PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The influence of childhood trauma on the treatment outcomes of pharmacological and/or psychological interventions for adolescents and adults with bipolar disorder: protocol for a systematic review and meta-analysis
AUTHORS	Wrobel, Anna; Russell, Samantha; Dean, Olivia; Cotton, Sue; Berk, Michael; Turner, Alyna

VERSION 1 – REVIEW

REVIEWER	Carl Castro University of Southern California
REVIEW RETURNED	13-Oct-2020

GENERAL COMMENTS	Trauma is a deeply systemic world wide problem, and can have a pervasive impact on mental health and wellbeing. This systematic review examines the relationship of childhood trauma and the treatment effectiveness for bipolar disorder. The current paper presents the rationale and methods for the proposed systematic review and meta-analysis. This is a worthwhile study. The comments provided below are intended to improve the study design. 1. The authors propose to use a "liberal design criteria." However, terms such as "inclusive" or "broad" instead of "liberal" might be a more neutral term in describing the proposed procedures. 2. Childhood is not defined anywhere in the paper, yet most certainly the age of the trauma will be important in understanding childhood trauma and response to treatment. For instance, if trauma occurs during major periods of brain development, one can easily imagine the trauma to have a greater impact than if the trauma occurred in late adolescent. The authors should consider capturing the time frame in which the trauma occurred. The authors do define "early life (</=) 18 years," yet it is unclear if this is also the definition of "childhood." 3. Although trauma is a major variable in the current study, trauma is viewed as unidimensional. However, the research in the trauma field clearly indicates that sexual and physical trauma impacts psychological health to a greater extent than does emotional trauma. And by extension, response to interventions are likewise expected to be impacted. The authors should attempt to evaluate the type of trauma and its relationship to treatment response to the greatest extent possible in their analyses. 4. Given that the focus of this review is on trauma, it was surprising not to see PTSD as a variable to explore in more detail. The authors should consider including PTSD as one of their secondary

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	outcomes. 5. Given that women and other ethnic/racial populations are more likely to experience certain types of trauma over other populations, the authors should consider looking at these subgroups individually. The authors list age and gender as "demographic," yet it is not clear how these two variables will be treated in the analyses. That is, will they be treated as predictors or control variables? 6. A stronger statement about the potential impact of this systematic should be provided. There are important implications for prevention, assessment, diagnoses, treatment, response to treatment, recovery, relapses, etc. Including a stronger potential impact statement will substantially validate the need for the proposed systematic review.

REVIEWER	Maria Dauvermann University of Cambridge, Psychiatry
REVIEW RETURNED	27-Oct-2020

GENERAL COMMENTS	Summary In this protocol for a systematic review and meta-analysis, the authors aim to characterise the role of childhood trauma (CT) on treatment outcome measures of either pharmacological or psychological interventions, or a combination of the two, in adolescents and adults with bipolar disorder (BD). The authors introduce the proposed systematic review by providing background to the available pharmacological and psychological treatment approaches to individuals with BD, prevalence of CT and related greater symptomatology in individuals with BD, before studies are cited who examined the potential moderating role of CT in treatment-related outcome measures. In the next step, the authors describe methodological steps of how to perform the systematic review and meta-analysis, if the data allows. However, there are several concerns that need to be addressed. 1) General comment re the focus (study objective) of the protocol manuscript: • Please add details of potential impact of the outcomes of the systematic review/meta-analysis to the abstract, article summary, introduction, objectives, and conclusions. There are brief attempts (in the objectives for a 'moderating role' and in the conclusion for 'clarification of the role of CT'). However, these statements are vague and very general. I also have a few questions: Why do the authors only propose a moderating role of CT? Why not any other potential role? For the moderating role, what is the theoretical hypothesis as this is not clear in the introduction (page 5). • Why do the authors propose to include adolescents? I recommend to focus on adults only for the following reasons: • As the authors point out, this would be the first systematic review (and meta-analysis) in this field. Therefore, I suggest to focus on the adult population group with a decent number of random clinical trials (RCT) and to provide a 'clean' systematic review. • Given the wide range of inclusion criteria for clinical interviews, assessment tools for CT, treatment options, and the emphasis on adults would help (to some extent) to interpret the findings and to streamline such a first systematic review on this topic. • Although I fully agree that it is a growing field to study young people with BD who have also experienced CT, there are less than a handful of studies in adolescents published currently.

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	• Following on from the previous point, the authors do not argue why adolescents should be included. • The authors write in the paragraph 'Ethics and dissemination' that 'multiple publications may be derived from this protocol': I do not think that this is possible, or feasible, based on single protocol for a systematic review (and meta-analysis) when the inclusion criteria are defined to lead to clearly interpretable findings. Given the wide range of inclusion criteria as mentioned above, I question whether the authors will find significant meta-analytic findings based on similar reviews/meta-analysis in the field of BD, CT, etc. When then adding the group of adolescents, I doubt that this will result in interpretable findings. If adolescents will be included, I suggest to write a separate systematic review/meta-analysis with age-appropriate clinical interviews, CT assessment tools, etc. that have to be clearly differentiated from the adult criteria. Finally, if adolescents were to be included, the diagnoses of BD would need to be adjusted to the age and developmental stage (for example, early-onset BD, etc.). 2) Definition of treatment outcome measures: • I agree with the authors that currently studied treatment outcome measures are not used in a unified version. The authors have a chance here of studying the most widely used outcome measures with additional measures to study this issue. After raising this point in the introduction, the authors do not follow up on this point in the methods section but rather leave this point open in a general way. I think this point here could become one of the major novelties in the field, for example, the outcome measure of number of suicidal attempts, in particular after the authors mention this symptom in the introduction. 3) Title: • I suggest to shorten the title by removing 'pharmacological and/or psychological' given that these are the commonly available options. In the introduction, the authors can then provide more details. 4) Article summary: • Fourth point of heterogeneity (also applies to the methodological section): • As this will be the first systematic analysis for this topic, I assume the authors aim to define 'liberal' study design criteria. However, this approach will likely result in non-significant findings based on the findings of previous systematic reviews and mega-analyses. Therefore, I recommend to be more stringent with the inclusion criteria to guarantee robust findings. In future separate reviews (when more original articles of RCTs will be available), it will be more feasible to refocus on more focused details of interest. Specific recommendation are here: • In particular, adolescents as a sample should be removed (please see comments above). • In addition, only RCTs should be included. • Please streamline the clinical interviews to adult age and the most commonly used ones. • Regarding the measurement of childhood trauma, I suggest to only include widely established questionnaires as the CTQ and ACE. In particular, please remove the inclusion of medical file information, as this is a 'routine' limitation in systematic reviews and meta-analyses. • Please limit the pharmacological mediation to some but not all of the listed medication.

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	5) Introduction: • In general, please add more details to the introduction of why it is so important to run a systematic review in this field. Please add more recent systematic reviews instead of original studies for references. • The authors write about the importance of mood symptoms but not about psychotic symptoms. Please add this aspect to the introduction. • Please add 'such as childhood trauma' after 'environmental risk factors in line 18 to create a link to the following paragraph. • Page 4: Please also add evidence from longitudinal studies to strengthen the relevance for treatment issues. • Page 5, last paragraph on inflammation: Although I agree on the potentially promising future of RCTs studying inflammatory markers, more details on this background are needed: Are these references in favour of low-grade inflammation in these individuals, what type of inflammatory markers are considered here (pro- or anti-inflammatory)? Please also give background/evidence in the literature to the inclusion of studying the effect of antipsychotics and/or antidepressants in this context of the systematic review, please. • Please clarify the second sentence in the last paragraph of the introduction. What are the differences between the three recovery types? Please rephrase. 6) Objectives: • Please rename 'disorder-related features' to 'clinical measures'. • I suggest to ask the authors to consider of adding typical clinical measures of rapid cycling and number of suicide attempts. • Please add symptom severity as one of the main outcome measures. • Please make sure that not only mood symptoms but also psychotic features are covered. 7) Methods and analysis • My general concern regarding the methodology lies in the lenient inclusion criteria (please see above). How do the authors propose to analyse the findings when it is commonly known that the variety of measures (for example, medical file entries for CT) cannot be compared with standardized questionnaires? The authors write that heterogeneity is likely given the 'lenient' criteria as one of the limitations. However, this not strong enough from the methodological perspective, where the authors should directly improve this limitation by defining stricter inclusion criteria (please see also above). • Page 7: Please rephrase the subheading to 'Groups of participants' and remove adolescents as my recommendation. • Page 8: Please rephrase the subheading to 'Study designs' and only focus on RCT as my recommendation following the authors' argumentation on pages 12-13. • Page 9, Types of outcome measures: What are the 'both' phases of the disorder? Please define here and previously in the introduction as it is currently missing. Please add measures for psychotic symptoms in here (and the following listing) and adjust the clinical interviews to adult age. • Page 13: Please add a reference for the 'rule of thumb'. • Page 13: Data synthesis and statistical analysis: • Please add what software you will use. • Page 14: Please correct to 'for continuous outcome variables' in the first paragraph.

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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Carl Castro
Institution and Country: University of Southern California

Comments to the Author
Trauma is a deeply systemic world wide problem, and can have a pervasive impact on mental health and wellbeing. This systematic review examines the relationship of childhood trauma and the treatment effectiveness for bipolar disorder. The current paper presents the rationale and methods for the proposed systematic review and meta-analysis. This is a worthwhile study. The comments provided below are intended to improve the study design.

1. The authors propose to use a "liberal design criteria." However, terms such as "inclusive" or "broad" instead of "liberal" might be a more neutral term in describing the proposed procedures.

RESPONSE: 'Liberal design criteria' has been changed to 'inclusive design criteria' or 'broad design criteria' throughout the manuscript (line 57 and line 209).

2. Childhood is not defined anywhere in the paper, yet most certainly the age of the trauma will be important in understanding childhood trauma and response to treatment. For instance, if trauma occurs during major periods of brain development, one can easily imagine the trauma to have a greater impact than if the trauma occurred in late adolescent. The authors should consider capturing the time frame in which the trauma occurred. The authors do define "early life (</=) 18 years," yet it is unclear if this is also the definition of "childhood."

RESPONSE: Thank you for picking up the lack of clarity in the definition. The sentence has been amended to read (line 219): "For the purpose of this review, childhood trauma is defined in the form of maltreatment and includes physical abuse, sexual abuse, emotional abuse, physical neglect, and emotional neglect experienced during childhood and early adolescence (≤ 18 years)." We have also added "Exposure details (e.g., n exposed, trauma types, time of exposure)" to the section explaining what data will be extracted (line 316).

3. Although trauma is a major variable in the current study, trauma is viewed as unidimensional. However, the research in the trauma field clearly indicates that sexual and physical trauma impacts psychological health to a greater extent than does emotional trauma. And by extension, response to interventions are likewise expected to be impacted. The authors should attempt to evaluate the type of trauma and its relationship to treatment response to the greatest extent possible in their analyses.

RESPONSE: Thank you for this suggestion. When conceptualising the protocol we had removed the exploration of trauma type from the manuscript, as we were concerned that we would not be able to address this based on the literature. However, we agree that we should attempt to evaluate this as much as possible. Therefore a subgroup analysis focusing on type of childhood trauma (physical, sexual, emotional) has been added back into the protocol (line 382). Please also see our response to your second to last comment.

4. Given that the focus of this review is on trauma, it was surprising not to see PTSD as a variable to explore in more detail. The authors should consider including PTSD as one of their secondary outcomes.

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RESPONSE: We agree that exploring treatment outcomes among people with bipolar disorder who report a comorbid diagnosis of PTSD would be a worthwhile addition to the already existing body of research. However, we believe that this would be best addressed in a separate review. Only a proportion of people who were exposed to trauma develop PTSD. Lewis et al. (2019), for example, report findings from a comprehensive epidemiological study conducted with young people and indicate that while 642 (31.1%) of 2064 their participants were exposed to trauma, only 160 (7.8%) experienced PTSD in adulthood. Of note, our team is in the process of completing another review that focuses more specifically on PTSD and bipolar disorder (PROSPERO reference number: CRD42020182540).

5. Given that women and other ethnic/racial populations are more likely to experience certain types of trauma over other populations, the authors should consider looking at these subgroups individually. The authors list age and gender as "demographic," yet it is not clear how these two variables will be treated in the analyses. That is, will they be treated as predictors or control variables?

RESPONSE: Thank you for highlighting that our section regarding the subgroup analyses needs further detail. We can confirm that these factors will be looked at separately. We have revised the relevant section; the manuscript now reads (line 382): "Where substantial heterogeneity is indicated ($I^2 \geq 50\%$) and sufficient data are available, subgroup and meta-regression analyses will be performed to explore potential effect modifiers. Individual subgroup analyses will be conducted for the following categorical variables: trauma type (physical, sexual, emotional); treatment type (pharmacological, psychological, combination); and demographic features (age group [adolescent, adult sample]). Meta-regression analyses will be conducted for continuous variables describing participants' clinical (age at onset [mean years], rapid cycling [%rapid cycling], number of episodes, number of suicide attempts) and demographic features (age [mean years], gender [%female]). Other subgroups may be identified where necessary."

6. A stronger statement about the potential impact of this systematic should be provided. There are important implications for prevention, assessment, diagnoses, treatment, response to treatment, recovery, relapses, etc. Including a stronger potential impact statement will substantially validate the need for the proposed systematic review.

RESPONSE: Thank you for the excellent suggestion. We agree that a stronger impact statement would be a worthwhile inclusion. The manuscript has been amended to read (line 155):

"To date, there has been no systematic reviews focusing on the influence of childhood trauma on the treatment outcomes of pharmacological, psychological, and combined interventions for adolescents and adults with bipolar disorder. This is despite current research demonstrating that experiences of childhood trauma may be highly relevant to the efficacy of treatments for bipolar disorder. Research that aims to improve the prediction of treatment outcomes can greatly benefit patients with psychiatric disorders as this knowledge may reduce the burden associated with receiving inappropriate and/or suboptimal treatments and decrease patients' risk of experiencing a chronic illness course.

Exploring the influence of exposure to childhood trauma on patients' treatment outcomes may thus assist the development of individualised interventions for people with bipolar disorder, promoting treatment success and ultimately facilitating recovery. Clarification on the role that childhood trauma plays in the treatment of bipolar disorder has clear translational value with the potential to inform clinical guidelines and practice. A systematic exploration of the available evidence is particularly suitable for this endeavour because it allows for data to be collated from a variety of sources and illustrate areas of research that are underscored by a limited number of patients and/or conflicting evidence."

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Reviewer: 2
Reviewer Name: Maria Dauvermann
Institution and Country: University of Cambridge, Department of Psychiatry

Comments to the Author
In this protocol for a systematic review and meta-analysis, the authors aim to characterise the role of childhood trauma (CT) on treatment outcome measures of either pharmacological or psychological interventions, or a combination of the two, in adolescents and adults with bipolar disorder (BD). The authors introduce the proposed systematic review by providing background to the available pharmacological and psychological treatment approaches to individuals with BD, prevalence of CT and related greater symptomatology in individuals with BD, before studies are cited who examined the potential moderating role of CT in treatment-related outcome measures. In the next step, the authors describe methodological steps of how to perform the systematic review and meta-analysis, if the data allows. However, there are several concerns that need to be addressed.

1) General comment re the focus (study objective) of the protocol manuscript:

a) Please add details of potential impact of the outcomes of the systematic review/meta-analysis to the abstract, article summary, introduction, objectives, and conclusions. There are brief attempts (in the objectives for a 'moderating role' and in the conclusion for 'clarification of the role of CT'). However, these statements are vague and very general.

RESPONSE: Thank you for the excellent suggestion. We have expanded the statement regarding the impact of this systematic review/meta-analysis in the introduction. It now reads (line 155): "To date, there has been no systematic reviews focusing on the influence of childhood trauma on the treatment outcomes of pharmacological, psychological, and combined interventions for adolescents and adults with bipolar disorder. This is despite current research demonstrating that experiences of childhood trauma may be highly relevant to the efficacy of treatments for bipolar disorder. Research that aims to improve the prediction of treatment outcomes can greatly benefit patients with psychiatric disorders as this knowledge may reduce the burden associated with receiving inappropriate and/or suboptimal treatments and decrease patients' risk of experiencing a chronic illness course.

Exploring the influence of exposure to childhood trauma on patients' treatment outcomes may thus assist the development of individualised interventions for people with bipolar disorder, promoting treatment success and ultimately facilitating recovery. Clarification on the role that childhood trauma plays in the treatment of bipolar disorder has clear translational value with the potential to inform clinical guidelines and practice. A systematic exploration of the available evidence is particularly suitable for this endeavour because it allows for data to be collated from a variety of sources and illustrate areas of research that are underscored by a limited number of patients and/or conflicting evidence." The impact statement has not been included in other sections of the manuscript according to the journal formatting requirements for protocol papers.

I also have a few questions: Why do the authors only propose a moderating role of CT? Why not any other potential role? For the moderating role, what is the theoretical hypothesis as this is not clear in the introduction (page 5).

RESPONSE: The prior research that we have cited in the introduction of this manuscript indicated childhood trauma as a potential moderator of the treatment outcomes among people with bipolar disorder (e.g., see the section on the study by Etain et al., 2017; line 109). For clarification, we have slightly amended the sentence that 'introduces' the previous literature. The manuscript now reads

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(line 102): “Due to the high prevalence of childhood trauma and its clear clinical relevance, research has recently begun to focus on childhood trauma as a potential moderator of treatment outcomes for both pharmacological and psychological interventions in bipolar disorder.”

b) Why do the authors propose to include adolescents? I recommend to focus on adults only for the following reasons:

- **As the authors point out, this would be the first systematic review (and meta-analysis) in this field. Therefore, I suggest to focus on the adult population group with a decent number of random clinical trials (RCT) and to provide a ‘clean’ systematic review.**
- **Given the wide range of inclusion criteria for clinical interviews, assessment tools for CT, treatment options, and the emphasis on adults would help (to some extent) to interpret the findings and to streamline such a first systematic review on this topic.**
- **Although I fully agree that it is a growing field to study young people with BD who have also experienced CT, there are less than a handful of studies in adolescents published currently.**
- **Following on from the previous point, the authors do not argue why adolescents should be included.**

RESPONSE: We agree that focusing exclusively on adult samples would result in a ‘cleaner’ review. However, we believe that the broad scope is a significant strength of our protocol and that this will increase the generalisability of the findings and facilitate the utility of the review. To emphasise this point, we have added the following sentence to the section detailing what types of participants are eligible for the review (line 190): “These inclusive eligibility criteria will permit a thorough assessment of the extant literature and support generalisability.” Additionally, the scoping exercise that we completed in preparation for formulating this protocol indicated a great diversity in age groups investigated in this field of research, underscored by a lack of RCTs conducted with adults. Future systematic reviews (when more original studies including RCTs have been published) should thus focus on more specific target populations and/or study designs.

Nevertheless, we agree that age will need to be considered as a factor of influence in this systematic review/meta-analysis. Therefore, we have planned a subgroup analysis considering age which will allow us to compare adolescents and adults. Also, if there is insufficient data for a meta-analysis and the planned subgroup analyses, we plan to discuss age in detail in the narrative evaluation of this systematic review. Please also note that previous high-quality systematic reviews/meta-analyses that focused on childhood trauma in bipolar disorder included both types of populations. For example, the large-scale meta-analysis by Agnew-Blais and Danese (2016) published in Lancet Psychiatry included participants as young as 10 years of age.

c) The authors write in the paragraph ‘Ethics and dissemination’ that ‘multiple publications may be derived from this protocol’: I do not think that this is possible, or feasible, based on single protocol for a systematic review (and meta-analysis) when the inclusion criteria are defined to lead to clearly interpretable findings. Given the wide range of inclusion criteria as mentioned above, I question whether the authors will find significant meta-analytic findings based on similar reviews/meta-analysis in the field of BD, CT, etc. When then adding the group of adolescents, I doubt that this will result in interpretable findings. If adolescents will be included, I suggest to write a separate systematic review/meta-analysis with age-appropriate clinical interviews, CT assessment tools, etc. that have to be clearly differentiated from the adult criteria. Finally, if adolescents were to be included, the diagnoses of BD would need to be adjusted to the age and developmental stage (for example, early-onset BD, etc.).

RESPONSE: We agree that it may not be possible to conduct a meta-analysis due to the heterogeneity in the extracted data. However, as we have touched on in our response to your

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previous comment, we do not believe that the current body of research allows for two separate reviews (adolescents and adults) on the topic.

Although we may not be able to conduct a meta-analysis, we will be able to critically review the existing evidence in the context of a narrative review. This comprehensive evaluation, in turn, will provide readers with an inclusive overview of the extant research and can guide future work on the topic. We realised that the manuscript heavily focuses on the quantitative/statistical evaluation and have added an explicit statement on the narrative evaluation to the section 'Data synthesis and statistical analyses' (line 355): "A narrative evaluation of these results will additionally be provided."

However, we agree with your suggestion and will publish two separate papers, one focusing on adolescents and the other focusing on adults, if there indeed are enough studies for two systematic reviews/meta-analyses. To allow for this option, we had included the sentence (line 406): "Multiple publications may be derived from this protocol.", in our manuscript.

To address your concern regarding the bipolar diagnoses included, the inclusion criteria for this systematic review allow all bipolar and related disorders to be considered. Additionally, we will extract data on other clinical features (e.g., age of onset, number of episodes) that will assist us in detailing their presentation further.

2) Definition of treatment outcome measures: I agree with the authors that currently studied treatment outcome measures are not used in a unified version. The authors have a chance here of studying the most widely used outcome measures with additional measures to study this issue. After raising this point in the introduction, the authors do not follow up on this point in the methods section but rather leave this point open in a general way. I think this point here could become one of the major novelties in the field, for example, the outcome measure of number of suicidal attempts, in particular after the authors mention this symptom in the introduction.

RESPONSE: In our introduction, we meant to highlight the importance of also considering treatment outcomes that address participants' functional (e.g., global functioning) and personal (e.g., quality of life) recovery as part of a comprehensive evaluation; rather than focusing on the reduction in symptoms (i.e., symptomatic recovery) alone. We have (also in response to one of your later comments) added a definition of personal recovery for clarity. The relevant section now reads (line 143):

"Additionally, a wide range of treatment outcomes have been considered in clinical research on bipolar disorder. Although researchers have traditionally focused on outcomes related to symptomatic and functional recovery, patients' personal recovery has increasingly received attention. Personal recovery is frequently conceptualised as the process an individual undergoes to psychologically adapt to their disorder; a definition that expands patients' recovery beyond the reduction of psychiatric symptoms and impairments in functioning. The evaluation of treatment outcomes that capture the experiences of the individual more broadly is encouraged as some patients continue to report significant impairments in functioning and QoL even though they only have relatively mild symptoms. Hence, symptom measures alone appear to be inadequate in assessing treatment effectiveness in bipolar disorder."

We included both improvement in functioning as well as quality of life as treatment outcomes in this systematic review/meta-analysis. Furthermore, the variety of measures/questionnaires/interviews that may be used in studies to assess each of the outcomes will be described in detail in the narrative review. We are particularly interested in exploring outcomes that detail patients' recovery (improvement, response, remission, relapse); however, we believe that number of suicide attempts

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should be included as part of the subgroup analysis that explores clinical features. Thank you for the suggestion.

3) Title: I suggest to shorten the title by removing 'pharmacological and/or psychological' given that these are the commonly available options. In the introduction, the authors can then provide more details.

RESPONSE: We agree that these are commonly available treatment options. However, we had specified the interventions that are of interest for this systematic review in line with the elaboration on the PRISMA-P guidelines (see Shamseer et al., 2015). There the authors advise to include a title that reflects the PICO approach. Also considering the rapid growth of lifestyle interventions for bipolar disorder, we believe that the title should be specific. However, to clarify this point, we have explicitly added lifestyle interventions as a type of intervention that will be excluded from the review to the protocol. The following sentence has been added to the section 'Types of interventions' (line 236): "Studies that exclusively investigated lifestyle interventions, however, will be excluded from this review."

4) Article summary:

a) Fourth point of heterogeneity (also applies to the methodological section): As this will be the first systematic analysis for this topic, I assume the authors aim to define 'liberal' study design criteria. However, this approach will likely result in non-significant findings based on the findings of previous systematic reviews and mega-analyses. Therefore, I recommend to be more stringent with the inclusion criteria to guarantee robust findings. In future separate reviews (when more original articles of RCTs will be available), it will be more feasible to refocus on more focused details of interest. Specific recommendation are here:

- **In particular, adolescents as a sample should be removed (please see comments above).**

RESPONSE: We agree that more stringent inclusion criteria would increase the likelihood of robust findings. However, we aim to provide the reader with a comprehensive evaluation of the already existing evidence. This is the first systematic review on the topic; as such, the broader inclusion criteria (e.g., regarding eligible participants, study designs, assessment tools, treatments of interest) will greatly increase its generalisability. Please see our response to one of your previous comments addressing the inclusion of adolescent participants.

- **In addition, only RCTs should be included.**

RESPONSE: We agree that RCTs are more likely to provide us with unbiased information about the differential effects of treatments than non-randomised studies of interventions. However, as touched on in one of our previous responses, our preliminary search of the existing body of research led us to conclude that there are insufficient RCTs that have considered childhood trauma as a potential influential factor. The Cochrane Collaboration indeed recognises the following as an appropriate justification for authors to also include non-randomised studies of interventions: "To provide evidence of the effects (benefit or harm) of interventions that can feasibly be studied in randomized trials, but for which only a small number of randomized trials is available (or likely to be available)."

Guided by the recommendations of the Cochrane Collaboration, we have planned to mitigate the risk of bias introduced by the inclusion of non-randomised studies as much as possible. For example, the manuscript reads (line 373): "As per guidelines from the Cochrane Handbook for Systematic Reviews of Interventions 6.0, randomised trials and non-randomised studies of interventions will not be combined in one meta-analysis. Instead, randomised trials and non-randomised studies will be

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separately analysed. Additionally, non-randomised studies of interventions that were judged to have a high risk of bias will be excluded from the meta-analysis."

- **Please streamline the clinical interviews to adult age and the most commonly used ones.**

RESPONSE: We agree that only studies with clearly defined diagnostic populations should be eligible for inclusion in the review. In our manuscript, we have outlined that only studies that have confirmed participants' diagnoses with clinical interviews/assessments that align with standardised diagnostic criteria such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD) will be included. We believe that this will sufficiently streamline the diagnostic assessments.

- **Regarding the measurement of childhood trauma, I suggest to only include widely established questionnaires as the CTQ and ACE. In particular, please remove the inclusion of medical file information, as this is a 'routine' limitation in systematic reviews and meta-analyses.**

RESPONSE: We agree that allowing for the inclusion of childhood trauma data that is collected via in chart review will need to be addressed as a limitation of this research in the discussion section of the systematic review. However, we do believe that including this information has significant merit when conducting a comprehensive first review of a topic as it reflects the "real-world" rather than just a research context. The file-audit method also has several other advantages of which the following two are particularly important for this systematic review (also see Conus et al., 2010):

1. it allows for the inclusion of data from patients who would be unlikely to participate in prospective studies requiring an informed consent procedure, such as those with highest illness severity, highest rate of comorbidity, and poor engagement in treatment;
2. the assessment of trauma over the entire duration of a treatment program and in the context of a trusting relationship with a clinician offers more opportunities for patients to talk about this difficult issue than during a single interview conducted by a research interviewer.

- **Please limit the pharmacological mediation to some but not all of the listed medication.**

RESPONSE: Thank you for your suggestion. We developed our research question with the aim to provide a reader with a comprehensive evaluation of the available evidence detailing the role of trauma in the treatment of bipolar disorder. As a variety of pharmacological and psychological are commonly used and recommended for the treatment of bipolar disorder (e.g., mood stabilisers, antidepressants, antipsychotics, cognitive behavioural therapy [CBT], interpersonal and social rhythm therapy [IPSRT], and family-focused therapy [FFT]), we prefer to keep a the scope of the review broad.

5) Introduction:

a) In general, please add more details to the introduction of why it is so important to run a systematic review in this field. Please add more recent systematic reviews instead of original studies for references.

RESPONSE: Thank you for the excellent suggestion. Additional justification for this systematic review has been added; the manuscript now reads (line 166): "Clarification on the role that childhood trauma plays in the treatment of bipolar disorder has clear translational value with the potential to inform clinical guidelines and practice. A systematic exploration of the available evidence is particularly suitable for this endeavour because it allows for data to be collated from a variety of sources and

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illustrate areas of research that are underscored by a limited number of patients and/or conflicting evidence." However, this is, to the best of our knowledge, the first systematic review exploring the impact of childhood trauma on the treatment outcomes in bipolar disorder. Therefore, previous reviews cannot be detailed in the introduction.

b) The authors write about the importance of mood symptoms but not about psychotic symptoms. Please add this aspect to the introduction.

RESPONSE: We agree that psychotic symptoms in bipolar disorder are of importance. However, we believe that these are best addressed in a review that focuses exclusively on bipolar I disorder or on psychotic disorders (including bipolar disorder) more generally. As our systematic review/meta-analysis includes the range of bipolar and related disorders, we put emphasis on the mood symptoms which are experienced across the different cohorts.

c) Please add 'such as childhood trauma' after 'environmental risk factors in line 18 to create a link to the following paragraph.

RESPONSE: The sentence has been amended and now reads (line 68): "These findings highlight the clinical importance of recognising environmental risk factors, such as childhood trauma, that contribute to the outcomes in bipolar disorder."

d) Page 4: Please also add evidence from longitudinal studies to strengthen the relevance for treatment issues.

RESPONSE: Thank you for the suggestion. We agree that it would be useful to add longitudinal studies to the introduction. The following section has been added (line 89): "The reviewers' findings are largely echoed in recent longitudinal studies. Andreu Pascual et al., for example, prospectively followed a large group of young people with bipolar disorder. The researchers demonstrated that the experience of at least one traumatic event in childhood was related to an earlier symptom onset, more severe affective symptoms, greater suicidal ideation, psychiatric comorbidities, and greater functional impairment. Additionally, Andreu Pascual et al. noted that people who were exposed to a traumatic event after achieving symptomatic recovery, were more likely to experience an affective relapse."

e) Page 5, last paragraph on inflammation: Although I agree on the potentially promising future of RCTs studying inflammatory markers, more details on this background are needed: Are these references in favour of low-grade inflammation in these individuals, what type of inflammatory markers are considered here (pro- or anti-inflammatory)?

RESPONSE: We agree that the study of inflammatory markers in bipolar disorder has great utility. However, as we reference the RCT that investigated the effectiveness of an anti-inflammatory agent solely to highlight the conflicting evidence in the field we will leave the elaboration on inflammatory markers to other research. If a significant body of research that focuses on anti-inflammatory agents in the context of childhood trauma is identified as part of this review, we will revisit this topic in the discussion of the publication of the systematic review/meta-analysis itself.

f) Please also give background/evidence in the literature to the inclusion of studying the effect of antipsychotics and/or antidepressants in this context of the systematic review, please.

RESPONSE: Antipsychotics and/or antidepressants are widely used for the management of bipolar disorder (Miziou et al., 2015); we aim to complete a comprehensive review that can provide an overview of the impact of childhood trauma on the majority of treatments used. Although we were unable to identify any studies that considered the impact of childhood trauma on the effectiveness of

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these medications in our scoping exercise, any studies that are identified during our systematic search will be included.

f) Please clarify the second sentence in the last paragraph of the introduction. What are the differences between the three recovery types? Please rephrase.

RESPONSE: Thank you for pointing out the need for clarification of this statement. The manuscript has been amended to read (line 144): “Although researchers have traditionally focused on outcomes related to symptomatic and functional recovery, patients’ personal recovery has increasingly received attention. Personal recovery is frequently conceptualised as the process an individual undergoes to psychologically adapt to their disorder; a definition that expands patients’ recovery beyond the reduction of psychiatric symptoms and impairments in functioning.”

6) Objectives:

a) Please rename ‘disorder-related features’ to ‘clinical measures’.

RESPONSE: ‘Disorder-related features’ has been changed to ‘clinical features’ throughout the manuscript.

b) I suggest to ask the authors to consider of adding typical clinical measures of rapid cycling and number of suicide attempts.

RESPONSE: Thank you for the excellent suggestion. We have added ‘rapid cycling’ and ‘number of suicide attempts’ as clinical features to the subgroup analyses planned for this systematic review/meta-analysis (line 382).

c) Please add symptom severity as one of the main outcome measures.

RESPONSE: Thank you for pointing out the lack of clarity in the objectives section. We have added to following sentence to allude to the treatment outcomes that will be considered in this systematic review (line 176): “Treatment outcomes detailing participants’ symptomatic severity as well as functional and personal recovery will be explored.”

d) Please make sure that not only mood symptoms but also psychotic features are covered.

RESPONSE: Please see our response addressing psychotic symptoms above.

7) Methods and analysis

a) My general concern regarding the methodology lies in the lenient inclusion criteria (please see above). How do the authors propose to analyse the findings when it is commonly known that the variety of measures (for example, medical file entries for CT) cannot be compared with standardized questionnaires? The authors write that heterogeneity is likely given the 'lenient' criteria as one of the limitations. However, this not strong enough from the methodological perspective, where the authors should directly improve this limitation by defining stricter inclusion criteria (please see also above).

RESPONSE: We agree that the broad inclusion criteria may prevent us from completing a meta-analysis. However, as we have outlined above, we will be able to critically evaluate the extant research in a narrative review. If a meta-analysis appears feasible after all, we are planning to

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conduct sensitivity analyses that can account for methodological differences in the studies included (e.g., chart review vs. standardised questionnaires).

b) Page 7: Please rephrase the subheading to 'Groups of participants' and remove adolescents as my recommendation.
c) Page 8: Please rephrase the subheading to 'Study designs' and only focus on RCT as my recommendation following the authors' argumentation on pages 12-13.

RESPONSE: Thank you for the suggestion. However, we prefer to leave the subheadings unchanged to keep them consistent with the other subheadings included in the manuscript. Please also see our previous responses above.

d) Page 9, Types of outcome measures: What are the 'both' phases of the disorder? Please define here and previously in the introduction as it is currently missing. Please add measures for psychotic symptoms in here (and the following listing) and adjust the clinical interviews to adult age.

RESPONSE: Thank you for highlighting that a clarification of the two phases of bipolar disorder is needed. A brief description of mania and depression has been added to the introduction (line 62): "A manic episode is typically marked by an unusually elevated or irritable mood, whereas low mood or a significant loss of interest or pleasure occurs in a depressive episode." The phrase 'in both phases of the disorder' has been removed from the outcomes section to reduce potential for confusion. Please see our response addressing psychotic symptoms above.

e) Page 13: Please add a reference for the 'rule of thumb'.

RESPONSE: The relevant reference has been added.

f) Page 13: Data synthesis and statistical analysis: Please add what software you will use.

RESPONSE: Thank you for pointing out that it is unclear what software we will be using for our quantitative analyses. We mentioned in the paragraph outlining the planned meta-analysis that we will use the software Comprehensive Meta-Analysis (CMA). We agree that this statement was not general enough to include all statistical analyses and have rephrased it (line 370): "All statistical analyses will be conducted with the software Comprehensive Meta-Analysis (CMA)."

g) Page 14: Please correct to 'for continuous outcome variables' in the first paragraph.

RESPONSE: This section in the manuscript has been amended. It now reads: "For categorical outcome variables, risk ratios (RR) or odds ratios (OR) with 95% confidence intervals will be calculated. For continuous outcome variables, mean differences or standardised mean differences with 95% confidence intervals will be calculated."

VERSION 2 – REVIEW

REVIEWER	Maria Dauvermann University of Cambridge, Psychiatry
REVIEW RETURNED	24-Dec-2020

GENERAL COMMENTS	I thank the reviewers for the replies and the changes made. I am happy with these.

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