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## Mapping of modifiable Barriers and Facilitators of Medication Adherence in Bipolar Disorder to the Theoretical Domains Framework: A Systematic Review Protocol

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# Mapping of modifiable Barriers and Facilitators of Medication Adherence in Bipolar Disorder to the Theoretical Domains Framework: A Systematic Review Protocol

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## Abstract

**Introduction:** People with bipolar disorder require long-term treatment but an estimated 40% of these people do not adhere to prescribed medication regimens. Non-adherence increases the risk of relapse, hospitalisation and suicide. Evidence syntheses report barriers to mental health treatment adherence but rarely delineate between modifiable and non-modifiable barriers. They also fail to distinguish between the patient perspective and that of other stakeholders such as clinicians despite their differing understanding and priorities about adherence. Facilitators of adherence, which are also important for informing adherence intervention design are also lacking from syntheses and few syntheses focus on bipolar medications.

This systematic review aims to identify modifiable barriers and facilitators (determinants) of medication adherence in bipolar disorder. We will also report and compare primary (participant reported) and secondary (author interpreted) determinants of medication adherence. A unique feature of this systematic review in the context of mental health is the use of the Theoretical Domains Framework to organise the literature identified determinants of medication adherence.

**Methods, Synthesis and Result Presentation:** The protocol adheres to Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols (PRISMA-P) and ENhancing Transparency in REporting the synthesis of Qualitative research (ENTREQ) guidelines. The review will include both qualitative and quantitative

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3 studies exploring determinants of medication adherence in bipolar disorder. We will  
4 search following databases using a pre-planned strategy: CINAHL, Cochrane Library  
5 (CENTRAL), Embase, LiLACS, Medline, PsychINFO, PubMed without language or  
6 date restrictions. We will report the quality of included studies using bespoke Critical  
7 Appraisal Skills Programme (CASP) qualitative or Appraisal of Survey or Cochrane  
8 risk of bias tool. We will use framework synthesis using the Theoretical Domains  
9 Framework (TDF) as an *a priori* 'framework'. We will map literature identified  
10 determinants to the domains of TDF and report the results using ENTREQ guidelines  
11 and PRISMA statement.  
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18 Study registration number: PROSPERO CRD42018096306  
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### 23 **Keywords**

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25 Determinant, compliance, concordance, psychotropic drug, mood stabilizer, mental  
26 health  
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### 29 **Strengths and limitations of this study**

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31
- 32 • As the Theoretical Domains Framework (TDF) has been mapped to evidence-  
33 based behaviour change techniques, mapping determinants of medication  
34 adherence in bipolar disorder to the TDF offer significant utility for intervention  
35 development.  
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  - 38 • This study will provide literature-identified barriers and facilitators (determinants)  
39 of medication adherence in bipolar disorder from the perspectives of patients,  
40 carers, healthcare professionals and other third parties such as researchers.  
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  - 43 • No date and language restrictions on the review maximise comprehensiveness.  
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  - 46 • Lack of data and quality of reporting may limit our ability to present determinants  
47 of adherence from perspectives of patients, carers, healthcare professionals and  
48 other third parties as clearly as we would like.  
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  - 51 • Variation in the terms used to describe determinants of adherence may introduce  
52 a risk of mapping errors through misinterpretation of the reported barrier or  
53 facilitator.  
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## Introduction

The lifetime prevalence of bipolar disorder is estimated at 1.4% of the UK adult population (1). Bipolar disorder featuring mood and activity level disturbance is a recurrent disorder and usually requires long-term maintenance therapy (1,2). However, an estimated 40% of people with bipolar disorder do not take their medication as prescribed (3). This non-adherence increases the risk of relapse, suicide and rehospitalisation (4,5). For example, the probability of hospitalisation in non-adherent patients with bipolar disorder is at least five times higher than adherent patients (6).

Adhering to prescribed medication regimes is a complex health behaviour which requires the patient to obtain the prescribed medication, have the physical and cognitive ability (practical function), and motivation (perceptual function) to take the medication. Furthermore, non-adherence may occur at initiation (i.e. patient may or may not start the treatment), implementation (i.e. patient may delay, omit or take extra doses during treatment) or persistence (i.e. patient may discontinue treatment after some time) phase (7). There are many reported barriers and facilitators (determinants) of medication adherence. For this review, a barrier is defined as “a circumstance that prevents the patient from taking their medication as prescribed”, whereas a facilitator is “a circumstance that makes the process easy or easier” (8). We are calling these barriers and facilitators “determinants”.

The challenges to successfully addressing non-adherence are to:

1. Accurately identify non-adherent patients
2. Determine individuals' determinants of medication adherence

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3 3. Select the most appropriate individualised adherence intervention(s) underpinned  
4  
5 by health psychology theory and empirical evidence (9,10).  
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9 There are various objective (e.g. drug plasma levels, pill counts and electronic  
10 monitoring of medication adherence such as medication event monitoring systems)  
11 and subjective (e.g. self-reported, carer or relative reported, clinician reported  
12 adherence rating scales) approaches to identifying patients not adhering to their  
13 prescribed medication for bipolar disorder (11). However, there are no validated tools  
14 for comprehensively eliciting from patients and/or their carers their individual  
15 determinants of adherence to their prescribed medication for bipolar disorder. There  
16 is also an absence of theory and evidence informed guidance for practitioners to  
17 work with patients in selecting the most effective interventions for identified  
18 determinants of an individual's non-adherent behaviour.  
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34 In order to generate such a tool, there is, therefore, a need to synthesize the  
35 available evidence regarding determinants of medication adherence in patients with  
36 bipolar disorder.  
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42 A recent systematic review (literature search restricted to 1990 - 2015) of adherence  
43 to antipsychotic medication in bipolar disorder and schizophrenia has provided a  
44 good overview of the likely barriers experienced by people with bipolar disorder (12).  
45 However, it failed to explore factors that might facilitate adherence and excluded  
46 studies involving medication other than antipsychotics, and therefore did not identify  
47 determinants of adherence to lithium and other mood stabilisers. This is a significant  
48 omission as lithium is considered the gold-standard first-line treatment for bipolar  
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3 disorder (1,13,14). The determinants of adherence may be different among patients  
4 taking lithium relative to other antipsychotics due to a variety of factors including  
5 regular blood test requirements of lithium, dietary restrictions and significant  
6 interactions with other medications. Thus, a systematic review without the date limits  
7 of the previous systematic review (12) is warranted to better represent the mood  
8 stabilisers which were the mainstay of treatment in the earlier decades not included  
9 in the previous review and to identify emerging research (15).  
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20 The dearth of adherence evidence syntheses in the mental health setting  
21 underpinned by health psychology theory (12,16–18) is of concern given its  
22 importance for informing intervention design and implementation (9,10). The  
23 Theoretical Domains Framework (TDF) is a comprehensive framework capturing 33  
24 theories and 84 theoretical constructs related to behaviour change (19). The TDF  
25 comprises fourteen domains each of which has been coupled with evidence based  
26 behaviour change techniques (20). The TDF therefore offers an appropriate theory  
27 for underpinning an evidence synthesis of determinants of adherence as it will  
28 enable determinants to be linked to evidence-based behaviour change techniques.  
29 This in turn will inform the development of an adherence intervention to support  
30 practitioners and patients to work together in identifying an individual's key  
31 determinants of adherence and select the most appropriate evidence-based  
32 interventions.  
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52 The perspective of patients, carers and healthcare professionals often differ in terms  
53 of the determinants of medication adherence due to differing priorities and  
54 knowledge of the situation (16,21–24). For example, the healthcare professional is  
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3 generally the expert regarding how the medication should be taken whilst the patient  
4 and carer are the experts in the patient's lived experience of taking or trying to take  
5 the prescribed medication. Furthermore, some determinants are not modifiable such  
6 as sex, age and ethnicity, and therefore have no related specific evidence-based  
7 behaviour change techniques.  
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17 We will explore the modifiable determinants of medication adherence among  
18 patients with bipolar disorder from the perspectives of the patient, carer, health care  
19 professional and other third parties such as researchers.  
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### 23 24 25 26 27 **Aim**

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30 To identify modifiable determinants of medication adherence in the treatment of  
31 bipolar disorder.  
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### 38 39 **Objectives**

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- 42 • To compare primary (participant reported) and secondary (author  
43 interpreted) determinants of medication adherence.
  - 44 • To describe the determinants of medication adherence from the perspectives  
45 of patients, carers, health care professionals and any other third parties.
  - 46 • To map reported determinants of medication adherence to the domains of  
47 the Theoretical Domains Framework.  
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## Method

This research protocol is based on ENhancing Transparency in REporting the synthesis of Qualitative research (ENTREQ) (25) and Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols (PRISMA-P) (26). The protocol is registered with PROSPERO- [www.crd.york.ac.uk/PROSPERO/](http://www.crd.york.ac.uk/PROSPERO/) - international prospective register of systematic reviews (Study registration number: PROSPERO CRD42018096306).

Figure 1 shows the PRISMA Flow Diagram and Figure 2 represents process and people involvement in the systematic review.

## Evidence Synthesis

We will use the TDF as an *a priori* framework for our review. We will code the data extracted from the included studies to the domains of this framework. The deductive approach of this framework synthesis method (27–30) has the potential to restrict the nature of identified determinants. However, the comprehensive nature of the TDF should enable identification of all determinants relevant to behaviour change and any determinants which cannot be mapped to a TDF domain will still be extracted and mapped to new domains if appropriate (31). A further benefit of mapping determinants to the TDF is its linkage to behaviour change techniques (17). This early identification of relevant behaviour change techniques affords a substantial

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3 advantage in terms of informing the design of theory and evidence-based medication  
4 adherence interventions for people prescribed medication for bipolar disorder.  
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### 8 **Approach to searching, search strategy and data sources**

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10 We will employ a pre-planned search strategy to seek all relevant studies. Our  
11 search strategy will consist of three parameters: disease (bipolar disorder), treatment  
12 (medication) and outcome (adherence). Following a scoping exercise of search  
13 terms (on Pubmed, Medline and Embase) to define our search strategy, we decided  
14 to use the MeSH (Medical Subject Heading) terms "Treatment Adherence and  
15 Compliance", "Bipolar Disorder" AND "Psychotropic Drugs" for our search. We will  
16 adapt these search terms for the databases that do not permit MeSH terms or uses  
17 different MeSH terms.  
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30 We will search the following databases: CINAHL, Cochrane Library (CENTRAL),  
31 Embase, LiLACS, Medline, PsychINFO, Pubmed and the reference list of all  
32 included studies will be reviewed for any further relevant studies.  
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### 40 **Study Inclusion criteria**

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42 We will include any primary studies (both qualitative and quantitative) explicitly  
43 reporting one or more determinants of medication adherence in the maintenance  
44 treatment of bipolar disorders from the perspective of patients, carers, clinicians or  
45 any other third parties. There will be no language or date restrictions. We will include  
46 studies of patients aged 18 years or over with bipolar disorder with or without other  
47 co-morbidities including dual diagnosis, other mental or physical health conditions to  
48 represent the real-world patient population. We will exclude reviews, letters,  
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3 editorials, commentaries, opinion pieces, clinical guidelines or general disease  
4 management articles and studies not in humans. We will also exclude studies  
5 involving short-term treatment of acute agitation or treatment other than medication  
6 such as psychotherapy.  
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## 11 **Study screening methods**

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18 Screening of studies for inclusion in this review will involve three distinct stages:  
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22 I. Title Screening: After removal of duplicates using the reference manager  
23 software Mendeley, the remaining studies will be screened for their  
24 relevance to the review. Definite non-relevant studies will be excluded while  
25 relevant, or unclear studies will be retained for abstract screening.  
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- 33 II. Abstract Screening: Abstracts of the remaining studies, will be screened by  
34 the primary reviewer (AP) and a second reviewer independently to identify  
35 studies that potentially meet the inclusion criteria outlined above. Any  
36 disagreement between the two reviewers will be resolved through further  
37 discussion and referral to a third reviewer (DB) if there is a failure to achieve  
38 agreement.  
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- 48 III. Full Article Screening: Full articles will be reviewed independently by two  
49 reviewers using pre-defined inclusion/exclusion criteria. Any disagreement  
50 between two reviewers will be resolved through discussion or the  
51 involvement of the third reviewer. We will use appropriate statistics to report  
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3 the level of agreement between 1<sup>st</sup> and 2<sup>nd</sup> reviewers in both stages 2 and  
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5 stage 3 of screening.  
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9 Within published syntheses of qualitative research there is often a lack of  
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11 transparency about the search processes employed, with neither the search strategy  
12  
13 nor databases detailed (25). For a comprehensive approach, we will use the  
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15 PRISMA flowchart (see fig 1 below) for reporting the different phases of searching,  
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17 screening and identifying studies for inclusion in the qualitative synthesis as  
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19 recommended by ENTREQ (25).  
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### 28 29 **Data extraction**

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32 Data related to determinants of adherence will be extracted verbatim from the  
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34 included studies by two reviewers independently. We will extract the determinants of  
35  
36 adherence from the results as well as discussion and conclusion sections to include  
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38 both primary (participant reported) and secondary (author interpreted) determinants.  
39  
40 If needed we will contact the corresponding author of the included study for any  
41  
42 missing data.  
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46 We plan to use bespoke Microsoft Excel 2016 to screen retrieved studies and the  
47  
48 computer software program Nvivo 12 (32) to extract data and to map the  
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50 determinants of medication adherence to the domains of the TDF. Extracted  
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52 information will include study characteristics (e.g. title, year of publication, country,  
53  
54 population, number of participants, data collection methodology, analysis, and  
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3 research questions), determinants of medication adherence in patients with bipolar  
4 disorder. The lead reviewer (AP) and second reviewers will extract the data  
5 independently and any disagreement between reviewers will be resolved through  
6 discussion or the involvement of the third reviewer.  
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## 10 **Mapping**

11 We will map each extracted determinant to one of the following domains of the TDF:

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14 1) Knowledge, 2) Skills, 3) Social Influences, 4) Memory, Attention and Decision  
15 Processes, 5) Behavioural Regulation, 6) Professional/Social Role and Identity, 7)  
16 Beliefs about Capabilities, 8) Belief about Consequences, 9) Optimism, 10)  
17 Intentions, 11) Goals, 12) Emotion, 13) Environmental Context and Resources and  
18 14) Reinforcement. We will use constructs within the domains and construct  
19 definitions of the TDF (19) to inform mapping decisions. Any determinants that do  
20 not fit within the existing domains will be organised into new domains as appropriate  
21 (31).  
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54 We will pilot mapping of the determinants from at least one study before embarking  
55 on full-scale mapping. Mapping will be led by two reviewers (AP and 2<sup>nd</sup> reviewer)  
56 independently. Any disagreement between reviewers will be resolved through  
57 discussion or the involvement of the third reviewer. We will report the level of  
58 agreement between two reviewers as well as resolutions to any discrepancies for  
59 transparency.  
60

## 61 **Quality assessment**

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3 No studies will be excluded based on quality as our aim is to identify determinants of  
4 medication adherence as comprehensively as possible. However, we will undertake  
5 a quality assessment for the purposes of characterising included studies. There is no  
6 gold standard tool for any study design, nor is there any widely accepted generic  
7 quality assessment tool that functions across multiple study types (33). We will use  
8 bespoke Critical Appraisal Skills Programme qualitative (CASP) (34), Critical  
9 appraisal of survey (35) and Cochrane risk of bias tool (36) to critically appraise  
10 qualitative studies, surveys and trials respectively. These tools meet the  
11 requirements of the study and provide key quality criteria such as validity, reliability  
12 and objectivity (37). Quality assessment will be carried out by two independent  
13 reviewers. Any disagreement between reviewers will be resolved through discussion  
14 and if necessary, referral to a third reviewer for arbitration.  
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## 38 **Results**

39 We will present the results as per the PRISMA flow diagram. We will report study  
40 and participants characteristics. We will describe the review findings in accordance  
41 with our objectives: including study comparison within and across studies;  
42 comparison of determinants from the perspectives of patients, carers and healthcare  
43 professionals; and mapping of those determinants to the domains of the TDF.  
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3 Quality assessment will be presented as a table using the questionnaires from the  
4 quality assessment tools namely, CASP qualitative (34), Appraisal of Survey (35)  
5 and Cochrane risk of bias (36).  
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10  
11 **Ethics and dissemination:** Ethical approval is not required as primary data will not  
12 be collected. The results will be disseminated through a peer-reviewed publication.  
13  
14

15  
16 **Funding statement:** This research is a part of the Clinical Doctoral Research  
17 Fellowship program funded by Health Education England / National Institute of  
18 Health Research. The funder has no role in the development of this protocol.  
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21  
22 **Competing interest statement:** Mr Prajapati reports personal fees from Accession  
23 Healthcare Consulting Ltd for research participation, outside the submitted work.  
24  
25

26  
27 **Author's contribution:** All authors helped conceive the study. AP and DB designed,  
28 wrote and reviewed the protocol. AP registered the study with PROSPERO. All other  
29 authors reviewed the protocol. All authors have approved the publication of this  
30 protocol.  
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Figure 1: PRISMA flow diagram

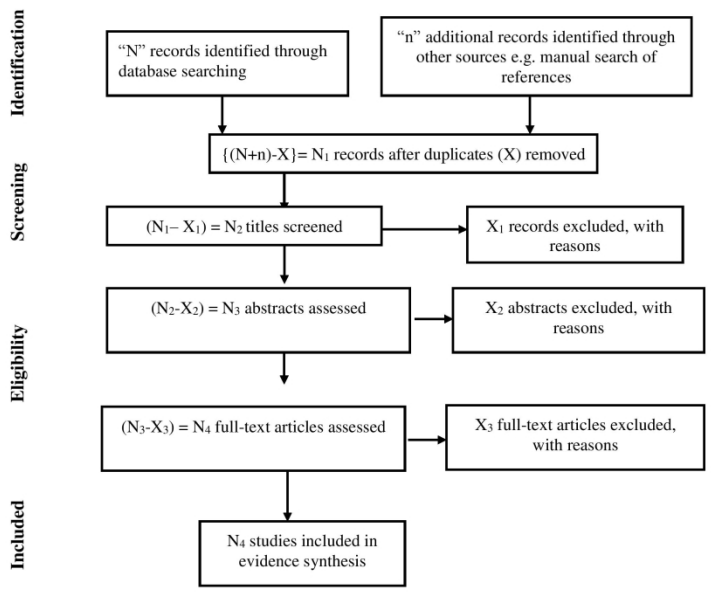


Figure 1 Prisma Flow Diagram  
210x297mm (300 x 300 DPI)

Figure 2: Processes and people involved

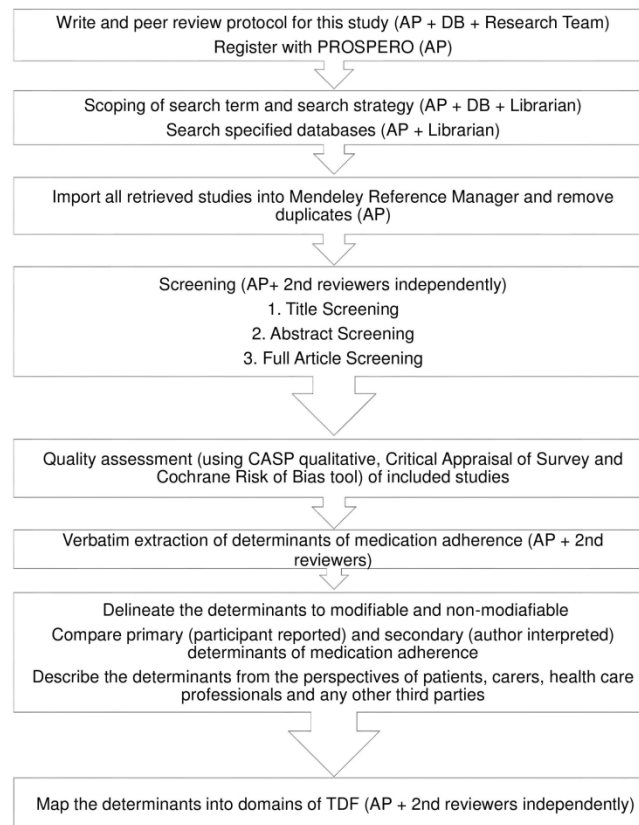


Figure 2 Process and People

210x297mm (300 x 300 DPI)

**Table 1: Enhancing transparency in reporting the synthesis of qualitative research: the ENTREQ statement**

**Reference:** Tong A, Flemming K, McInnes E, Oliver S, Craig J. Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ. BMC Med Res Methodol. 2012;12(181). Available from: <https://bmcmedresmethodol.biomedcentral.com/track/pdf/10.1186/1471-2288-12-181>

No	Item	Guide and description	Reported on Manuscript Page no.
1	Aim	State the research question the synthesis addresses. <hr/>	6
2	Synthesis methodology	Identify the synthesis methodology or theoretical framework which underpins the synthesis, and describe the rationale for choice of methodology ( <i>e.g. meta-ethnography, thematic synthesis, critical interpretive synthesis, grounded theory synthesis, realist synthesis, meta-aggregation, meta-study, framework synthesis</i> ). <hr/>	7
3	Approach to searching	Indicate whether the search was pre-planned ( <i>comprehensive search strategies to seek all available studies</i> ) or iterative ( <i>to seek all available concepts until they theoretical saturation is achieved</i> ). <hr/>	8

No	Item	Guide and description	Reported on Manuscript Page no.
4	Inclusion criteria	Specify the inclusion/exclusion criteria ( <i>e.g. in terms of population, language, year limits, type of publication, study type</i> ).	8-9
5	Data sources	Describe the information sources used ( <i>e.g. electronic databases (MEDLINE, EMBASE, CINAHL, psycINFO, Econlit), grey literature databases (digital thesis, policy reports), relevant organisational websites, experts, information specialists, generic web searches (Google Scholar) hand searching, reference lists</i> ) and when the searches conducted; provide the rationale for using the data sources.	8
6	Electronic Search strategy	Describe the literature search ( <i>e.g. provide electronic search strategies with population terms, clinical or health topic terms, experiential or social phenomena related terms, filters for qualitative research, and search limits</i> ).	8-9
7	Study screening methods	Describe the process of study screening and sifting ( <i>e.g. title, abstract and full text review, number of independent reviewers who screened studies</i> ).	9



No	Item	Guide and description	Reported on Manuscript Page no.
8	Study characteristics	Present the characteristics of the included studies ( <i>e.g. year of publication, country, population, number of participants, data collection, methodology, analysis, research questions</i> ).	12
9	Study selection results	Identify the number of studies screened and provide reasons for study exclusion ( <i>e.g. for comprehensive searching, provide numbers of studies screened and reasons for exclusion indicated in a figure/flowchart; for iterative searching describe reasons for study exclusion and inclusion based on modifications to the research question and/or contribution to theory development</i> ).	11
10	Rationale for appraisal	Describe the rationale and approach used to appraise the included studies or selected findings ( <i>e.g. assessment of conduct (validity and robustness), assessment of reporting (transparency), assessment of content and utility of the findings</i> ).	13
11	Appraisal items	State the tools, frameworks and criteria used to appraise the studies or selected findings ( <i>e.g. Existing tools: CASP, QARI, COREQ, Mays and Pope [25]; reviewer developed tools; describe the domains assessed: research team, study design, data analysis and</i>	13

No	Item	Guide and description	Reported on Manuscript Page no.
		<i>interpretations, reporting).</i>	
12	Appraisal process	Indicate whether the appraisal was conducted independently by more than one reviewer and if consensus was required.	13
13	Appraisal results	Present results of the quality assessment and indicate which articles, if any, were weighted/excluded based on the assessment and give the rationale.	13
14	Data extraction	Indicate which sections of the primary studies were analysed and how were the data extracted from the primary studies? ( <i>e.g. all text under the headings “results /conclusions” were extracted electronically and entered into a computer software</i> ).	11-12
15	Software	State the computer software used, if any.	12

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No	Item	Guide and description	Reported on Manuscript Page no.
16	Number of reviewers <hr/>	Identify who was involved in coding and analysis. <hr/>	12
17	Coding <hr/>	Describe the process for coding of data ( <i>e.g. line by line coding to search for concepts</i> ). <hr/>	12
18	Study comparison <hr/>	Describe how were comparisons made within and across studies ( <i>e.g. subsequent studies were coded into pre-existing concepts, and new concepts were created when deemed necessary</i> ). <hr/>	11
19	Derivation of themes <hr/>	Explain whether the process of deriving the themes or constructs was inductive or deductive. <hr/>	7
20	Quotations <hr/>	Provide quotations from the primary studies to illustrate themes/constructs, and identify whether the quotations were participant quotations of the author's interpretation. <hr/>	7

No	Item	Guide and description	Reported on Manuscript Page no.
21	Synthesis output	Present rich, compelling and useful results that go beyond a summary of the primary studies (e.g. <i>new interpretation, models of evidence, conceptual models, analytical framework, development of a new theory or construct</i> ).	7

**Table 2** : PRISMA-P (preferred reporting items for systematic review and meta-analysis protocols) 2015 checklist: recommended items to address in a systematic review protocol)

Reference: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (prisma-p) 2015: Elaboration and explanation. BMJ. 2015;349. Available from: <https://www.bmj.com/content/349/bmj.g7647>

Section and topic	Item No	Checklist item	Reported on Manuscript Page no.
<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	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2 & 7
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	15
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	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	15
Sponsor	5b	Provide name for the review funder and/or sponsor	15
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	15
<b>Introduction</b>			

Section and topic	Item No	Checklist item	Reported on Manuscript Page no.
Rationale	6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
<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	8-9
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	8
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	8
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	12
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)	9
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	11-12
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	12
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	14	Describe anticipated methods for assessing risk of bias of individual studies, including	13

Section and topic	Item No	Checklist item	Reported on Manuscript Page no.
individual studies		whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	NA
	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 $\tau$ )	NA
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	NA
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	NA
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	13

# BMJ Open

## Mapping of modifiable Barriers and Facilitators of Medication Adherence in Bipolar Disorder to the Theoretical Domains Framework (TDF): A Systematic Review Protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-026980.R1
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Date Submitted by the Author:	17-Dec-2018
Complete List of Authors:	Prajapati, Asta; Norfolk and Suffolk NHS Foundation Trust, Pharmacy; University of East Anglia, Pharmacy Dima, Alexandra; University of Lyon Clark, Allan; Norwich Medical School Gant, Claire Gibbons, Chris; Harvard Medical School, Faculty of Medicine Gorrod, Richard Mosa, George; Norfolk and Suffolk NHS Foundation Trust Scott, Sion; University of East Anglia, Pharmacy Song, Fujian; University of East Anglia, Teague, Bonnie; Norfolk and Suffolk NHS Foundation Trust, Research Twigg, Michael; University of East Anglia, School of Pharmacy Wilson, Jon Bhattacharya, Debi; University of East Anglia, School of Pharmacy
<b>Primary Subject Heading</b>:	Mental health
Secondary Subject Heading:	Mental health
Keywords:	Determinant, Compliance, Concordance, psychotropic drug, Mood stabilizer, MENTAL HEALTH

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Manuscripts



# Mapping of modifiable Barriers and Facilitators of Medication Adherence in Bipolar Disorder to the Theoretical Domains Framework (TDF): A Systematic Review Protocol

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1= Norfolk and Suffolk NHS Foundation NHS Trust, 2 = University of East Anglia, 3= University of Lyon, 4 = Harvard University, 5 = Patient and carer representatives

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## Abstract

**Introduction:** People with bipolar disorder require long-term treatment but an estimated 40% of these people do not adhere to prescribed medication regimens. Non-adherence increases the risk of relapse, hospitalisation and suicide. Some evidence syntheses report barriers to mental health treatment adherence but rarely delineate between modifiable and non-modifiable barriers. They also fail to distinguish between the patient perspective and that of other stakeholders such as clinicians despite their differing understanding and priorities about adherence. Facilitators of adherence, which are also important for informing adherence intervention design are also lacking from syntheses and few syntheses focus on medications for bipolar disorder.

This systematic review aims to identify modifiable barriers and facilitators (determinants) of medication adherence in bipolar disorder. We also plan to report determinants of medication adherence from perspectives of patients, carers, healthcare professionals and other third parties. A unique feature of this systematic review in the context of mental health is the use of the Theoretical Domains Framework (TDF) to organise the literature identified determinants of medication adherence.

**Methods, Synthesis and Result Presentation:** The protocol adheres to Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols (PRISMA-P) and ENhancing Transparency in REporting the synthesis of Qualitative research

(ENTREQ) guidelines. The review will include both qualitative and quantitative primary studies exploring determinants of medication adherence in bipolar disorder. We will search following databases using a pre-planned strategy: CINAHL, Cochrane Library (CENTRAL), Embase, LiLACS, Medline, PsychINFO, PubMed without date restrictions. We will report the quality of included studies. We will use framework synthesis using the Theoretical Domains Framework (TDF) as an *a priori* 'framework'. We will map literature identified modifiable determinants to the domains of TDF and report the results using ENTREQ guidelines and PRISMA statement.

Study registration number: PROSPERO CRD42018096306

### **Keywords**

Determinant, compliance, concordance, psychotropic drug, mood stabilizer, mental health

### **Strengths and limitations of this study**

- As the Theoretical Domains Framework (TDF) has been mapped to evidence-based behaviour change techniques, mapping modifiable determinants of medication adherence in bipolar disorder to the TDF offer significant utility for intervention development.
- This study will provide literature-identified barriers and facilitators (determinants) of medication adherence in bipolar disorder from the perspectives of patients, carers, healthcare professionals and other third parties such as researchers.
- Lack of data and quality of reporting may limit our ability to present determinants of adherence from perspectives of patients, carers, healthcare professionals and other third parties as clearly as we would like.
- Variation in the terms used to describe determinants of adherence may introduce a risk of mapping errors through misinterpretation of the reported barrier or facilitator.

## Introduction

The lifetime prevalence of bipolar disorder is estimated at 1.4% of the UK adult population (1). Bipolar disorder featuring mood and activity level disturbance is a recurrent disorder and usually requires long-term maintenance therapy (1,2). However, an estimated 40% of people with bipolar disorder do not take their medication as prescribed (3). This non-adherence (generally described as taking less than 80% of prescribed doses of medication) (4) increases the risk of relapse, suicide and rehospitalisation (5,6). For example, the probability of hospitalisation in non-adherent patients with bipolar disorder is at least five times higher than adherent patients (7).

Adhering to prescribed medication regimes is a complex health behaviour which requires the patient to obtain the prescribed medication, have the physical and cognitive ability (practical function), and motivation (perceptual function) to take the medication. Furthermore, non-adherence may occur at initiation (i.e. patient may or may not start the treatment), implementation (i.e. patient may delay, omit or take extra doses during treatment) or persistence (i.e. patient may discontinue treatment after some time) phase (8). There are many reported barriers and facilitators (determinants) of medication adherence. For this review, a barrier is defined as “a circumstance that prevents the patient from taking their medication as prescribed”, whereas a facilitator is “a circumstance that makes the process easy or easier” (9). We are calling these barriers and facilitators “determinants”.

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3 The challenges to successfully addressing non-adherence are to:  
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- 5 1. Accurately identify non-adherent patients
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- 7 2. Determine individuals' determinants of medication adherence
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- 10 3. Select the most appropriate individualised adherence intervention(s) underpinned
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- 12 by health psychology theory and empirical evidence (10,11).
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17 There are various objective (e.g. drug plasma levels, pill counts and electronic  
18 monitoring of medication adherence such as medication event monitoring systems)  
19 and subjective (e.g. self-reported, carer or relative reported, clinician reported  
20 adherence rating scales) approaches to identifying patients not adhering to their  
21 prescribed medication for bipolar disorder (12). However, there are no validated tools  
22 for comprehensively eliciting from patients and/or their carers their individual  
23 determinants of adherence to their prescribed medication for bipolar disorder. There  
24 is also an absence of theory and evidence informed guidance for practitioners to work  
25 with patients in selecting the most effective interventions for identified determinants of  
26 an individual's non-adherent behaviour.  
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43 In order to generate such a tool, there is, therefore, a need to synthesize the available  
44 evidence regarding determinants of medication adherence in patients with bipolar  
45 disorder.  
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52 A recent systematic review (literature search restricted to 1990 - 2015) of adherence  
53 to antipsychotic medication in bipolar disorder and schizophrenia has provided a good  
54 overview of the likely barriers experienced by people with bipolar disorder (13).  
55 However, it failed to explore factors that might facilitate adherence and excluded  
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3 studies involving medication other than antipsychotics, and therefore did not identify  
4 determinants of adherence to lithium and other mood stabilisers. This is a significant  
5 omission as lithium is considered the gold-standard first-line treatment for bipolar  
6 disorder (1,14,15). The determinants of adherence may be different among patients  
7 taking lithium relative to other antipsychotics due to a variety of factors including  
8 regular blood test requirements of lithium, dietary restrictions and significant  
9 interactions with other medications. Thus, a systematic review without the date limits  
10 of the previous systematic review (13) is warranted to better represent the mood  
11 stabilisers which were the mainstay of treatment in the earlier decades not included in  
12 the previous review and to identify emerging research (16).  
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29 The dearth of adherence evidence syntheses in the mental health setting underpinned  
30 by health psychology theory (13,17–19) is of concern given its importance for  
31 informing intervention design and implementation (10,11). The Theoretical Domains  
32 Framework (TDF) is a comprehensive framework capturing 33 theories and 84  
33 theoretical constructs related to behaviour change (20). The TDF comprises fourteen  
34 domains each of which has been coupled with evidence based behaviour change  
35 techniques (21). The TDF therefore offers an appropriate theory for underpinning an  
36 evidence synthesis of determinants of adherence as it will enable determinants to be  
37 linked to evidence-based behaviour change techniques. This in turn will inform the  
38 development of an adherence intervention to support practitioners and patients to work  
39 together in identifying an individual's key determinants of adherence and select the  
40 most appropriate evidence-based interventions.  
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3 The perspective of patients, carers and healthcare professionals often differ in terms  
4 of the determinants of medication adherence due to differing priorities and knowledge  
5 of the situation (17,22–25). For example, the healthcare professional is generally the  
6 expert regarding how the medication should be taken whilst the patient and carer are  
7 the experts in the patient's lived experience of taking or trying to take the prescribed  
8 medication. Furthermore, some determinants are not modifiable such as sex, age and  
9 ethnicity, and therefore have no related specific evidence-based behaviour change  
10 techniques.  
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26 A literature review matching adherence interventions to determinants of adherence  
27 concluded that adherence interventions are often not congruent with the modifiable  
28 determinants of adherence (26). We will explore the modifiable determinants of  
29 medication adherence among patients with bipolar disorder from the perspectives of  
30 the patient, carer, health care professional and other third parties such as researchers.  
31 For the purpose of this systematic review we define modifiable as “any determinants  
32 (barriers or facilitators) of medication adherence that can be modified by the patient,  
33 carer or the prescriber to improve adherence. Modifiable in the context of an individual  
34 being able to effect the change themselves or in partnership with their carer or  
35 healthcare team within a short timeframe.”  
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52 For example, knowledge about the condition / treatment can be changed within days  
53 or weeks. In contrast, whilst substance abuse can be changed over an extended  
54 period, a change is unlikely to be achievable within the timeframes acceptable for  
55 improving adherence.  
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3 This systematic review is a part of the Collaborative Medication Adherence in Bipolar  
4 disorder (C-MAB) project funded by Health Education England / National Institute of  
5 Health Research UK. The C-MAB project aims to develop a medication adherence  
6 tool for people with bipolar disorder. The tool is intended to both identify non-adherent  
7 behaviour and the individual's determinants of non-adherence. Following the  
8 systematic review we will develop the tool in the form of statements derived from the  
9 literature identified modifiable determinants of adherence. We will then refine the  
10 statements by conducting focus groups and interviews with patients with bipolar  
11 disorder and their carers to better understand and prioritise the literature identified  
12 modifiable determinants. After appropriate refinement, the tool will be tested with  
13 patients with bipolar disorder.  
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## 32 **Aim**

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35 To identify modifiable determinants of medication adherence in the treatment of  
36 bipolar disorder.  
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## 44 **Objectives**

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47 • To describe the modifiable determinants of medication adherence from the  
48 perspectives of patients, carers, health care professionals and any other  
49 third parties.  
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54 • To map reported modifiable determinants of medication adherence to the  
55 domains of the TDF.  
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## Method

This research protocol is based on ENhancing Transparency in REporting the synthesis of Qualitative research (ENTREQ) (27) and Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols (PRISMA-P) (28). The protocol is registered with PROSPERO- [www.crd.york.ac.uk/PROSPERO/](http://www.crd.york.ac.uk/PROSPERO/) - international prospective register of systematic reviews (Study registration number: PROSPERO CRD42018096306).

## Evidence Synthesis

We will use the TDF as an *a priori* framework for our review. We will map the extracted modifiable determinants of adherence from the included studies to the domains of the TDF. The deductive approach of this framework synthesis method (29–32) has the potential to restrict the nature of identified determinants. However, the comprehensive nature of the TDF should enable identification of all determinants relevant to behaviour change and any determinants which cannot be mapped to a TDF domain will still be extracted and mapped to new domains if appropriate (33). A further benefit of mapping determinants to the TDF is its linkage to behaviour change techniques (17). This approach was successfully applied by Allemann and colleagues to match adherence interventions to patient determinants of adherence (26). This early identification of relevant behaviour change techniques affords a substantial advantage in terms of informing the design of theory and evidence-based medication adherence interventions for people prescribed medication for bipolar disorder.



### **Approach to searching, search strategy and data sources**

We will employ a pre-planned search strategy to seek all relevant studies. Our search strategy will consist of three parameters: disease (bipolar disorder), treatment (medication) and outcome (adherence). Following a scoping exercise of search terms (on Pubmed, Medline and Embase) to define our search strategy, we decided to use the MeSH (Medical Subject Heading) terms "Treatment Adherence and Compliance", "Bipolar Disorder" AND "Psychotropic Drugs" for our search. We will adapt these search terms for the databases that do not permit MeSH terms or uses different MeSH terms.

We will search the following databases: CINAHL, Cochrane Library (CENTRAL), Embase, LiLACS, Medline, PsychINFO, Pubmed and the reference list of all included studies will be reviewed for any further relevant studies.

### **Study Inclusion criteria**

We will include any primary studies; both qualitative and quantitative e.g. focus groups, interviews and surveys; explicitly reporting one or more modifiable determinants of medication adherence in the maintenance treatment of bipolar disorders from the perspective of patients, carers, healthcare professionals or any other third parties. explicitly reporting one or more modifiable determinants of medication adherence in the maintenance treatment of bipolar disorders from the perspective of patients, carers, clinicians or any other third parties. There will be no date restrictions. We will include studies of patients aged 18 years or over with bipolar disorder with or without other co-morbidities including dual diagnosis, other mental or physical health

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3 conditions to represent the real-world patient population. We will exclude reviews,  
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5 intervention studies to improve adherence, case reports, letters, editorials,  
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7 commentaries, opinion pieces, clinical guidelines or general disease management  
8  
9 articles and studies not in humans. We will also exclude studies involving short-term  
10  
11 treatment of acute agitation or treatment other than medication such as  
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13 psychotherapy. Studies where effect of individual barriers/facilitators to adherence  
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15 could not be isolated / extracted from composite measures (such as adherence rating  
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17 scale) will be excluded.  
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### 26 **Study screening methods**

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28 We will use computer software Covidence (34); an online systematic review program;  
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30 for screening retrieved studies. Screening of studies for inclusion in this review will  
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32 involve three distinct stages:  
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- 38 I. Title Screening: After removal of duplicates using the reference manager  
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40 software Mendeley, the remaining studies will be screened for their relevance  
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42 to the review. Definite non-relevant studies will be excluded while relevant, or  
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44 unclear studies will be retained for abstract screening.  
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- 49 II. Abstract Screening: Abstracts of the remaining studies will be screened by the  
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51 primary reviewer (AP) and second reviewers (CG, DB, FS, GM, JW and SS)  
52  
53 independently to identify studies that potentially meet the inclusion criteria  
54  
55 outlined above. Any disagreement between the two reviewers will be  
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3 resolved through further discussion and referral to a third reviewer (DB) if  
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5 there is a failure to achieve agreement.  
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10 III. Full Article Screening: Full articles will be reviewed independently by two  
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12 reviewers (AP, CG, DB, FS, GM, JW and SS) using pre-defined  
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14 inclusion/exclusion criteria. Any disagreement between two reviewers will  
15  
16 be resolved through discussion or the involvement of the third reviewer. We  
17  
18 will use Cohen's kappa to report the level of agreement between 1<sup>st</sup> and 2<sup>nd</sup>  
19  
20 reviewers.  
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26 Within published syntheses of qualitative research there is often a lack of transparency  
27  
28 about the search processes employed, with neither the search strategy nor databases  
29  
30 detailed (27). For a comprehensive approach, we will use the PRISMA flowchart for  
31  
32 reporting the different phases of searching, screening and identifying studies for  
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34 inclusion in the qualitative synthesis as recommended by ENTREQ (27).  
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#### 40 **Data extraction and mapping**

41  
42 We will use the computer software program Nvivo 12 (35) to extract data and to map  
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44 the modifiable determinants of medication adherence to the domains of the TDF. While  
45  
46 medication adherence is generally described as taking  $\geq 80\%$  doses of prescribed  
47  
48 medications some studies report adherence in gradient terms (e.g. good, moderate,  
49  
50 low adherence and non-adherence) (4). Yet, in some cases (e.g. in HIV) adherence  
51  
52 means taking  $\geq 95\%$  doses of prescribed medications (36)(36). Acknowledging this  
53  
54 wide variation on definition of medication adherence we will report the definition used  
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56 for adherence in included studies for transparency and comparison among studies.  
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Extracted information will include study characteristics (e.g. title, year of publication, country, study design, population, number of participants, definition and rate of adherence) and modifiable determinants of medication adherence in patients with bipolar disorder.

We will map each extracted determinant to one of the following domains of the TDF:

1) Knowledge, 2) Skills, 3) Social Influences, 4) Memory, Attention and Decision Processes, 5) Behavioural Regulation, 6) Professional/Social Role and Identity, 7) Beliefs about Capabilities, 8) Belief about Consequences, 9) Optimism, 10) Intentions, 11) Goals, 12) Emotion, 13) Environmental Context and Resources and 14) Reinforcement. We will use constructs within the domains and construct definitions of the TDF (20) to inform mapping decisions. Any determinants that do not fit within the existing domains will be organised into an “Others” domain (33).

Within Nvivo12 we will create four themes in line with the aim of the study:

1. Patient Perspective
2. Carers Perspective
3. HealthCare Professional Perspective
4. Others Perspectives

Within each theme we will create two sub-themes (Barriers and Facilitators) and within each of these sub-themes we will create 15 domains (14 TDF plus “Others”).

Two reviewers will pilot data extraction and coding of determinants of adherence to the domains of TDF from four studies. For example, if the following text were extracted from a study “Forgetting to take medication or being careless at times about taking

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3 medication was reported to be experienced by x participants”, this would be coded to  
4 the TDF domain “Memory, attention and decision process”. The reviewers will then  
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6 compare and discuss their coding to generate consensus in interpretation of literature-  
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8 identified determinants. After piloting, all data will be extracted by one reviewer and  
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10 independently checked by second reviewer for completeness.  
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17 All extracted determinants will be independently mapped onto the 14 domains of the  
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19 TDF or “Others” category by two reviewers. The two reviewers will meet and discuss  
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21 their mapping regularly. Any disagreement in mapping will be resolved through  
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23 discussion between the two reviewers and referral to a third reviewer as adjudicator if  
24  
25 the two reviewers fail to agree. We will use Cohen’s kappa to report agreement  
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27 between the 1st and 2nd reviewers as we are dealing with nominal data i.e. agreement  
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29 or not with the domain to which a determinant is mapped onto the TDF.  
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### 36 **Quality assessment**

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39 No studies will be excluded based on quality as our aim is to identify determinants of  
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41 medication adherence as comprehensively as possible. However, we will undertake a  
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43 quality assessment for the purposes of characterising included studies. There is no  
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45 gold standard tool for any study design, nor is there any widely accepted generic  
46  
47 quality assessment tool that functions across multiple study types (37). We will use  
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49 bespoke Critical Appraisal Skills Programme qualitative (CASP) (38), Critical appraisal  
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51 of survey (39) and Cochrane risk of bias tool (40) to critically appraise qualitative  
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53 studies, surveys and trials respectively. These tools meet the requirements of the  
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55 study and provide key quality criteria such as validity, reliability and objectivity (41).  
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58 Quality assessment will be carried out by two independent reviewers. Any  
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3 disagreement between reviewers will be resolved through discussion and if necessary,  
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5 referral to a third reviewer for arbitration.  
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## 10 **Patient and Public Involvement (PPI)**

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12 This systematic review is a part of the C-MAB project which include three patients  
13 and a carer as research advisory board members. PPI has influenced the study  
14 design with two notable recommendations: inclusion of the carer's perspective on  
15 medication adherence and differentiating between modifiable from non-modifiable  
16 determinants of medication adherence. Two PPI representatives (CG and RG) are  
17 listed as authors.  
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30 **Ethics and dissemination:** Ethical approval is not required as primary data will not  
31 be collected. The results will be disseminated through a peer-reviewed publication.  
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34 **Funding statement:** This research is a part of the Clinical Doctoral Research  
35 Fellowship program funded by Health Education England / National Institute of Health  
36 Research. The funder has no role in the development of this protocol.  
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41 **Competing interest statement:** No, there are no competing interest for any authors.  
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45 **Author's contribution:** All authors (AP, AD, AC, CG5, CG4, RG, GM, SS, FS, BM,  
46 MT, JW and DB) helped conceive the study, reviewed the protocol and provided  
47 intellectual critique. AP and DB designed and wrote the protocol. AP registered the  
48 study with PROSPERO. All authors (AP, AD, AC, CG5, CG4, RG, GM, SS, FS, BM,  
49 MT, JW and DB) have approved the publication of this protocol.  
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**Table 1: Enhancing transparency in reporting the synthesis of qualitative research: the ENTREQ statement**

**Reference:** Tong A, Flemming K, McInnes E, Oliver S, Craig J. Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ. BMC Med Res Methodol. 2012;12(181). Available from: <https://bmcmedresmethodol.biomedcentral.com/track/pdf/10.1186/1471-2288-12-181>

No	Item	Guide and description	Reported on Manuscript Page no.
1	Aim	State the research question the synthesis addresses. <hr/>	6
2	Synthesis methodology	Identify the synthesis methodology or theoretical framework which underpins the synthesis, and describe the rationale for choice of methodology ( <i>e.g. meta-ethnography, thematic synthesis, critical interpretive synthesis, grounded theory synthesis, realist synthesis, meta-aggregation, meta-study, framework synthesis</i> ). <hr/>	7
3	Approach to searching	Indicate whether the search was pre-planned ( <i>comprehensive search strategies to seek all available studies</i> ) or iterative ( <i>to seek all available concepts until they theoretical saturation is achieved</i> ). <hr/>	8

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No	Item	Guide and description	Reported on Manuscript Page no.
4	Inclusion criteria <hr/>	Specify the inclusion/exclusion criteria ( <i>e.g. in terms of population, language, year limits, type of publication, study type</i> ). <hr/>	8-9
5	Data sources <hr/>	Describe the information sources used ( <i>e.g. electronic databases (MEDLINE, EMBASE, CINAHL, psycINFO, Econlit), grey literature databases (digital thesis, policy reports), relevant organisational websites, experts, information specialists, generic web searches (Google Scholar) hand searching, reference lists</i> ) and when the searches conducted; provide the rationale for using the data sources. <hr/>	8
6	Electronic Search strategy <hr/>	Describe the literature search ( <i>e.g. provide electronic search strategies with population terms, clinical or health topic terms, experiential or social phenomena related terms, filters for qualitative research, and search limits</i> ). <hr/>	8-9
7	Study screening methods <hr/>	Describe the process of study screening and sifting ( <i>e.g. title, abstract and full text review, number of independent reviewers who screened studies</i> ). <hr/>	9

No	Item	Guide and description	Reported on Manuscript Page no.
8	Study characteristics	Present the characteristics of the included studies ( <i>e.g. year of publication, country, population, number of participants, data collection, methodology, analysis, research questions</i> ).	12
9	Study selection results	Identify the number of studies screened and provide reasons for study exclusion ( <i>e.g. for comprehensive searching, provide numbers of studies screened and reasons for exclusion indicated in a figure/flowchart; for iterative searching describe reasons for study exclusion and inclusion based on modifications to the research question and/or contribution to theory development</i> ).	11
10	Rationale for appraisal	Describe the rationale and approach used to appraise the included studies or selected findings ( <i>e.g. assessment of conduct (validity and robustness), assessment of reporting (transparency), assessment of content and utility of the findings</i> ).	13
11	Appraisal items	State the tools, frameworks and criteria used to appraise the studies or selected findings ( <i>e.g. Existing tools: CASP, QARI, COREQ, Mays and Pope [25]; reviewer developed tools; describe the domains assessed: research team, study design, data analysis and</i>	13

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No	Item	Guide and description	Reported on Manuscript Page no.
		<i>interpretations, reporting).</i> _____	
12	Appraisal process _____	Indicate whether the appraisal was conducted independently by more than one reviewer and if consensus was required. _____	13
13	Appraisal results _____	Present results of the quality assessment and indicate which articles, if any, were weighted/excluded based on the assessment and give the rationale. _____	13
14	Data extraction _____	Indicate which sections of the primary studies were analysed and how were the data extracted from the primary studies? ( <i>e.g. all text under the headings “results /conclusions” were extracted electronically and entered into a computer software</i> ). _____	11-12
15	Software _____	State the computer software used, if any. _____	12

No	Item	Guide and description	Reported on Manuscript Page no.
16	Number of reviewers _____	Identify who was involved in coding and analysis. _____	12
17	Coding _____	Describe the process for coding of data ( <i>e.g. line by line coding to search for concepts</i> ). _____	12
18	Study comparison _____	Describe how were comparisons made within and across studies ( <i>e.g. subsequent studies were coded into pre-existing concepts, and new concepts were created when deemed necessary</i> ). _____	11
19	Derivation of themes _____	Explain whether the process of deriving the themes or constructs was inductive or deductive. _____	7
20	Quotations _____	Provide quotations from the primary studies to illustrate themes/constructs, and identify whether the quotations were participant quotations of the author's interpretation. _____	7



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No	Item	Guide and description	Reported on Manuscript Page no.
21	Synthesis output	Present rich, compelling and useful results that go beyond a summary of the primary studies (e.g. <i>new interpretation, models of evidence, conceptual models, analytical framework, development of a new theory or construct</i> ).	7

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**Table 2** : PRISMA-P (preferred reporting items for systematic review and meta-analysis protocols) 2015 checklist: recommended items to address in a systematic review protocol)

Reference: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (prisma-p) 2015: Elaboration and explanation. *BMJ*. 2015;349. Available from: <https://www.bmj.com/content/349/bmj.g7647>

Section and topic	Item No	Checklist item	Reported on Manuscript Page no.
<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	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2 & 7
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	15
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	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	15
Sponsor	5b	Provide name for the review funder and/or sponsor	15
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	15
<b>Introduction</b>			

Section and topic	Item No	Checklist item	Reported on Manuscript Page no.
Rationale	6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
<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	8-9
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	8
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	8
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	12
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)	9
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	11-12
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	12
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	14	Describe anticipated methods for assessing risk of bias of individual studies, including	13

Section and topic	Item No	Checklist item	Reported on Manuscript Page no.
individual studies		whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	NA
	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 $\tau$ )	NA
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	NA
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	NA
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	13

# BMJ Open

## Mapping of modifiable Barriers and Facilitators of Medication Adherence in Bipolar Disorder to the Theoretical Domains Framework (TDF): A Systematic Review Protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-026980.R2
Article Type:	Protocol
Date Submitted by the Author:	02-Jan-2019
Complete List of Authors:	Prajapati, Asta; Norfolk and Suffolk NHS Foundation Trust, Pharmacy; University of East Anglia, Pharmacy Dima, Alexandra; University of Lyon Clark, Allan; Norwich Medical School Gant, Claire Gibbons, Chris; Harvard Medical School, Faculty of Medicine Gorrod, Richard Mosa, George; Norfolk and Suffolk NHS Foundation Trust Scott, Sion; University of East Anglia, Pharmacy Song, Fujian; University of East Anglia, Teague, Bonnie; Norfolk and Suffolk NHS Foundation Trust, Research Twigg, Michael; University of East Anglia, School of Pharmacy Wilson, Jon Bhattacharya, Debi; University of East Anglia, School of Pharmacy
<b>Primary Subject Heading</b>:	Mental health
Secondary Subject Heading:	Mental health
Keywords:	Determinant, Compliance, Concordance, psychotropic drug, Mood stabilizer, MENTAL HEALTH

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Manuscripts

# Mapping of modifiable Barriers and Facilitators of Medication Adherence in Bipolar Disorder to the Theoretical Domains Framework (TDF): A Systematic Review Protocol

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## Abstract

**Introduction:** People with bipolar disorder require long-term treatment but an estimated 40% of these people do not adhere to prescribed medication regimens. Non-adherence increases the risk of relapse, hospitalisation and suicide. Some evidence syntheses report barriers to mental health treatment adherence but rarely delineate between modifiable and non-modifiable barriers. They also fail to distinguish between the patient perspective and that of other stakeholders such as clinicians despite their differing understanding and priorities about adherence. Facilitators of adherence, which are also important for informing adherence intervention design are also lacking from syntheses and few syntheses focus on medications for bipolar disorder.

This systematic review aims to identify modifiable barriers and facilitators (determinants) of medication adherence in bipolar disorder. We also plan to report determinants of medication adherence from perspectives of patients, carers, healthcare professionals and other third parties. A unique feature of this systematic review in the context of mental health is the use of the Theoretical Domains Framework (TDF) to organise the literature identified determinants of medication adherence.

**Methods and analysis:** The protocol adheres to Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols (PRISMA-P) and Enhancing Transparency in REporting the synthesis of Qualitative research (ENTREQ)

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3 guidelines. The review will include both qualitative and quantitative primary studies  
4 exploring determinants of medication adherence in bipolar disorder. We will search  
5 following databases using a pre-planned strategy: CINAHL, Cochrane Library  
6 (CENTRAL), Embase, LiLACS, Medline, PsychINFO, PubMed without date  
7 restrictions. We will report the quality of included studies. We will use framework  
8 synthesis using the TDF as an *a priori* 'framework'. We will map the literature identified  
9 modifiable determinants to the domains of TDF.  
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18 **Ethics and dissemination:** Ethical approval is not required as primary data will not  
19 be collected. The results will be disseminated through a peer-reviewed publication.  
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24 Study registration number: PROSPERO CRD42018096306  
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### 29 **Keywords**

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31 Determinant, compliance, concordance, psychotropic drug, mood stabilizer, mental  
32 health  
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### 35 **Strengths and limitations of this study**

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- As the Theoretical Domains Framework (TDF) has been mapped to evidence-based behaviour change techniques, mapping modifiable determinants of medication adherence in bipolar disorder to the TDF offer significant utility for intervention development.
  - This study will provide literature-identified barriers and facilitators (determinants) of medication adherence in bipolar disorder from the perspectives of patients, carers, healthcare professionals and other third parties such as researchers.
  - Lack of data and quality of reporting may limit our ability to present determinants of adherence from perspectives of patients, carers, healthcare professionals and other third parties as clearly as we would like.

- Variation in the terms used to describe determinants of adherence may introduce a risk of mapping errors through misinterpretation of the reported barrier or facilitator.

## Introduction

The lifetime prevalence of bipolar disorder is estimated at 1.4% of the UK adult population (1). Bipolar disorder featuring mood and activity level disturbance is a recurrent disorder and usually requires long-term maintenance therapy (1,2). However, an estimated 40% of people with bipolar disorder do not take their medication as prescribed (3). This non-adherence (generally described as taking less than 80% of prescribed doses of medication) (4) increases the risk of relapse, suicide and rehospitalisation (5,6). For example, the probability of hospitalisation in non-adherent patients with bipolar disorder is at least five times higher than adherent patients (7).

Adhering to prescribed medication regimes is a complex health behaviour which requires the patient to obtain the prescribed medication, have the physical and cognitive ability (practical function), and motivation (perceptual function) to take the medication (8). Furthermore, non-adherence may occur at initiation (i.e. patient may or may not start the treatment), implementation (i.e. patient may delay, omit or take extra doses during treatment) or persistence (i.e. patient may discontinue treatment after some time) phase (9). There are many reported barriers and facilitators (determinants) of medication adherence. For this review, a barrier is defined as “a circumstance that prevents the patient from taking their medication as prescribed”,



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3 whereas a facilitator is “a circumstance that makes the process easy or easier” (10).  
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5 We are calling these barriers and facilitators “determinants”.  
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10 The challenges to successfully addressing non-adherence are to:

- 11 1. Accurately identify non-adherent behaviour
- 12 2. Determine individuals’ determinants of medication adherence
- 13 3. Select the most appropriate individualised adherence intervention(s) underpinned  
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by health psychology theory and empirical evidence (11,12).

There are various objective (e.g. drug plasma levels, pill counts and electronic monitoring of medication adherence such as medication event monitoring systems) and subjective (e.g. self-reported, carer or relative reported, clinician reported adherence rating scales) approaches to identifying patients not adhering to their prescribed medication for bipolar disorder (13). However, there are no validated tools for comprehensively eliciting from patients and/or their carers their individual determinants of adherence to their prescribed medication for bipolar disorder. There is also an absence of theory and evidence informed guidance for practitioners to work with patients in selecting the most effective interventions for identified determinants of an individual’s non-adherent behaviour.

In order to generate such a tool, there is, therefore, a need to synthesize the available evidence regarding determinants of medication adherence in patients with bipolar disorder.

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3 A recent systematic review (literature search restricted to 1990 - 2015) of adherence  
4 to antipsychotic medication in bipolar disorder and schizophrenia has provided a good  
5 overview of the likely barriers experienced by people with bipolar disorder (14).  
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7 However, it failed to explore factors that might facilitate adherence and excluded  
8 studies involving medication other than antipsychotics, and therefore did not identify  
9 determinants of adherence to lithium and other mood stabilisers. This is a significant  
10 omission as lithium is considered the gold-standard first-line treatment for bipolar  
11 disorder (1,15,16). The determinants of adherence may be different among patients  
12 taking lithium relative to other antipsychotics due to a variety of factors including  
13 regular blood test requirements of lithium, dietary restrictions and significant  
14 interactions with other medications. Thus, a systematic review without the date limits  
15 of the previous systematic review (14) is warranted to better represent the mood  
16 stabilisers which were the mainstay of treatment in the earlier decades not included in  
17 the previous review and to identify emerging research (17).  
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38 The dearth of adherence evidence syntheses in the mental health setting underpinned  
39 by health psychology theory (14,18–20) is of concern given its importance for  
40 informing intervention design and implementation (11,12). The Theoretical Domains  
41 Framework (TDF) is a comprehensive framework capturing 33 theories and 84  
42 theoretical constructs related to behaviour change (21). The TDF comprises fourteen  
43 domains each of which has been coupled with evidence based behaviour change  
44 techniques (22). The TDF therefore offers an appropriate theory for underpinning an  
45 evidence synthesis of determinants of adherence as it will enable determinants to be  
46 linked to evidence-based behaviour change techniques. This in turn will inform the  
47 development of an adherence intervention to support practitioners and patients to work  
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3 together in identifying an individual's key determinants of adherence and select the  
4 most appropriate evidence-based interventions.  
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11 The perspective of patients, carers and healthcare professionals often differ in terms  
12 of the determinants of medication adherence due to differing priorities and knowledge  
13 of the situation (18,23–26). For example, the healthcare professional is generally the  
14 expert regarding how the medication should be taken whilst the patient and carer are  
15 the experts in the patient's lived experience of taking or trying to take the prescribed  
16 medication. Furthermore, some determinants are not modifiable such as sex, age and  
17 ethnicity, and therefore have no related specific evidence-based behaviour change  
18 techniques.  
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34 A literature review matching adherence interventions to determinants of adherence  
35 concluded that adherence interventions are often not congruent with the modifiable  
36 determinants of adherence (27). We will explore the modifiable determinants of  
37 medication adherence among patients with bipolar disorder from the perspectives of  
38 the patient, carer, health care professional and other third parties such as researchers.  
39 For the purpose of this systematic review we define modifiable as “any determinants  
40 (barriers or facilitators) of medication adherence that can be modified by the patient,  
41 carer or the prescriber to improve adherence. Modifiable in the context of an individual  
42 being able to effect the change themselves or in partnership with their carer or  
43 healthcare team within a short timeframe.”  
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3 For example, knowledge about the condition / treatment can be changed within days  
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5 or weeks. In contrast, whilst substance abuse can be changed over an extended  
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7 period, a change is unlikely to be achievable within the timeframes acceptable for  
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9 improving adherence.  
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13 This systematic review is a part of the Collaborative Medication Adherence in Bipolar  
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15 disorder (C-MAB) project funded by Health Education England / National Institute of  
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17 Health Research UK. The C-MAB project aims to develop a medication adherence  
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19 tool for people with bipolar disorder. The tool is intended to both identify non-adherent  
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21 behaviour and the individual's determinants of non-adherence. Following the  
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23 systematic review we will develop the tool in the form of statements derived from the  
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25 literature identified modifiable determinants of adherence. We will then refine the  
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27 statements by conducting focus groups and interviews with patients with bipolar  
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29 disorder and their carers to better understand and prioritise the literature identified  
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31 modifiable determinants. After appropriate refinement, the tool will be tested with  
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33 patients with bipolar disorder.  
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### 43 **Aim**

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45 To identify modifiable determinants of medication adherence in the treatment of  
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47 bipolar disorder.  
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### 52 **Objectives**

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- To describe the modifiable determinants of medication adherence from the perspectives of patients, carers, health care professionals and any other third parties.
- To map reported modifiable determinants of medication adherence to the domains of the TDF.

## Method

This research protocol is based on ENhancing Transparency in REporting the synthesis of Qualitative research (ENTREQ) (28) and Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols (PRISMA-P) (29). The protocol is registered with PROSPERO- [www.crd.york.ac.uk/PROSPERO/](http://www.crd.york.ac.uk/PROSPERO/) - international prospective register of systematic reviews.

## Evidence Synthesis

We will use the TDF as an *a priori* framework for our review. We will map the extracted modifiable determinants of adherence from the included studies to the domains of the TDF. The deductive approach of this framework synthesis method (30–33) has the potential to restrict the nature of identified determinants. However, the comprehensive nature of the TDF should enable identification of all determinants relevant to behaviour change and any determinants which cannot be mapped to a TDF domain will still be extracted and mapped to new domains if appropriate (34). A further benefit of mapping determinants to the TDF is its linkage to behaviour change techniques (17). This approach was successfully applied by Allemann and colleagues to match adherence interventions to patient determinants of adherence (27). This early identification of

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3 relevant behaviour change techniques affords a substantial advantage in terms of  
4 informing the design of theory and evidence-based medication adherence  
5 interventions for people prescribed medication for bipolar disorder.  
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### 14 **Approach to searching, search strategy and data sources**

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17 We will employ a pre-planned search strategy to seek all relevant studies. Our search  
18 strategy will consist of three parameters: disease (bipolar disorder), treatment  
19 (medication) and outcome (adherence). Following a scoping exercise of search terms  
20 (on Pubmed, Medline and Embase) to define our search strategy, we decided to use  
21 the MeSH (Medical Subject Heading) terms "Treatment Adherence and Compliance",  
22 "Bipolar Disorder" AND "Psychotropic Drugs" for our search. We will adapt these  
23 search terms for the databases that do not permit MeSH terms or uses different MeSH  
24 terms.  
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38 We will search the following databases: CINAHL, Cochrane Library (CENTRAL),  
39 Embase, LiLACS, Medline, PsychINFO, Pubmed and the reference list of all included  
40 studies will be reviewed for any further relevant studies.  
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### 48 **Study Inclusion criteria**

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51 We will include any primary studies; both qualitative and quantitative e.g. focus groups,  
52 interviews and surveys; explicitly reporting one or more modifiable determinants of  
53 medication adherence in the maintenance treatment of bipolar disorders from the  
54 perspective of patients, carers, healthcare professionals or any other third parties  
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3 explicitly reporting one or more modifiable determinants of medication adherence in  
4 the maintenance treatment of bipolar disorders from the perspective of patients,  
5 carers, clinicians or any other third parties. There will be no date restrictions but we  
6 will only include the studies published in English language. We will include studies of  
7 patients aged 18 years or over with bipolar disorder with or without other co-morbidities  
8 including dual diagnosis, other mental or physical health conditions to represent the  
9 real-world patient population. We will exclude reviews, intervention studies to improve  
10 adherence, case reports, letters, editorials, commentaries, opinion pieces, clinical  
11 guidelines or general disease management articles and studies not in humans. We  
12 will also exclude studies involving short-term treatment of acute agitation or treatment  
13 other than medication such as psychotherapy. Studies where effect of individual  
14 barriers/facilitators to adherence could not be isolated / extracted from composite  
15 measures (such as adherence rating scale) will be excluded.  
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### 37 **Study screening methods**

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40 We will use computer software Covidence (35); an online systematic review program;  
41 for screening retrieved studies. Screening of studies for inclusion in this review will  
42 involve three distinct stages:  
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- 49 I. Title Screening: After removal of duplicates using the reference manager  
50 software Mendeley, the remaining studies will be screened for their relevance  
51 to the review. Definite non-relevant studies will be excluded while relevant, or  
52 unclear studies will be retained for abstract screening.  
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3 II. Abstract Screening: Abstracts of the remaining studies will be screened by the  
4 primary reviewer (AP) and second reviewers (CG, DB, FS, GM, JW and SS)  
5 independently to identify studies that potentially meet the inclusion criteria  
6 outlined above. Any disagreement between the two reviewers will be  
7 resolved through further discussion and referral to a third reviewer (DB) if  
8 there is a failure to achieve agreement.  
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19 III. Full Article Screening: Full articles will be reviewed independently by two  
20 reviewers (AP, CG, DB, FS, GM, JW and SS) using pre-defined  
21 inclusion/exclusion criteria. Any disagreement between two reviewers will  
22 be resolved through discussion or the involvement of the third reviewer. We  
23 will use Cohen's kappa to report the level of agreement between 1<sup>st</sup> and 2<sup>nd</sup>  
24 reviewers.  
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36 Within published syntheses of qualitative research there is often a lack of transparency  
37 about the search processes employed, with neither the search strategy nor databases  
38 detailed (28). For a comprehensive approach, we will use the PRISMA flowchart for  
39 reporting the different phases of searching, screening and identifying studies for  
40 inclusion in the qualitative synthesis as recommended by ENTREQ (28).  
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### 49 **Data extraction and mapping**

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52 We will use the computer software program Nvivo 12 (36) to extract data and to map  
53 the modifiable determinants of medication adherence to the domains of the TDF. While  
54 medication adherence is generally described as taking  $\geq 80\%$  doses of prescribed  
55 medications some studies report adherence in gradient terms (e.g. good, moderate,  
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3 low adherence and non-adherence) (4). Yet, in some cases (e.g. in HIV) adherence  
4 means taking  $\geq 95\%$  doses of prescribed medications (37)(36). Acknowledging this  
5 wide variation on definition of medication adherence we will report the definition used  
6 for adherence in included studies for transparency and comparison among studies.  
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Extracted information will include study characteristics (e.g. title, year of publication, country, study design, population, number of participants, definition and rate of adherence) and modifiable determinants of medication adherence in patients with bipolar disorder.

We will map each extracted determinant to one of the following domains of the TDF:  
1) Knowledge, 2) Skills, 3) Social Influences, 4) Memory, Attention and Decision Processes, 5) Behavioural Regulation, 6) Professional/Social Role and Identity, 7) Beliefs about Capabilities, 8) Belief about Consequences, 9) Optimism, 10) Intentions, 11) Goals, 12) Emotion, 13) Environmental Context and Resources and 14) Reinforcement. We will use constructs within the domains and construct definitions of the TDF (21) to inform mapping decisions. Any determinants that do not fit within the existing domains will be organised into an “Others” domain (34).

Within Nvivo12 we will create four themes in line with the aim of the study:

1. Patient Perspective
2. Carers Perspective
3. HealthCare Professional Perspective
4. Others Perspectives

Within each theme we will create two sub-themes (Barriers and Facilitators) and within each of these sub-themes we will create 15 domains (14 TDF domains plus “Others”).

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5 Two reviewers will pilot data extraction and coding of determinants of adherence to  
6 the domains of TDF from four studies. For example, if the following text were extracted  
7 from a study “Forgetting to take medication or being careless at times about taking  
8 medication was reported to be experienced by x participants”, this would be coded to  
9 the TDF domain “Memory, attention and decision process”. The reviewers will then  
10 compare and discuss their coding to generate consensus in interpretation of literature-  
11 identified determinants. After piloting, all data will be extracted by one reviewer and  
12 independently checked by second reviewer for completeness.  
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26 All extracted determinants will be independently mapped onto the 14 domains of the  
27 TDF or “Others” category by two reviewers. The two reviewers will meet and discuss  
28 their mapping regularly. Any disagreement in mapping will be resolved through  
29 discussion between the two reviewers and referral to a third reviewer as adjudicator if  
30 the two reviewers fail to agree. We will use Cohen’s kappa to report agreement  
31 between the 1st and 2nd reviewers as we are dealing with nominal data i.e. agreement  
32 or not with the domain to which a determinant is mapped onto the TDF.  
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### 45 **Quality assessment**

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48 No studies will be excluded based on quality as our aim is to identify determinants of  
49 medication adherence as comprehensively as possible. However, we will undertake a  
50 quality assessment for the purposes of characterising included studies. There is no  
51 gold standard tool for any study design, nor is there any widely accepted generic  
52 quality assessment tool that functions across multiple study types (38). We will use  
53 bespoke Critical Appraisal Skills Programme qualitative (CASP) (39), Critical appraisal  
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3 of survey (40) and Cochrane risk of bias tool (41) to critically appraise qualitative  
4 studies, surveys and trials respectively. These tools meet the requirements of the  
5 study and provide key quality criteria such as validity, reliability and objectivity (42).  
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10 Quality assessment will be carried out by two independent reviewers. Any  
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12 disagreement between reviewers will be resolved through discussion and if necessary,  
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14 referral to a third reviewer for arbitration.  
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### 20 **Patient and Public Involvement (PPI)**

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22 This systematic review is a part of the C-MAB project which include three patients  
23 and a carer as research advisory board members. PPI has influenced the study  
24 design with two notable recommendations: inclusion of the carer's perspective on  
25 medication adherence and differentiating between modifiable from non-modifiable  
26 determinants of medication adherence. Two PPI representatives (CG and RG) are  
27 listed as authors.  
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39 **Ethics and dissemination:** Ethical approval is not required as primary data will not  
40 be collected. The results will be disseminated through a peer-reviewed publication.  
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44 **Funding statement:** This research is a part of the Clinical Doctoral Research  
45 Fellowship program funded by Health Education England / National Institute of Health  
46 Research. The funder has no role in the development of this protocol.  
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50 **Competing interest statement:** No, there are no competing interest for any authors.  
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54 **Author's contribution:** All authors (AP, AD, AC, CG5, CG4, RG, GM, SS, FS, BT,  
55 MT, JW and DB) helped conceive the study, reviewed the protocol and provided  
56 intellectual critique. AP and DB designed and wrote the protocol. AP registered the  
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3 study with PROSPERO. All authors (AP, AD, AC, CG5, CG4, RG, GM, SS, FS, BT,  
4 MT, JW and DB) have approved the publication of this protocol.  
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**Table 1: Enhancing transparency in reporting the synthesis of qualitative research: the ENTREQ statement**

**Reference:** Tong A, Flemming K, McInnes E, Oliver S, Craig J. Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ. BMC Med Res Methodol. 2012;12(181). Available from: <https://bmcmedresmethodol.biomedcentral.com/track/pdf/10.1186/1471-2288-12-181>

No	Item	Guide and description	Reported on Manuscript Page no.
1	Aim	State the research question the synthesis addresses. <hr/>	6
2	Synthesis methodology	Identify the synthesis methodology or theoretical framework which underpins the synthesis, and describe the rationale for choice of methodology ( <i>e.g. meta-ethnography, thematic synthesis, critical interpretive synthesis, grounded theory synthesis, realist synthesis, meta-aggregation, meta-study, framework synthesis</i> ). <hr/>	7
3	Approach to searching	Indicate whether the search was pre-planned ( <i>comprehensive search strategies to seek all available studies</i> ) or iterative ( <i>to seek all available concepts until they theoretical saturation is achieved</i> ). <hr/>	8

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No	Item	Guide and description	Reported on Manuscript Page no.
4	Inclusion criteria <hr/>	Specify the inclusion/exclusion criteria ( <i>e.g. in terms of population, language, year limits, type of publication, study type</i> ). <hr/>	8-9
5	Data sources <hr/>	Describe the information sources used ( <i>e.g. electronic databases (MEDLINE, EMBASE, CINAHL, psycINFO, Econlit), grey literature databases (digital thesis, policy reports), relevant organisational websites, experts, information specialists, generic web searches (Google Scholar) hand searching, reference lists</i> ) and when the searches conducted; provide the rationale for using the data sources. <hr/>	8
6	Electronic Search strategy <hr/>	Describe the literature search ( <i>e.g. provide electronic search strategies with population terms, clinical or health topic terms, experiential or social phenomena related terms, filters for qualitative research, and search limits</i> ). <hr/>	8-9
7	Study screening methods <hr/>	Describe the process of study screening and sifting ( <i>e.g. title, abstract and full text review, number of independent reviewers who screened studies</i> ). <hr/>	9

No	Item	Guide and description	Reported on Manuscript Page no.
8	Study characteristics	Present the characteristics of the included studies ( <i>e.g. year of publication, country, population, number of participants, data collection, methodology, analysis, research questions</i> ).	12
9	Study selection results	Identify the number of studies screened and provide reasons for study exclusion ( <i>e.g. for comprehensive searching, provide numbers of studies screened and reasons for exclusion indicated in a figure/flowchart; for iterative searching describe reasons for study exclusion and inclusion based on modifications to the research question and/or contribution to theory development</i> ).	11
10	Rationale for appraisal	Describe the rationale and approach used to appraise the included studies or selected findings ( <i>e.g. assessment of conduct (validity and robustness), assessment of reporting (transparency), assessment of content and utility of the findings</i> ).	13
11	Appraisal items	State the tools, frameworks and criteria used to appraise the studies or selected findings ( <i>e.g. Existing tools: CASP, QARI, COREQ, Mays and Pope [25]; reviewer developed tools; describe the domains assessed: research team, study design, data analysis and</i>	13

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No	Item	Guide and description	Reported on Manuscript Page no.
		<i>interpretations, reporting).</i> _____	
12	Appraisal process _____	Indicate whether the appraisal was conducted independently by more than one reviewer and if consensus was required. _____	13
13	Appraisal results _____	Present results of the quality assessment and indicate which articles, if any, were weighted/excluded based on the assessment and give the rationale. _____	13
14	Data extraction _____	Indicate which sections of the primary studies were analysed and how were the data extracted from the primary studies? ( <i>e.g. all text under the headings “results /conclusions” were extracted electronically and entered into a computer software</i> ). _____	11-12
15	Software _____	State the computer software used, if any. _____	12

No	Item	Guide and description	Reported on Manuscript Page no.
16	Number of reviewers _____	Identify who was involved in coding and analysis. _____	12
17	Coding _____	Describe the process for coding of data ( <i>e.g. line by line coding to search for concepts</i> ). _____	12
18	Study comparison _____	Describe how were comparisons made within and across studies ( <i>e.g. subsequent studies were coded into pre-existing concepts, and new concepts were created when deemed necessary</i> ). _____	11
19	Derivation of themes _____	Explain whether the process of deriving the themes or constructs was inductive or deductive. _____	7
20	Quotations _____	Provide quotations from the primary studies to illustrate themes/constructs, and identify whether the quotations were participant quotations of the author's interpretation. _____	7

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No	Item	Guide and description	Reported on Manuscript Page no.
21	Synthesis output	Present rich, compelling and useful results that go beyond a summary of the primary studies (e.g. <i>new interpretation, models of evidence, conceptual models, analytical framework, development of a new theory or construct</i> ).	7

For peer review only

**Table 2** : PRISMA-P (preferred reporting items for systematic review and meta-analysis protocols) 2015 checklist: recommended items to address in a systematic review protocol)

Reference: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (prisma-p) 2015: Elaboration and explanation. *BMJ*. 2015;349. Available from: <https://www.bmj.com/content/349/bmj.g7647>

Section and topic	Item No	Checklist item	Reported on Manuscript Page no.
<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	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2 & 7
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	15
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	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	15
Sponsor	5b	Provide name for the review funder and/or sponsor	15
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	15
<b>Introduction</b>			

Section and topic	Item No	Checklist item	Reported on Manuscript Page no.
Rationale	6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
<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	8-9
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	8
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	8
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	12
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)	9
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	11-12
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	12
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	14	Describe anticipated methods for assessing risk of bias of individual studies, including	13



Section and topic	Item No	Checklist item	Reported on Manuscript Page no.
individual studies		whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	NA
	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 $\tau$ )	NA
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	NA
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	NA
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	13