by the Author:	15-Sep-2016
Complete List of Authors:	Martínez, Pablo; Universidad de Chile, Department of Psychiatry and Mental Health, Clinical Hospital; Universidad de Santiago de Chile, Information Technology Innovation Centre for Social Applications (CITIAPS) Castro, Ariel; Universidad de Chile, School of Medicine, Faculty of Medicine Alonso, Diego; Universidad de Chile, School of Medicine, Faculty of Medicine Vöhringer, Paul A; Universidad de Chile, Department of Psychiatry and Mental Health, Clinical Hospital; Tufts University, Mood Disorders Program, Tufts Medical Center Rojas, Graciela; Universidad de Chile, Department of Psychiatry and Mental Health, Clinical Hospital; Millenium Institute for Depression and Personality Research (MIDAP)
<b>Primary Subject Heading</b>:	Mental health
Secondary Subject Heading:	Evidence based practice, Pharmacology and therapeutics
Keywords:	Depressive Disorder, Chronic Disease, Disease Management, Systematic Review, Study Protocol

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**TITLE**

Effectiveness of the Management of Major Depressive Episodes/Disorder in Adults with Comorbid Chronic Physical Diseases: A protocol for a systematic review and meta-analysis

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## ABSTRACT

### INTRODUCTION

Depression is a global-scale public health problem, and a significant association has been established between depression and chronic physical diseases. This growing comorbidity pose a challenge to health care systems. We aim to assess the effectiveness of the management of Major Depressive Episodes/Disorder in adults with comorbid chronic physical diseases.

### METHODS AND ANALYSIS

We will conduct a systematic review and meta-analysis of randomized clinical trials. Two databases MEDLINE and Cochrane Library (Cochrane Database for Systematic Reviews and CENTRAL), and the reference lists of the included articles, will be searched for studies either in English or Spanish with published results within the 2005-2015 period. Studies must fulfil the following conditions: i) participants aged 18 years or older, diagnosed as having a Major Depressive Episode/Disorder according to standardized criteria and chronic physical diseases; ii) interventions (be it pharmacological, psychological, psychosocial, or a combination) must be compared to control conditions (other “active” intervention, treatment as usual, waiting list, or placebo); iii) and must report reduction in depressive symptoms after treatment, response to treatment, remission of Major Depressive Episodes/Disorder, and significant improvement in quality of life. Data extraction, risk of bias evaluation, results summarization, and quality of the evidence (GRADE), will be performed as recommended by the Cochrane Collaboration. A qualitative synthesis and a random effects meta-analysis will be carried out. Effect sizes will be calculated (relative risk and Cohen’s d),  $I^2$  and Q statistics will be employed to study heterogeneity, and publication bias analysis will be performed. Subgroup analyses and meta-regression will be carried out.

### DISSEMINATION

Results are expected to be published in specialized peer-reviewed journals.

### REGISTRATION

The protocol for systematic review and meta-analysis was submitted in the International Prospective Register of Systematic Reviews (PROSPERO) on January 11 2016, under record number CRD42016029166.

### STRENGTHS AND LIMITATIONS OF THIS STUDY

- The PRISMA-P checklist was used for the publication of this protocol.
- A more stringent definition of depression will be employed (standardized diagnostic criteria).
- The Cochrane Handbook for Systematic Reviews of Interventions was used to assist the design of this systematic review.

- Subgroup analyses and meta-regression will be carried out to assess possible sources of heterogeneity.
- Effects of physical conditions will not be taken into account, possibly affecting the rates of depression and the estimation of treatment effect.

### AMENDMENTS

If any changes are introduced to the protocol after its publication, they will be included in this section. These changes will not be incorporated into the text of the protocol.

For peer review only



## INTRODUCTION

Depression is a global-scale public health problem due to its frequency, associated disabilities, and recurrence. At the start of the present decade, it was estimated that the world prevalence of major depressive disorder had reached 4.4%,<sup>[1]</sup> thus establishing itself as the main cause of years lived with disability (YLD), explaining 8.2% of the total YLDs in 2010.<sup>[2]</sup>

The lack of timely treatment for unipolar depression is a predictor of poorer response, lower likelihood of remission, higher recurrence, and greater risk of chronicity.<sup>[3]</sup> This situation, in addition to inconsistencies in the management of the disease in real contexts and the insufficient resources assigned to mental health,<sup>[4-5]</sup> amplify the impact of depression as a public health problem.

In addition, a significant association has been established globally between depression and chronic diseases such as asthma, angina, and diabetes,<sup>[6]</sup> which illustrates the complex interaction between mental diseases –especially depression– and other health conditions, thus highlighting the notion that there can be no health without mental health,<sup>[7]</sup> and stressing the need to develop responsive health services.<sup>[8]</sup>

It has also been documented that depression is a risk factor for chronic physical diseases,<sup>[9-11]</sup> and that it significantly worsens the health<sup>[6,12-13]</sup> and the prognosis of its sufferers,<sup>[14-19]</sup> which results in a greater usage rate of health care services<sup>[20]</sup> and low treatment adherence;<sup>[21]</sup> likewise, poor health<sup>[22]</sup> and the presence of chronic diseases are risk factors for depression.<sup>[11, 22-23]</sup>

The strong link between depression and chronic physical diseases signals the presence of complex underlying biological mechanisms.<sup>[24]</sup> Recent evidence strongly supports this notion: clear links have been observed between such pathologies, in the form of deregulations in the activity of the hypothalamic-pituitary-adrenal axis (HPA),<sup>[25-26]</sup> a rise in metabolic stress,<sup>[27-28]</sup> increased cellular ageing,<sup>[29]</sup> and an alteration of innate inflammatory response.<sup>[30-33]</sup> These shared biological pathways and lifestyle-associated factors may be the basis of morbimortality and disability in sufferers of these diseases,<sup>[16]</sup> rather than the specific mechanisms of each health condition, which stresses the need to approach these problems in an integrated fashion.<sup>[34]</sup> In this context, timely treatment for depression has been shown to have a major impact on the control of chronic diseases<sup>[35]</sup> and on the reduction of health care costs.<sup>[36-37]</sup>

The global health situation, characterized by a tendency towards ageing populations, along with a higher prevalence of chronic diseases and their increased degree of associated disability,<sup>[38]</sup> pose a challenge to health care systems, which will also need to deal with a greater number of mental patients.<sup>[39]</sup> In this context, the search for effective treatments for depression in people with comorbid chronic physical diseases gains relevance.

The most recent efforts made to summarize this evidence have been mainly limited by their use of studies that include subjects classed as depressed according to either validated questionnaires or standardized diagnostic criteria,<sup>[40-44]</sup> which constitutes a potential source of heterogeneity, and by their focus on depression in specific chronic diseases<sup>[40-42,44]</sup> or on a single type of therapeutic approach, such as psychoactive drugs.<sup>[43,45]</sup> In view of the aforementioned, the present systematic review is intended to assess the effectiveness of the management of

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3 Major Depressive Episodes/Disorder in adults with comorbid chronic physical  
4 diseases.  
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## 7 OBJECTIVES

8 The objective of this systematic review is to assess the effectiveness of the  
9 available treatments for Major Depressive Episodes/Disorder in adults who suffer  
10 from chronic physical diseases. In order to do this, the present systematic review  
11 and meta-analysis seek to answer the following questions:  
12

- 13 1. Which treatments are effective in reducing depressive symptoms in adults  
14 with Major Depressive Episodes/Disorder and comorbid chronic physical  
15 diseases?
- 16 2. Which treatments for Major Depressive Episodes/Disorder in adults with  
17 comorbid chronic physical diseases are effective in achieving a response?  
18
- 19 3. Which treatments are effective in achieving the remission of Major  
20 Depressive Episodes/Disorder in adults with comorbid chronic physical  
21 diseases?  
22
- 23 4. Which treatments are effective in attaining a significant improvement in the  
24 quality of life of adults with Major Depressive Episodes/Disorder and  
25 comorbid chronic physical diseases?  
26

## 27 METHODS AND ANALYSIS

28 The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols  
29 (PRISMA-P) checklist[46] was used for the publication of the protocol of the  
30 present systematic review and meta-analysis.  
31

## 32 STUDY ELEGIBILITY CRITERIA

### 33 Participants

- 34 1. Participant characteristics  
35 Adults, aged 18 years or older, with no distinction of sex or ethnicity,  
36 diagnosed with Major Depressive Episodes/Disorder and one (or more)  
37 comorbid chronic physical disease(s).  
38
- 39 2. Diagnosis of Major Depression  
40 The review will only include studies whose participants were diagnosed with  
41 Major Depressive Episodes/Disorder using the following standardized  
42 criteria: ICD-9,[47] ICD-10,[48] DSM-III,[49] DSM-IV,[50] or DSM-5.[51] The  
43 diagnosis must have been provided by a qualified individual, either a  
44 psychiatrist or another suitably trained health professional.  
45
- 46 3. Comorbidities  
47 Comorbid physical diseases are not the main concern of this review;  
48 however, they must be diagnosed using well-established standardized  
49 criteria applied by qualified health professionals.  
50 Patients with one or more of the following conditions will be included:  
51 diabetes, cancer, cardiovascular diseases, chronic respiratory diseases, HIV  
52 infection, rheumatic diseases, and gastrointestinal disease.  
53  
54  
55

### 56 Interventions

- 57 1. Pharmacological treatment  
58  
59  
60

Involving the use of tricyclic antidepressants (for example, amitriptyline), selective serotonin re-uptake inhibitors (for example, fluoxetine), monoamine oxidase inhibitors (for example, phenelzine), serotonin and norepinephrine reuptake inhibitors (for example, venlafaxine), non classified antidepressants (for example, bupropion), and/or any new antidepressant agents.[52]

## 2. Psychological therapy

Any standardized treatment method with a well-defined psychotherapeutic content in which a collaborative bond is established between a patient and a provider (a psychologist or a suitably trained health professional), aimed at reducing the gravity of the symptoms of Major Depressive Episode/Disorder and attaining a better level of functioning.[53]

Treatments can be intended for individuals, families, or groups, in either a face-to-face or distance format, through the use of information and communication technologies.

Examples of psychological therapies that may be included are: behavioural, cognitive, interpersonal, among others.

## 3. Psychosocial interventions

Treatments intended to supply help, education, or orientation to patients concerning Major Depression Episode/Disorder. These can include psychoeducational strategies, self-help groups, psychosocial rehabilitation strategies, support for reintegration to society or the workplace, and monitoring, among others.[54]

## 4. Any combination of points 1, 2, and 3.

### Comparators

1. Comparison between one or more treatments labelled "interventions" by the researchers and which are consistent with the previous section ("interventions").[55]
2. Treatment as usual/standard treatment for the management of the disease, established according to current norms or according to the criterion of the clinician at the relevant level of health care, conducted naturalistically.[55]
3. Waiting list in which patients are temporarily assigned to the *treatment as usual/standard treatment* condition until treatment and follow-up have been completed for those in the intervention group.[55]
4. Placebo: any control condition defined by the researchers as lacking an active component.[55]

### Outcomes

Studies must specify the following outcomes: reduction in depressive symptoms after treatment, response to treatment, remission of Major Depressive Episodes/Disorder, and significant improvement in quality of life.

Further details are included in the section "Outcomes and prioritisation".

### Study design

Randomized clinical trials, systematic reviews, or meta-analyses published in the databases defined for the searches.

## Context

There is no restriction of setting; that is, patients can come from the primary, secondary, or tertiary health care levels, from any health care system, and from any country. The population included must be receiving treatment at a health care facility.

## REPORT ELIGIBILITY CRITERIA

Studies must have been published in English or Spanish. Publications must have an abstract available which includes its results. Study protocols will be excluded. Studies must have been published within the last 10 years, from 30/08/2005 to 30/08/2015.

## INFORMATION SOURCES

The databases defined as information sources were MEDLINE and Cochrane Library (Cochrane Database for Systematic Reviews and CENTRAL). The search strategy for both sources is described in the relevant section.

In addition, the researchers reviewed the reference lists of the articles included in order to facilitate the identification of relevant studies.

## SEARCH STRATEGY

Table 1 includes the search strategies for each information source.

**Table 1. Search Strategies**

MEDLINE	<ol style="list-style-type: none"> <li>1. Depression[Mesh] OR (depress*[Title/Abstract] AND care[Title/Abstract] AND manag*[Title/Abstract]) OR (depress*[Title/Abstract] AND (therapy[Title/Abstract] OR treatment[Title/Abstract] OR psychotherapy[Title/Abstract] OR counseling[Title/Abstract] OR antidepress*[Title/Abstract])</li> <li>2. Chronic Disease[Mesh] OR Diabetes Mellitus[Mesh] OR Chronic Obstructive Pulmonary Disease[Mesh] OR Chronic Respiratory Disease[Title/Abstract] OR Ashtma[Title/Abstract] OR Neoplasms[Mesh] OR Cancer[Title/Abstract] OR Cardiovascular Diseases[Mesh] OR HIV Infections[Mesh] OR Rheumatic Diseases[Mesh] OR Gastrointestinal Diseases[Mesh]</li> <li>3. Randomized Controlled Trial[Publication type] OR Controlled Clinical Trial[Publication Type] OR Random Allocation[Mesh] OR Placebos[Mesh] OR Control Groups[Mesh] OR Clinical Trials As A Topic[Mesh] OR Meta-Analysis[Publication Type] OR Systematic Review[Title/Abstract]</li> <li>4. #1 AND #2 AND #3</li> </ol>
Cochrane Library*	<ol style="list-style-type: none"> <li>1. [mh "Depression"] OR [mh "Depressive Disorder"] OR ((depress*:ti,ab) AND (care OR manag*):ti,ab) OR ((depress*:ti,ab) AND (therapy OR treatment OR psychotherapy OR counseling OR antidepress*):ti,ab)</li> </ol>

- |  |   |
|--|---|
|  | <p>2. [mh “Chronic Disease”] OR [mh “Diabetes Mellitus”] OR [mh “Chronic Obstructive Pulmonary Disease”] OR (“Chronic Respiratory Disease”:ti,ab) OR (Asthma:ti,ab) OR [mh Neoplasms] OR (Cancer:ti,ab) OR [mh “Cardiovascular Diseases”] OR [mh “HIV Infections”] OR [mh “Rheumatic Diseases”] OR [mh “Gastrointestinal Diseases”]</p> <p>3. #1 AND #2</p> |
|--|---|

## STUDY RECORDS

All the records yielded by the database search will be compiled and duplicates will be removed. Two authors (DA and PM) will review all the titles and abstracts independently and in duplicate to assess the eligibility of the publications. The results of this phase will be discussed within the group (AC, DA, and PM), which will make it possible to estimate the degree of agreement reached. AC will provide his assistance to solve any disagreements that may arise.

Publications selected after reviewing their title and abstract, and those whose inclusion is in doubt, will be evaluated in full by three of the authors (AC, DA, and PM). Disagreements will be solved through discussion and with the assistance of a fourth author (GR) whenever necessary.

Multiple publications of a single study will be grouped together to avoid repeating the same data. This is how the final list of studies included in the review will be defined.

To extract data from the studies selected, and to present their characteristics, the format recommended in the Cochrane Handbook for Systematic Reviews of Interventions will be used.[56]

To follow this format, a piloting process will be conducted which will make it possible to estimate the degree of agreement reached. Three studies will be randomly selected and the authors (AC, DA, and PM), independently and in duplicate, will extract information from them. The results obtained will be compared within the group, disagreements will be resolved through discussion, and the consensual criteria for extracting information will be refined.

After this piloting process, the authors (AC, DA, and PM) will divide the studies among themselves to extract data independently and will meet periodically to evaluate the fidelity of the process. The assistance provided by a fourth author (GR), will be used to solve substantial disagreements and to randomly evaluate the correspondence between the data reported by the studies and those extracted for the review.

## DATA ITEMS

Using the extraction format specified in the previous section,[56] the data included will concern: the study (author, year), details about its design and the duration of the follow-up process, participant characteristics (setting, sex, age, type of chronic physical diseases [if specified], Major Depressive Episode/Disorder, gravity of the symptoms [if specified], and any specific characteristics of the sample which are relevant to the clinical trial), intervention specifications (active and control groups), and the main results of the study which are relevant to the review.

## OUTCOMES AND PRIORITISATION

### Primary outcomes

1. Effectiveness in the reduction of depressive symptoms  
Significant differences between the intervention and control groups in terms of depressive symptomatology after treatment, measured using validated questionnaires for depression: the Beck Depression Inventory,[57] the Hamilton Depression Rating Scale,[58] the Patient Health Questionnaire,[59] or the Montgomery-Åsberg Depression Scale,[60] among others.  
Timing: not specified. At least two follow-up measures.
2. Treatment response  
According to standard definition,[61] a change of over 50% in depression scores on validated questionnaires, compared with baseline scores.  
Timing: not specified. At least two follow-up measures.
3. Remission of Major Depressive Episodes/Disorder  
Absence of clinical depression after treatment completion, according to depression scores on validated questionnaires.  
Timing: not specified. At least two follow-up measures.

### Secondary outcomes

1. Significant improvement in quality of life, evaluated through validated instruments, such as the SF-36 Health Survey[62] or the WHO Quality of Life-BREF instrument (WHOQOL-BREF).[63]  
Timing: not specified. At least two follow-up measures.

## RISK OF BIAS - INDIVIDUAL STUDIES

Risk of bias will be assessed with the Cochrane Risk of Bias Tool, as per the Cochrane Handbook for Systematic Reviews of Interventions.[56] This tool includes an assessment of six well-defined bias sources: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Each of these sources is associated with specific criteria for classifying the risk of bias as high, low, or unclear.

Usually, in randomized clinical trials of psychological interventions, it is not possible to blind the participants and providers.[64] Even though this aspect will be considered and discussed as a plausible source of bias, it will not be prioritised in the evaluation compared to other potential sources of bias in studies of psychological interventions.

The same piloting process used for extracting data from the studies included will be carried out. AC, DA, and PM will participate directly, while GR will supervise the process, providing her assistance to solve substantial disagreements and to randomly evaluate the fidelity of the data extracted vis-à-vis the original material. No studies will be excluded from later analyses, regardless of the assessment of their risk of bias; however, this issue will be taken into account when discussing the effects of the studies on treatment effectiveness outcomes.

## DATA SYNTHESIS

1  
2  
3 In this stage, all the authors (AC, DA, GR, PM, PV) will work together.  
4 A qualitative synthesis of all the studies included will be conducted in order to  
5 provide an overview of the effectiveness of treatments for Major Depressive  
6 Episodes/Disorder in adults with chronic physical diseases.  
7 A meta-analytic methodology will be applied, including a random effects model of  
8 the studies with relatively similar characteristics, since it is assumed that multiple  
9 sources of heterogeneity will exist (the studies are not identical).[65]  
10 As effect size measures, in each of the selected studies, relative risk (RR) will be  
11 calculated for dichotomous outcomes, while the standardized mean difference  
12 (SMD) (Cohen's d) between treatment groups will be calculated for continuous  
13 data.[66]  
14 In general, the treatments described in the intervention section will be compared  
15 with the control condition selected for each study in order to assess their effect on  
16 the primary and secondary outcome measures relevant to the present review.  
17 Heterogeneity between randomized clinical trials will be studied by visually  
18 inspecting the resulting forest plots and by employing the  $I^2$  and Q statistics.[67]  
19 Results will be summarized using the Summary of Findings table recommended in  
20 the Cochrane Handbook for Systematic Reviews of Interventions.[56] This table will  
21 include:  
22  
23  
24  
25

- 26 a. Reduction in depressive symptoms achieved by the treatments,  
27 reported as a continuous outcome measure.
- 28 b. Response to treatments for Major Depressive Episodes/Disorder,  
29 reported as a dichotomous outcome measure.
- 30 c. Remission of Major Depressive Episodes/Disorder achieved by the  
31 treatments, reported as a dichotomous outcome measure.
- 32 d. Significant improvement in the quality of life of adults with Major  
33 Depressive Episodes/Disorder and chronic physical diseases  
34 achieved by the treatments, reported as a continuous outcome  
35 measure.  
36

37 Subgroup analyses will be conducted by: ethnicity, setting, type of physical chronic  
38 condition, psychiatric comorbidities, and treatment type.

39 In addition, a meta-regression will be carried out. In order to do this, the sample will  
40 be stratified according to the initial severity of the Major Depressive  
41 Episodes/Disorder, which will make it possible to assess the potential differential  
42 effect of a treatment in connection with the severity of the disorder.  
43  
44

#### 45 META-BIAS(ES)

46 Funnel plots and Egger's test will be used to assess potential publication  
47 biases.[68]  
48  
49

#### 50 CONFIDENCE IN CUMULATIVE EVIDENCE

51 After presenting this summary of findings, the quality of the whole set of tests for  
52 each individual result will be assessed using the GRADE approach, as  
53 recommended in the Cochrane Handbook for Systematic Reviews of  
54 Interventions.[56] This approach considers the following aspects: within-study risk  
55 of bias, directness of evidence, heterogeneity, precision of effect estimates, and  
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3 risk of publication bias. This approach specifies four levels of quality (high,  
4 moderate, low, and very low).  
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### 7 **DISSEMINATION**

8 Results are expected to be published in specialized peer-reviewed journals  
9 (preferred topics: Mental Health, Psychology, Psychiatry, and/or Systematic  
10 Reviews) and dissemination activities will be targeted to all the health-care  
11 providers.  
12

### 13 **CONTRIBUTORSHIP STATEMENT**

14 GR is in charge of the review, of supervising the process, and of providing her  
15 expert opinion on the subject. DA, AC, and PM made contributions to the  
16 development of the selection criteria and the search strategy, and will be tasked  
17 with extracting the data and evaluating the risk of bias. PV provided his statistical  
18 and clinical expertise and will help to supervise the process. All the authors  
19 contributed equally to the study design, and edited, modified, and approved the  
20 final version of the manuscript.  
21  
22

### 23 **COMPETING INTERESTS**

24 All authors have completed the ICMJE uniform disclosure form. The authors have  
25 no competing interests to disclose.  
26  
27  
28

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36 Information Technology Innovation Centre for Social Applications (CITIAPS).  
37 Financial backers are not involved in any other aspect of the project.  
38  
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### 41 **DATA SHARING STATEMENT**

42 No additional data available.  
43  
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**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol\***

Section and topic	Item No	Checklist item	Reported in page #
<b>ADMINISTRATIVE INFORMATION</b>			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	11
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	3
Support:			
Sources	5a	Indicate sources of financial or other support for the review	11
Sponsor	5b	Provide name for the review funder and/or sponsor	11
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	11
<b>INTRODUCTION</b>			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
<b>METHODS</b>			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5-7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7-8

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$ , Kendall's $\tau$ )	10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	10

**\* It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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