PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Mapping of modifiable Barriers and Facilitators of Medication Adherence in Bipolar Disorder to the Theoretical Domains Framework (TDF): A Systematic Review Protocol
AUTHORS	Prajapati, Asta; Dima, Alexandra; Clark, Allan; Gant, Claire; Gibbons, Chris; Gorrod, Richard; Mosa, George; Scott, Sion; Song, Fujian; Teague, Bonnie; Twigg, Michael; Wilson, Jon; Bhattacharya, Debi

VERSION 1 – REVIEW

REVIEWER	Samuel Allemann University of Basel, Pharmaceutical Sciences
REVIEW RETURNED	16-Oct-2018

GENERAL COMMENTS	This is a study protocol for a systemativ review to map modifiable determinants of medication adherence in Bipolar Disorder to the Theoretical Domains Framework. The protocol is well-written and the study will be relevant to advance adherence research and management in Bipolar Disorder. I would like to offer the following comments and recommend publication of the manuscript after minor revisions: Page 4, lines 22-29: There is a published (open-access) study from 2016 that matches adherence interventions to patient determinants using the theoretical domains framework. The determinants were also classified as modifiable or unmodifiable and it used a similar approach to mapping determinants to the TDF. Instead of the 14 original TDF domains, only 11 domains were retained for the final synthesis. If you find it relevant for your study, you may consider to refer to this publication: Allemann, Samuel Sebastian, Robby Nieuwlaat, Van Den Bemt, Bart J. F, Kurt E. Hersberger, und Isabelle Arnet. „Matching Adherence Interventions to Patient Determinants Using the Theoretical Domains Framework“. Frontiers in Pharmacology 7 (2016). https://doi.org/10.3389/fphar.2016.00429. Page 8, line 20; Approach to searching, search strategy and data sources: You state that your search focuses on medication adherence. Please explain why you used the general MeSH term "Treatment Adherence and Compliance" instead of the more specific MeSH term “Medication Adherence”. Does the search include MeSH terms below this term in the hierarchy? Page 9, Line 33; Study screening methods (abstract screening): Who will be the secondary reviewer?

	Page 9, Line 48; Study screening methods (Full Article Screening): Who will be the reviewers? When will the third reviewer be involved? Who will be the third reviewer? What will be the "appropriate statistics to report the level of agreement" (e.g. Kappa statistics, Krippendorff's Alpha, or (intra-class) correlation coefficients)? Page 10, line 46; Data extraction: You plan to use "bespoke" Microsoft Excel. "Bespoke software" typically refers to proprietary software written for a specific client, while Microsoft Excel is available to the public. Please clarify the meaning of "bespoke" in this context (and add an appropriate reference for it).

REVIEWER	Janet Long Macquarie University, Australia
REVIEW RETURNED	22-Oct-2018

GENERAL COMMENTS	This is a study protocol for a project to identify barriers and facilitators to adherence that are amenable to interventions for people with bipolar disorder. This is an interesting and appropriate aim and promises to have a significant outcome for patients. The case for the gap in the literature is well made. Having said that I believe half the protocol is missing. The systematic search for literature is well described but it ends prematurely with the identification of the literature. There is no detail around the actual data being collated and how it will be synthesised, and how then used. These aspects of the study are the hardest to do and require detail on the exact process that will be followed. Until that is done I cannot recommend its acceptance. More information required: • How will you define non-adherence? In other literature on non-adherence of medication (e.g., people using medicated eyedrops to prevent vision loss in glaucoma), non-adherence refers to any deviation from "as prescribed" medication. Is that true here? Is it only referring to someone who stops their medication all together? What about a patient who forgets to take their medication because they are on holidays and out of routine; or forgot to refill their script before a long weekend, or who varies their dosage for some reason? Need to explain the extent of influence of non-adherence and define your target group better. • What type of study design will be included? Interviews, surveys, quantitative audits of some sort (e.g., no. of prescriptions filled). • What is your strategy for extracting the data? What data you will be extracting from the studies? Giving an example will make it easier to judge whether this approach will work. • p13. "No studies will be excluded based on quality as our aim is to identify determinants of medication adherence as comprehensively as possible." Not sure this is a wise approach. If a study is seriously flawed, for example an uninformed opinion of non-adherence, or misleadingly skewed survey results. If quality is already being assessed, then it makes sense to include this to assure the reader that the determinants are accurate. • Will you be training the coders in TDF so that they accurately understand the constructs? Having done this work myself we needed extensive input from two TDF experts to train us, amend and then ratify our results. • How will you identify the modifiable factors, and those that are not? • What is the process by which you will use the TDF barriers to address these factors? Will you be matching behaviour change techniques to the barrier domains? Which taxonomy of BCTs will

	you use? How will you ensure these are feasible and appropriate? Will their be some kind of co-design with clinicians and patients or is this a theoretical exercise only? Can recommend a recent paper that did something similar to your project that might help: Craig LE, McInnes E, Taylor N, Grimley R, Cadilhac DA, Considine J, Middleton S: Identifying the barriers and enablers for a triage, treatment, and transfer clinical intervention to manage acute stroke patients in the emergency department: a systematic review using the theoretical domains framework (TDF). Implementation Science (2016), 11:157. Other minor issues: p9 line 55 “appropriate statistics” – need to spell out which. I presume you mean a Kappa inter-rater reliability test or Fleiss kappa if more than one reviewer? p10 line 46 The word “spreadsheet” is missing after “Microsoft Excel 2016” P11 line 30 missing a word in this sentence.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:
Response
We would like to thank both reviewers for their valuable and constructive feedback. Much appreciated.

Reviewer: 1

1. The protocol is well-written and the study will be relevant to advance adherence research and management in Bipolar Disorder.

Response
Thank you.

2. I would like to offer the following comments and recommend publication of the manuscript after minor revisions:

Page 4, lines 22-29: There is a published (open-access) study from 2016 that matches adherence interventions to patient determinants using the theoretical domains framework. The determinants were also classified as modifiable or unmodifiable and it used a similar approach to mapping determinants to the TDF. Instead of the 14 original TDF domains, only 11 domains were retained for the final synthesis. If you find it relevant for your study, you may consider to refer to this publication: Allemann, Samuel Sebastian, Robby Nieuwlaat, Van Den Bemt, Bart J. F, Kurt E. Hersberger, und Isabelle Arnet. „Matching Adherence Interventions to Patient Determinants Using the Theoretical Domains Framework“. Frontiers in Pharmacology 7 (2016). https://doi.org/10.3389/fphar.2016.00429.

Response
Many thanks for highlighting this very relevant piece of research. The protocol has been amended in both the Introduction and Evidence Synthesis sections as follows:

Introduction:

“A literature review matching adherence interventions to determinants of adherence concluded that adherence interventions are often not congruent with the modifiable determinants of adherence (26).”

Evidence synthesis:
“This approach was successfully applied by Allemann and colleagues to match adherence interventions to patient determinants of adherence (26).”

3. Page 8, line 20; Approach to searching, search strategy and data sources: You state that your search focuses on medication adherence. Please explain why you used the general MeSH term "Treatment Adherence and Compliance" instead of the more specific MeSH term “Medication Adherence”. Does the search include MeSH terms below this term in the hierarchy?

Response
Yes, ‘Treatment Adherence and Compliance’ covers ‘Medication Adherence’ as well as others such as ‘Patient acceptance of health care’, ‘patient compliance’, ‘patient dropouts’ etc. Our intention was to be as inclusive as possible to limit the chances of missing relevant studies hence we searched the MeSH term higher up in the hierarchy.

4. Page 9, Line 33; Study screening methods (abstract screening): Who will be the secondary reviewer?

Response
The protocol has been amended to read as follows:
“Abstracts of the remaining studies will be screened by the primary reviewer (AP) and second reviewers (CG, DB, FS, GM, JW and SS) independently”

5. Page 9, Line 48; Study screening methods (Full Article Screening): Who will be the reviewers? When will the third reviewer be involved? Who will be the third reviewer? What will be the “appropriate statistics to report the level of agreement” (e.g. Kappa statistics, Krippendorff’s Alpha, or (intra-class) correlation coefficients)?

Response
The protocol has been amended to read as follows:
“Full articles will be reviewed independently by two reviewers (CG, DB, FS, GM, JW and SS) using pre-defined inclusion/exclusion criteria.”
“We will use Cohen’s kappa to report the level of agreement between the 1st and 2nd reviewer.”

6. Page 10, line 46; Data extraction: You plan to use “bespoke” Microsoft Excel. “Bespoke software” typically refers to proprietary software written for a specific client, while Microsoft Excel is available to the public. Please clarify the meaning of “bespoke” in this context (and add an appropriate reference for it).

Response
Since submitting the protocol we have secured funds for using the computer software ‘Covidence’ in place of Excel. The protocol has been amended to read as follows:
“We will use computer software Covidence (34); an online systematic review program; for screening retrieved studies.”
“We will use the computer software program Nvivo 12 (34) to extract data and to map the determinants of medication adherence to the domains of the TDF.”

Reviewer: 2

7. This is an interesting and appropriate aim and promises to have a significant outcome for patients. The case for the gap in the literature is well made. Having said that I believe half the protocol is missing. The systematic search for literature is well described but it ends prematurely with the identification of the literature. There is no detail around the actual data being collated and how it will be synthesised, and how then used. These aspects of the study are the hardest to do and require detail on the exact process that will be followed. Until that is done I cannot recommend its acceptance.

Response
Thank you for alerting us to this omission. We think that we have addressed the comment about details of the data being collected and synthesis in the new text added in our response to review comment 10 below. In response to your query about how we will use the findings from the synthesis, we have amended the protocol with the following additional text at the end of the 'Introduction' section:
"This systematic review is a part of the Collaborative Medication Adherence in Bipolar disorder (C-MAB) project funded by Health Education England / National Institute of Health Research UK. The C-MAB project aims to develop a medication adherence tool for people with bipolar disorder. The tool is intended to both identify non-adherent behaviour and the individual's determinants of non-adherence. Following the systematic review we will develop the tool in the form of statements derived from the literature identified modifiable determinants of adherence. We will then refine the statements by conducting focus groups and interviews with patients with bipolar disorder and their carers to better understand and prioritise the literature identified modifiable determinants. After appropriate refinement, the tool will be tested with patients with bipolar disorder."

More information required:
8. How will you define non-adherence? In other literature on non-adherence of medication (e.g., people using medicated eyedrops to prevent vision loss in glaucoma), non-adherence refers to any deviation from "as prescribed" medication. Is that true here? Is it only referring to someone who stops their medication all together? What about a patient who forgets to take their medication because they are on holidays and out of routine; or forgot to refill their script before a long weekend, or who varies their dosage for some reason? Need to explain the extent of influence of non-adherence and define your target group better.

Response
The protocol has been amended to read as follows:

"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)." – See 'Introduction' section 1st paragraph.

"While medication adherence is generally described as taking ≥80% doses of prescribed medications some studies report adherence in gradient terms (e.g. good, moderate, low adherence and non-adherence) (4). Yet, in some cases (e.g. in HIV) adherence means taking ≥95% doses of prescribed medications (36). Acknowledging this wide variation on definition of medication adherence we will report the definition used for adherence in included studies for transparency and comparison among studies." -See 'Data Extraction' section paragraph 1

9. What type of study design will be included? Interviews, surveys, quantitative audits of some sort (e.g., no. of prescriptions filled).

Response
The protocol has been amended to read as follows (See 'inclusion criteria' section paragraph 1):

"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."

10. What is your strategy for extracting the data? What data you will be extracting from the studies? Giving an example will make it easier to judge whether this approach will work.

Response
We have rewritten the data extraction and mapping sections to read as follows:
Data extraction and mapping
We will use the computer software program Nvivo 12 (35) to extract data and to map the modifiable determinants of medication adherence to the domains of the TDF. While medication adherence is generally described as taking ≥80% doses of prescribed medications some studies report adherence in gradient term (e.g. good, moderate, low adherence and non-adherence) (4). Yet, in some cases (e.g. in HIV) adherence means taking ≥95% doses of prescribed medications (36). Acknowledging this wide variation on definition of medication adherence we will report the definition used for adherence in included studies for transparency and comparison among studies. Extracted data will include study characteristics (e.g. title, year of publication, country, study design, population, number of participants, definition of adherence and rate of adherence,), 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 (32).

Within Nvivo12 we will create four codes in accordance with the study aims:

1. Patient Perspective
2. Carer Perspective
3. HealthCare Professional Perspective
4. Other Perspectives e.g. friends and researchers

Within each code we will create two sub-codes (Barriers and Facilitators) and within each of these sub-codes 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 medication was reported to be experienced by x participants", this would be coded to the TDF domain 'Memory, attention and decision process'. The reviewers will then compare and discuss their coding to generate consensus in interpretation of literature-identified determinants. After piloting, all data will be extracted by one reviewer and independently checked by second reviewer for completeness.
All extracted determinants will be independently mapped onto the 14 domains of the TDF or 'Others' category by two reviewers. The two reviewers will meet and discuss their mapping regularly. Any

disagreement in mapping will be resolved through discussion between the two reviewers and referral to a third reviewer as adjudicator if the two reviewers fail to agree. We will use Cohen's kappa to report agreement between the 1st and 2nd reviewers as we are dealing with nominal data i.e. agreement or not with the domain to which a determinant is mapped onto the TDF."

11. p13. "No studies will be excluded based on quality as our aim is to identify determinants of medication adherence as comprehensively as possible." Not sure this is a wise approach. If a study is seriously flawed, for example an uninformed opinion of non-adherence, or misleadingly skewed survey results. If quality is already being assessed, then it makes sense to include this to assure the reader that the determinants are accurate.

Response
Our aim is to elicit determinants of medication adherence as comprehensively as possible. If data collection in a study is perhaps not generalizable or transferable, it is still of interest to us because it has been experienced by some patients/clinicians/carers. If reported determinants from studies of lower quality are inconsistent with the general findings from other studies, we will be able to provide relevant commentary.

12. Will you be training the coders in TDF so that they accurately understand the constructs? Having done this work myself we needed extensive input from two TDF experts to train us, amend and then ratify our results.

Response

Two reviewers (SS and DB) have relevant training and extensive experience of using the TDF in similar projects. https://onlinelibrary.wiley.com/doi/full/10.1111/ijpp.12491
AD is a health psychologist and AP has undertaken some training in the using the TDF. We are therefore confident that we have sufficient expertise within the group to successfully deliver this project.

13. How will you identify the modifiable factors, and those that are not?

Response
The protocol has been amended to clarify this and the protocol now reads (See 'Introduction' section penultimate paragraph):

"We will explore the modifiable determinants of medication adherence among patients with bipolar disorder from the perspectives of the patient, carer, health care professional and other third parties such as researchers. For the purpose of this systematic review we define modifiable as 'Any determinants (barriers or facilitators) of medication adherence that can be modified by the patient, carer or the prescriber to improve adherence. Modifiable in the context of an individual being able to effect the change themselves or in partnership with their carer or healthcare team within a short timeframe.'

For example, knowledge about the condition / treatment can be changed within days or weeks. In contrast, whilst substance abuse can be changed over an extended period, a change is unlikely to be achievable within the timeframes acceptable for improving adherence.

14. What is the process by which you will use the TDF barriers to address these factors? Will you be matching behaviour change techniques to the barrier domains? Which taxonomy of BCTs will you

use? How will you ensure these are feasible and appropriate? Will their be some kind of co-design with clinicians and patients or is this a theoretical exercise only?

Response
The scope of this systematic review is to identify determinants of medication adherence and mapping them to the domains of the TDF. For the current project (C-MAB) as mentioned in response to feedback no. 7, we are trying to developing a medication adherence tool which will identify non-adherence and individual determinants of non-adherence. After completion of C-MAB project we plan to conduct next phase of research to match behaviour change techniques to TDF domains, intervention design and feasibility testing in partnership with patients and clinicians.

15. Can recommend a recent paper that did something similar to your project that might help: Craig LE, McInnes E, Taylor N, Grimley R, Cadilhac DA, Considine J, Middleton S: Identifying the barriers and enablers for a triage, treatment, and transfer clinical intervention to manage acute stroke patients in the emergency department: a systematic review using the theoretical domains framework (TDF). Implementation Science (2016), 11:157.

Response
Thank you. Yes, Natalie Taylor was also a co-author on some previous very similar work conducted by our team: Barriers to medication adherence in patients prescribed medicines for the prevention of cardiovascular disease: a conceptual framework
Claire Easthall Natalie Taylor Debi Bhattacharya https://doi.org/10.1111/ijpp.12491

Other minor issues:
16. p9 line 55 “appropriate statistics” – need to spell out which. I presume you mean a Kappa inter-rater reliability test or Fleiss kappa if more than one reviewer? –

Response
The protocol has been amended to clarify this and the protocol now reads:
“We will use Cohen’s kappa to report agreement between the 1st and 2nd reviewers as we are dealing with nominal data i.e. agreement or not with the domain to which a determinant is mapped onto the TDF.”

17. p10 line 46 The word “spreadsheet” is missing after “Microsoft Excel 2016” –

Response
Since submitting the protocol we have secured funds for using the computer software ‘Covidence’ in place of Excel. The protocol has been amended to read as follows:
“We will use computer software Covidence (34); an online systematic review program; for screening retrieved studies.”
“We will use the computer software program Nvivo 12 (34) to extract data and to map the determinants of medication adherence to the domains of the TDF.”

18. P11 line 30 missing a word in this sentence. –

Response
Sentence corrected and the protocol now reads (See last paragraph on section - Data extraction and mapping):
“Any disagreement between mapping determinants to the TDF domains will be resolved through discussion between the two reviewers.”

VERSION 2 – REVIEW

REVIEWER	Janet Long Macquarie University, Sydney, Australia
REVIEW RETURNED	20-Dec-2018

GENERAL COMMENTS	Dear Authors, Thank you for comprehensively responding to all my concerns. It now reads very well and it is much easier to follow. I look forward to reading of your findings. The tool it will inform has great potential I think to improve medication compliance/effectiveness.

VERSION 2 – AUTHOR RESPONSE

Many thanks for your email. We have now added ‘Ethics and dissemination’ section in the abstract, removed the duplicate reference to the PRIMSA-P and ENTREQ reporting guidelines in the 'Methods and Analysis' section of abstract and made minor changes to heading (e.g. now reads "Method and analysis" instead of previous "Methods, synthesis and result presentation". Hope the changes made satisfies the need of the Journal's formatting style.

Please let me know if you need me to do anything else. Many thanks.