BIPOLAR DISORDER (UPDATE) – REVIEW PROTOCOLS

Reviews relating to the experience of carers and the physical health of people with serious mental illness were undertaken in conjunction with a NICE guideline being developed at the same time, *Psychosis and Schizophrenia in Adults* (2014), which includes the full methods and results of those reviews, including the review protocols.

1) Case identification and assessment

Topic	Interventions
Review question(s)	RQ 1.1: For adults at risk of or suspected as having bipolar disorder, what identification instruments when compared to a gold standard diagnosis (based on DSM or ICD criteria) have adequate clinical utility (i.e. clinically useful with good sensitivity and specificity) and reliability? RQ 1.2: For children (less than 13 years) and young people (13 to 18 years)at risk of or suspected of having bipolar disorder, what identification instruments when compared to a gold standard diagnosis (based on DSM or ICD criteria) have adequate clinical utility (i.e. clinically useful with good sensitivity and specificity) and reliability? RQ 1.3: For people with possible bipolar disorder, what are the key components of, and the most effective structure for, diagnostic assessment? What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender, (iii) children and young people, (iv) older adults?
Objectives	For RQ 1.1 and RQ 1.2: To identify brief screening instruments to assess need for further assessment of people with suspected bipolar disorder and to assess their diagnostic accuracy. For RQ 1.3: To identify the key components of a comprehensive assessment
Criteria for considering studies for the review	
• Intervention	For case identification (RQ 1.1 and RQ 1.2): Brief screening questionnaires (<15 items) identified by the GDG
• Comparator	Gold standard: DSM or ICD diagnosis of bipolar disorder
• Types of participants	Children and young people (aged 18 years and younger) and adults with suspected bipolar disorder
• Outcomes	Sensitivity (percentage of true cases identified). Specificity (percentage of non-cases excluded).
• Study design	Studies had to include participants with and without bipolar disorder completing a case-identification instrument and a diagnostic interview.
Search strategy	Databases searched: Embase, Medline, PreMedline, PsycINFO Date restrictions: database inception to 20 January 2014
Study design filter/limit used	None; no language restriction
Question specific search strategy	Yes
Amendments to search	None

strategy/study design filter	
Searching other resources	
The review strategy	To conduct pooled test accuracy meta-analyses on the sensitivity and specificity of case identification instruments where possible.
Note.	

2) *Pharmacological and medical interventions for acute episodes*

Pharmacological and nutritional interventions for mania, hypomania, and mixed episodes for adults with bipolar disorder

Topic	Interventions
Review question(s)	RQ2.1: For adults with bipolar disorder, what are the relative benefits and harms of pharmacological and nutritional interventions for mania, hypomania and mixed episodes? What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender, (iii) adults (18 to 64) and older adults (65+)?
Objectives	To estimate the efficacy of interventions to treat mania, hypomania and mixed episodes.
Criteria for considering studies for the review	
• Intervention	All licensed oral medications (and their combinations). Nutritional interventions will be analysed separately.
• Comparator	Placebo Other interventions
• Types of participants	Adults (18+) with bipolar disorder who are experiencing an acute episode. Special consideration will be given to the groups above.
• Outcomes	1) Response (50% reduction in symptoms) 2) Discontinuation (due to side effect, other)
• Time	The main analysis will include outcomes at the end of the acute treatment phase.
• Study design	Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design in which providers and participants were blind to treatment. Quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth, and single-blind studies will be excluded.
• Dosage	Fixed or flexible doses within the therapeutic range (BNF recommended).
• Study setting	Primary, secondary, tertiary, health and social care
Search strategy	**Databases searched**: RCT: CENTRAL, CINAHL, Embase, MEDLINE, PreMEDLINE, PsycINFO SR: CDSR, CINAHL, DARE, Embase, MEDLINE, PreMEDLINE, PsycINFO **Date limits:** RCT: 2005 to 20 January 2014; SR: 2005 to 11 November 2012
Study design filter/limit used	RCT; SR Language restrictions: none
Question specific search strategy	No
Amendments to search strategy/study design filter	None
Searching other resources	The NCCMH review team will write to all stakeholders, authors of all included studies, and manufacturers of all licensed drugs to request unpublished studies.
The review strategy	The GDG will search for systematic reviews that compare all eligible trials using an appropriate statistical method.

	If reviews are found, the GDG will assess their quality, completeness and applicability to the NHS. If the GDG identify a systematic review appropriate to the review question, they will search for RCTs conducted or published since the review was conducted, and will assess if any additional trials could affect the conclusions of the previous review. If new trials could change the conclusions, the GDG will update the review and conduct a new analysis. If new trials could not change the conclusions of an existing review, the GDG will use the existing review to inform their recommendations. In no reviews are found, the GDG plans to compare all eligible interventions using pairwise meta-analyses and, if appropriate, conduct a network meta-analysis comparing response and discontinuation at the end of the acute treatment. The GDG will conduct pairwise analyses using random effects models of interventions that are not connected to the main network, including studies with no connected intervention or control group and studies of specific subpopulations (for example, people with comorbid substance abuse). For each study, the following will be extracted: year of study; country; total number of study participants in each included group; inclusion and exclusion criteria; age (mean); gender (percent female); race (percent black and minority ethnic [BME]); diagnosis (percent bipolar I disorder); risk of bias. For each intervention or comparison group of interest, dose, frequency and duration will also be extracted.
Note.	

Pharmacological and nutritional interventions for episodes of acute bipolar depression in adults

Topic	Interventions
Review question(s)	RQ2.2: For adults with bipolar disorder, what are the relative benefits and harms of pharmacological and nutritional interventions for acute episodes of acute bipolar depression? What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender, (iii) adults (18 to 64) and older adults (65+)?
Objectives	To estimate the efficacy of interventions to treat acute episodes of bipolar depression.
Criteria for considering studies for the review	
• Intervention	All licensed oral medications (and their combinations). Nutritional interventions will be analysed separately.
• Comparator	Placebo Other interventions
• Types of participants	Adults (18+) with bipolar disorder who are experiencing an acute episodes of bipolar depression. Special consideration will be given to the groups above.
• Outcomes	1) Response (50% reduction in symptoms) 2) Discontinuation (due to side effect, other)
• Time	The main analysis will include outcomes at the end of the acute treatment phase.
• Study design	Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design in which providers and participants were blind to treatment. Quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth, and single-blind studies, will be excluded.
• Dosage	Fixed or flexible doses within the therapeutic range (BNF recommended).
• Minimum sample size	To be included in a network meta-analysis, drugs must have been evaluated in at least 20 participants.
• Study setting	Primary, secondary, tertiary, health and social care
Search strategy	**Databases searched**: RCT: CENTRAL, CINAHL, Embase, MEDLINE, PreMEDLINE, PsycINFO SR: CDSR, CINAHL, DARE, Embase, MEDLINE, PreMEDLINE, PsycINFO **Date limits:** RCT: 2005 to 20 January 2014; SR: 2005 to 11 November 2012
Study design filter/limit used	RCT; SR Language restrictions: none
Question specific search strategy	No
Amendments to search strategy/study design filter	None
Searching other resources	The NCCMH review team will write to all stakeholders, authors of all included studies, and manufacturers of all licensed drugs to request unpublished studies.
The review strategy	The GDG will search for systematic reviews that compare all eligible trials using an appropriate statistical method.

	If reviews are found, the GDG will assess their quality, completeness and applicability to the NHS. If they identify a systematic review appropriate to the review question, they will search for RCTs conducted or published since the review was conducted, and the GDG will assess if any additional trials could affect the conclusions of the previous review. If new trials could change the conclusions, the GDG will update the review and conduct a new analysis. If new trials could not change the conclusions of an existing review, the GDG will use the existing review to inform their recommendations. In no reviews are found, the GDG plans to compare all eligible interventions using pairwise meta-analyses and, if appropriate, conduct a network meta-analysis comparing response, symptoms of depression and discontinuation at the end of the acute treatment. The GDG will conduct pairwise analyses using random effects models of interventions that are not connected to the main network, including studies with no connected intervention or control group and studies of specific subpopulations (for example, people with comorbid substance abuse). For each study, the following will be extracted: year of study; country; total number of study participants in each included group; inclusion and exclusion criteria; age (mean); gender (percent female); race (percent BME); diagnosis (percent bipolar I disorder); and risk of bias. For each intervention or comparison group of interest, dose, frequency and duration will also be extracted..
Note.	

Non-pharmacological interventions for adults with bipolar disorder

Topic	Interventions
Review question(s)	RQ 2.3: For adults with bipolar disorder, what are the relative benefits and harms of acupuncture, bright light therapy, transcranial magnetic stimulation (TMS), and vagus nerve stimulation for mania, hypomania, and mixed episodes; RQ 2.4: For adults with bipolar disorder, what are the relative benefits and harms of acupuncture, bright light therapy, transcranial magnetic stimulation (TMS), and vagus nerve stimulation for depressive episodes; What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender, (iii) adults (18 to 64) and older adults (65+)?
Objectives	To estimate the efficacy of physical interventions for adults with bipolar disorder.
Criteria for considering studies for the review	
• Intervention	Non-pharmacological medical interventions
• Comparator	A credible no-intervention control (for example, sham intervention).
• Types of participants	Adults (18+) with bipolar disorder who are experiencing an acute episode. Special consideration will be given to the groups above.
• Outcomes	1) Change in symptoms (of mania or depression) 2) Response (50% reduction or greater) 3) Discontinuation
• Time	The main analysis will include outcomes at the end of the acute treatment phase.
• Study design	Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design. Quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth, will be excluded.
• Study setting	Primary, secondary, tertiary, health and social care
• Comparator	A credible no-intervention control (e.g. sham intervention).
• Types of participants	Adults (18+) with bipolar disorder who are experiencing an acute episode. Special consideration will be given to the groups above.
• Outcomes	4) Change in symptoms (of mania or depression) 5) Response (50% reduction or greater) 6) Discontinuation
• Time	The main analysis will include outcomes at the end of the acute treatment phase.
• Study design	Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design. We will exclude quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth.
• Study setting	Primary, secondary, tertiary, health and social care
Search strategy	**Databases searched**: RCT: CENTRAL, CINAHL, Embase, Medline, PreMedline, PsycINFO SR: CDSR, CINAHL, DARE, Embase, Medline, PreMedline, PsycINFO **Date limits:** RCT: 2005 to 20 January 2014; SR: 2005 to 11 November 2012
Study design filter/limit used	RCT; SR Language restrictions: none
Question specific search	No

strategy	
Amendments to search strategy/study design filter	None
Searching other resources	The NCCMH review team will write to all stakeholders and authors of all included studies to request unpublished studies.
The review strategy	The GDG will conduct pairwise analyses for all comparisons and outcomes using random effects models. For each study, the GDG will also extract: year of study; country; total number of study participants in each included group; inclusion and exclusion criteria; age (mean); gender (percent female); race (percent BME); diagnosis (percent Bipolar I); risk of bias. For each intervention or comparison group of interest, dose, frequency and duration will also be extracted.
Note.	

3) Long term management of bipolar disorder

Service-level intervention for bipolar disorder

Topic	Interventions
Review question(s)	RQ3.1: For adults with bipolar disorder, what are the relative benefits and harms of service-level interventions that are designed specifically for people bipolar disorder? What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender, and (iii) adults (18 to 64) and older adults (65+)?
Objectives	To estimate the efficacy of services in treating bipolar disorder.
Criteria for considering studies for the review	
• Intervention	Lithium Clinics Mood clinics Collaborative care
• Comparator	Treatment-as-usual Other services
• Types of participants	Adults (18+) with suspected bipolar disorder. Special consideration will be given to the groups above.
• Outcomes	1) Relapse (all, mania/mixed, depression) 2) Hospitalisation (rate, duration) 3) Quality of life 4) Mortality
• Time	At least 1 year after initiating treatment.
• Study design	Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design. We will exclude quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth.
Search strategy	**Databases searched**: RCT: CENTRAL, CINAHL, Embase, Medline, PreMedline, PsycINFO SR: CDSR, CINAHL, DARE, Embase, Medline, PreMedline, PsycINFO **Date limits:** RCT: 2005 to 20 January 2014; SR: 2005 to 11 November 2012
Study design filter/limit used	RCT; SR Language restrictions: none
Question specific search strategy	No
Amendments to search strategy/study design filter	None
Searching other resources	The NCCMH review team will write to all stakeholders and authors of all included studies to request unpublished studies.
The review strategy	We will conduct pairwise analyses for all comparisons and outcomes using random effects models. For each study, the GDG will also extract: year of study; country; total number of study participants in each included group; inclusion and exclusion criteria; age (mean); gender (percent female); race (percent BME); diagnosis (percent Bipolar I); number of previous episodes; risk of bias.
Note.	

Communication technologies for monitoring the symptoms of bipolar disorder

Topic	Interventions
Review question(s)	RQ3.3: What are the relative benefits and harms of information and communication technologies (e.g. text messaging)for monitoring symptoms? What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender, and (iii) adults (18 to 64) and older adults (65+)?
Objectives	To estimate the efficacy of communication technologies for monitoring symptoms.
Criteria for considering studies for the review	
• Intervention	Internet and computer programmes, automated telephone systems, and text messaging.
• Comparator	Waitlist, no-intervention and other interventions.
• Types of participants	People with bipolar disorder. Special consideration will be given to the groups above.
• Outcomes	1) Relapse (all, mania/mixed, depression) 2) Hospitalisation (rate, duration) 3) Mortality (all cause, suicide attempts, suicides completed)
• Time	Outcomes will be grouped by time point.
• Study design	Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design. We will exclude quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth.
• Study setting	Primary, secondary, tertiary, health and social care
Search strategy	**Databases searched**: RCT: CENTRAL, CINAHL, Embase, Medline, PreMedline, PsycINFO SR: CDSR, CINAHL, DARE, Embase, Medline, PreMedline, PsycINFO **Date limits:** RCT: 2005 to 20 January 2014 SR: 2005 to 11 November 2012
Study design filter/limit used	RCT; SR Language restrictions: none
Question specific search strategy	No
Amendments to search strategy/study design filter	None
Searching other resources	The NCCMH review will team write to all stakeholders and authors of all included studies to request unpublished studies.
The review strategy	The GDG will conduct pairwise analyses for all comparisons and outcomes using random effects models. For each study, the GDG will also extract: year of study; country; total number of study participants in each included group; inclusion and exclusion criteria; age (mean); gender (percent female); race (percent BME); diagnosis (percent Bipolar I); number of previous episodes; risk of bias.
Note.	

Pharmacological and medical interventions for long-term management of adults with bipolar disorder

Topic	Interventions
Review question(s)	RQ3.4: For adults with bipolar disorder, what are the relative benefits and harms of starting a new pharmacological intervention outside of an acute episode? RQ3.5: For adults with bipolar disorder, what are the relative benefits and harms of continuing an acute treatment for 1 year or more? What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender, and (iii) adults (18 to 64) and older adults (65+)?
Objectives	To estimate the efficacy of interventions for the long-term management of bipolar disorder.
Criteria for considering studies for the review	
• Intervention	All licensed oral medications (and their combinations) delivered for 1 year or more
• Comparator	Pill placebo Other pharmacological interventions
• Types of participants	Adults (18+) with bipolar disorder. Special consideration will be given to the groups above.
• Outcomes	1) Relapse (all, mania/mixed, depression) (for the purposes of the guideline, relapse was defined as a new episode meeting criteria for MDD or mania) 2) Discontinuation (due to side effect, other) 3) Hospitalisation (rate) 4) Quality of life 5) Mortality (all cause, suicides completed) 6) Weight
• Time	Included studies must have included controlled measures of outcomes at 12 months or later.
• Study design	Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design. We will exclude quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth.
• Include unpublished data?	Unpublished research may be included.
• Restriction by date?	No limit.
• Dosage	Fixed or flexible doses within the therapeutic range (BNF recommended).
• Minimum sample size	10 participants per group
• Study setting	Primary, secondary, tertiary, health and social care
Search strategy	**Databases searched**: RCT: CENTRAL, CINAHL, Embase, Medline, PreMedline, PsycINFO SR: CDSR, CINAHL, DARE, Embase, Medline, PreMedline, PsycINFO **Date limits:** RCT: 2005 to 20 January 2014 SR: 2005 to 11 November 2012
Study design filter/limit used	RCT; SR Language restrictions: none

Question specific search strategy	No
Amendments to search strategy/study design filter	None
Searching other resources	The NCCMH review team will write to all stakeholders, authors of all included studies, and manufacturers of all licensed drugs to request unpublished studies.
The review strategy	The GDG will search for systematic reviews that compare all eligible trials using an appropriate statistical method. If reviews are found, the GDG will assess their quality, completeness, and applicability to the NHS. If the GDG identify a systematic review appropriate to the review question, we will search for RCTs conducted or published since the review was conducted, and the GDG will assess if any additional trials could affect the conclusions of the previous review. If new trials could change the conclusions, the GDG will update the review and conduct a new analysis. If new trials could not change the conclusions of an existing review, the GDG will use the existing review to inform their recommendations. If no reviews are found, we plan to compare all eligible interventions using pairwise meta-analyses and, if appropriate, conduct a network meta-analysis comparing relapse and discontinuation. The GDG will conduct pairwise analyses using random effects models of interventions that are not connected to the main network, including studies with no connected intervention or control group and studies of specific subpopulations (e.g. people with comorbid substance abuse). For each study, we will also extract: year of study; country; total number of study participants in each included group; inclusion and exclusion criteria; age (mean); gender (percent female); race (percent BME); diagnosis (percent Bipolar I); number of previous episodes; risk of bias. For each intervention or comparison group of interest, dose, frequency and duration will also be extracted.
Note.	

4) Psychological and Psychosocial interventions for adults with bipolar disorder

Topic	Interventions
Review question(s)	*Mania* RQ 4.1: For adults with bipolar disorder, what are the relative benefits and harms of psychological and psychosocial interventions for mania, hypomania, and mixed episodes; RQ 4.2: For adults with bipolar disorder, what are the relative benefits and harms of combined psychological and pharmacological interventions for mania, hypomania, and mixed episodes; *Depression* RQ 4.3: For adults with bipolar disorder, what are the relative benefits and harms of psychological and psychosocial interventions for depression; RQ 4.4: For adults with bipolar disorder, what are the relative benefits and harms of combined psychological and pharmacological interventions for depression; *Long-term management* RQ 4.5: For adults with bipolar disorder, what are the relative benefits and harms of psychological and psychosocial interventions for long-term management; RQ 4.6: For adults with bipolar disorder, what are the relative benefits and harms of combined psychological and pharmacological interventions for long-term management; What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender?
Sub-question(s)	Does the effectiveness of treatment vary: 1. For RQ 6.4 to RQ 6.11: For people taking a mood stabiliser (e.g. lithium or valproate) and people not taking a mood stabiliser; 2. For RQ 6.12 to RQ 6.15: For people whose most-recent episode was depressive and people whose most-recent episode was manic; 3. For people with Bipolar I and Bipolar II; 4. For adults (18 to 64) and older adults (65+).
Objectives	To estimate the efficacy of interventions to treat depression.
Criteria for considering studies for the review	
• Intervention	RQ 4.1 to RQ 4.6: All psychological and psychosocial interventions (e.g. cognitive behavioural therapy), all combined psychological with (licensed) pharmacological interventions.
• Comparator	Wait-list, placebo, and other interventions.
• Types of participants	Adults (18+) with bipolar disorder. Special consideration will be given to the groups above.
• Outcomes	**FOR PEOPLE IN AN ACUTE EPISODE** **1)** Change in symptoms of depression **2)** Change in symptoms of mania **3)** Response (50% reduction or greater) **4)** Discontinuation

	5) Quality of life **6)** Psychosocial functioning **FOR PEOPLE WHO ARE EUTHYMIC AT BASELINE** **1)** Relapse **2)** Discontinuation **3)** Hospitalisation **4)** Quality of life **5)** Psychosocial functioning
• Time	The main analysis will include outcomes at the end of treatment. For interventions the GDG considers recommending based on post-treatment results, additional analyses will be conducted for further follow-up data.
• Study design	Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design. We will exclude quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth.
• Study setting	Primary, secondary, tertiary, health and social care
Search strategy	**Databases searched**: RCT: CENTRAL, CINAHL, Embase, Medline, PreMedline, PsycINFO SR: CDSR, CINAHL, DARE, Embase, Medline, PreMedline, PsycINFO **Date limits:** RCT: 2005 to 20 January 2014; SR: 2005 to 11 November 2012
Study design filter/limit used	RCT; SR Language restrictions: none
Question specific search strategy	No
Amendments to search strategy/study design filter	None
Searching other resources	The NCCMH review team will write to stakeholders and authors of all included studies to request unpublished studies.
The review strategy	The GDG will conduct pairwise analyses for all comparisons and outcomes using random effects models. For each study, the GDG will also extract: year of study; country; total number of study participants in each included group; inclusion and exclusion criteria; age (mean); gender (percent female); race (percent BME); diagnosis (percent Bipolar I); number of previous episodes; risk of bias For each intervention or comparison group of interest, dose, frequency and duration will also be extracted.
Note.	

5) Interventions for children and young people with bipolar disorder

Pharmacological and nutritional interventions for mania, hypomania and mixed episodes of bipolar disorder in children and young people

Topic	Interventions
Review question(s)	RQ 5.1: For children and young people with bipolar disorder, what are the relative benefits and harms of pharmacological and nutritional interventions for mania, hypomania and mixed episodes? What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender, (iii) for children (younger than 13 years) and young people (13 to 18 years).
Objectives	To estimate the efficacy of interventions to treat manic, hypomanic and mixed episodes.
Criteria for considering studies for the review	
• Intervention	All licensed oral medications (and their combinations). Nutritional interventions (for example, herbal supplements, fatty acid supplementation).
• Comparator	Waitlist, no intervention, placebo and other interventions.
• Types of participants	Children (younger than 13 years) and young people (13 to 18 years) with bipolar disorder. Special consideration will be given to the groups above.
• Outcomes	1) Change in symptoms of mania 2) Response (50% reduction or greater) 3) Discontinuation (because of side effects, other)
• Time •	The main analysis will include outcomes at the end of the acute treatment phase.
• Study design	Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design in which providers and participants were blind to treatment. Quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth, and single-blind studies, will be excluded.
• Dosage	Fixed or flexible doses within the therapeutic range (BNF recommended).
• Study setting	Primary, secondary, tertiary health and social care
Search strategy	Databases searched: RCT: CENTRAL, CINAHL, Embase, MEDLINE, PreMEDLINE, PsycINFO SR: CDSR, CINAHL, DARE, Embase, MEDLINE, PreMEDLINE, PsycINFO Date restrictions: RCT: 2005 to 20 January 2014 SR: 2005 to 11 November 2012
Study design filter/limit used	RCT: all languages SR: English language limit
Question specific search strategy	No
Amendments to search strategy/study design filter	None
Searching other resources	The NCCMH review team will write to all stakeholders and authors of all included studies to request unpublished studies.
The review strategy	The GDG will conduct pairwise analyses for all comparisons and outcomes using random effects models. For each study, the following will be extracted: year of study; country; total number of study participants in

	each included group; inclusion and exclusion criteria; age (mean); gender (percent female); race (percent black and minority ethnic [BME]); diagnosis (percent bipolar I); risk of bias. For each intervention or comparison group of interest, dose, frequency and duration will also be extracted.
Note.	

Pharmacological and nutritional interventions for episodes of bipolar depression in children and young people

Topic	Interventions
Review question(s)	RQ 5.2: For children and young people with bipolar disorder, what are the relative benefits and harms of pharmacological and nutritional interventions for episodes of bipolar depression? What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender, (iii) for children (younger than 13 years) and young people (13 to 18 years).
Objectives	To estimate the efficacy of interventions to treat episodes of bipolar depression.
Criteria for considering studies for the review	
• Intervention	All licensed oral medications (and their combinations). Nutritional interventions (for example, herbal supplements, fatty acid supplementation).
• Comparator	Waitlist, no intervention, placebo and other interventions.
• Types of participants	Children (younger than 13 years) and young people (13 to 18 years) with bipolar disorder. Special consideration will be given to the groups above.
• Outcomes	1) Change in symptoms of depression 2) Response (50% reduction or greater) 3) Discontinuation (due to side effect, other)
• Time •	The main analysis will include outcomes at the end of the acute treatment phase.
• Study design	RCTs and cluster RCTs with a parallel group design in which providers and participants were blind to treatment. Quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth, and single-blind studies, will be excluded.
• Dosage	Fixed or flexible doses within the therapeutic range (BNF recommended).
• Study setting	Primary, secondary, tertiary health and social care
Search strategy	Databases searched: RCT: CENTRAL, CINAHL, Embase, MEDLINE, PreMEDLINE, PsycINFO SR: CDSR, CINAHL, DARE, Embase, MEDLINE, PreMEDLINE, PsycINFO Date restrictions: RCT: 2005 to 20 January 2014; SR: 2005 to 11 November 2012
Study design filter/limit used	RCT: all languages SR: English language limit
Question specific search strategy	No
Amendments to search strategy/study design filter	None
Searching other resources	The NCCMH review team will write to all stakeholders and authors of all included studies to request unpublished studies.
The review strategy	The GDG will conduct pairwise analyses for all comparisons and outcomes using random effects models. For each study, the following will be extracted: year of study; country; total number of study participants in each included group; inclusion and exclusion criteria; age (mean); gender (percent female); race (percent BME); diagnosis (percent bipolar I); risk of

	bias. For each intervention or comparison group of interest, dose, frequency and duration will also be extracted.
Note.	

Pharmacological and nutritional interventions for long-term management of bipolar disorder in children and young people

Topic	Interventions
Review question(s)	RQ 5.3: For children and young people with bipolar disorder, what are the relative benefits and harms of pharmacological and nutritional interventions for long-term management? What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender, (iii) for children (younger than 13 years) and young people (13 to 18 years).
Objectives	To estimate the efficacy of interventions for the long-term management of bipolar disorder.
Criteria for considering studies for the review	
• Intervention	All licensed oral medications (and their combinations) or nutritional intervention delivered for 1 year or more.
• Comparator	Pill placebo Other pharmacological or nutritional interventions
• Types of participants	Children (younger than 13 years) and young people (13 to 18 years) with bipolar disorder. Special consideration will be given to the groups above.
• Outcomes	1) Relapse (all, mania/mixed, depression) 2) Discontinuation (due to side effect, other) 3) Hospitalisation (rate) 4) Quality of life 5) Mortality (all cause, suicides completed) 6) Weight
• Time	At least 1 year after initiating treatment.
• Study design	RCTs and cluster RCTs with a parallel group design. Quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth, will be excluded.
• Study setting	Primary, secondary, tertiary health and social care
Search strategy	Databases searched: RCT: CENTRAL, CINAHL, Embase, MEDLINE, PreMEDLINE, PsycINFO SR: CDSR, CINAHL, DARE, Embase, MEDLINE, PreMEDLINE, PsycINFO Date restrictions: RCT: 2005 to 20 January 2014 SR: 2005 to 11 November 2012
Study design filter/limit used	RCT: all languages SR: English language limit
Question specific search strategy	No
Amendments to search strategy/study design filter	None
Searching other resources	The NCCMH review team will write to all stakeholders and authors of all included studies to request unpublished studies.
The review strategy	The GDG will conduct pairwise analyses for all comparisons and outcomes using random effects models. For each study, the following will be extracted: year of study; country; total number of study participants in each included group; inclusion and exclusion criteria; age (mean); gender (percent female); race (percent BME); diagnosis (percent Bipolar I);

	number of previous episodes; risk of bias. For each intervention or comparison group of interest, dose, frequency and duration will also be extracted.
Note.	

Psychological interventions for bipolar disorder in children and young people

Topic	Interventions
Review question(s)	RQ 5.4: For children and young people with bipolar disorder, what are the relative benefits and harms of psychological and psychosocial interventions for episodes of bipolar depression? RQ 5.5: For children and young people with bipolar disorder, what are the relative benefits and harms of psychological and psychosocial interventions for long-term management? What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender, (iii) for children (younger than 13 years) and young people (13 to 18 years).
Objectives	To estimate the efficacy of psychological interventions to manage bipolar disorder in children and young people.
Criteria for considering studies for the review	
• Intervention	All psychological and psychosocial interventions (for example, cognitive behavioural therapy) with or without pharmacological interventions.
• Comparator	Waitlist, no intervention and other interventions.
• Types of participants	Children (younger than 13 years) and young people (13 to 18 years) with bipolar disorder. Special consideration will be given to the groups above.
• Outcomes	1) Change in symptoms of depression 2) Response (50% reduction or greater) 3) Relapse (all, mania/mixed, depression) 4) Discontinuation (due to side effect, other)
• Time •	For treatments, the main analysis will include outcomes at the end of the intervention. For long-term management, the main analysis will include outcomes after at least 1 year.
• Study design	RCTs and cluster RCTs with a parallel group design. Quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth, will be excluded.
• Study setting	Primary, secondary, tertiary health and social care
Search strategy	**Databases searched**: RCT: CENTRAL, CINAHL, Embase, MEDLINE, PreMEDLINE, PsycINFO SR: CDSR, CINAHL, DARE, Embase, MEDLINE, PreMEDLINE, PsycINFO **Date restrictions:** RCT: 2005 to 20 January 2014 SR: 2005 to 11 November 2012
Study design filter/limit used	RCT: all languages SR: English language limit
Question specific search strategy	No
Amendments to search strategy/study design filter	None
Searching other resources	The NCCMH review team will write to all stakeholders and authors of all included studies to request unpublished studies.
The review strategy	The GDG will conduct pairwise analyses for all comparisons and outcomes using random effects models. For each study, the following will be extracted: year of study; country; total number of study participants in each included group; inclusion and exclusion criteria; age (mean); gender

	(percent female); race (percent BME); diagnosis (percent Bipolar I); number of previous episodes; risk of bias. For each intervention or comparison group of interest, dose, frequency and duration will also be extracted.
Note.	

Service-level intervention for bipolar disorder

Topic	Interventions
Review question(s)	RQ5.6: For children and young people with bipolar disorder, what are the relative benefits and harms of service-level interventions that are designed specifically for people bipolar disorder? What amendments, if any, need to be made for (i) particular cultural or minority ethnic groups, (ii) gender
Objectives	To estimate the efficacy of services in treating bipolar disorder.
Criteria for considering studies for the review	
• Intervention	Lithium Clinics Mood clinics Collaborative care
• Comparator	Treatment-as-usual Other services
• Types of participants	Children and young people (aged 18 years and younger) with suspected bipolar disorder. Special consideration will be given to the groups above.
• Outcomes	5) Relapse (all, mania/mixed, depression) 6) Hospitalisation (rate, duration) 7) Quality of life 8) Mortality
• Time	At least 1 year after initiating treatment.
• Study design	Randomised controlled trials (RCTs) and cluster RCTs with a parallel group design. We will exclude quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth.
Search strategy	**Databases searched**: RCT: CENTRAL, CINAHL, Embase, Medline, PreMedline, PsycINFO SR: CDSR, CINAHL, DARE, Embase, Medline, PreMedline, PsycINFO **Date limits:** RCT: 2005 to 20 January 2014; SR: 2005 to 11 November 2012
Study design filter/limit used	RCT; SR Language restrictions: none
Question specific search strategy	No
Amendments to search strategy/study design filter	None
Searching other resources	The NCCMH review team will write to all stakeholders and authors of all included studies to request unpublished studies.
The review strategy	We will conduct pairwise analyses for all comparisons and outcomes using random effects models. For each study, the GDG will also extract: year of study; country; total number of study participants in each included group; inclusion and exclusion criteria; age (mean); gender (percent female); race (percent BME); diagnosis (percent Bipolar I); number of previous episodes; risk of bias.
Note.	