PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

Mechanism-based modular psychotherapy vs. cognitive behavioral therapy for adolescents and young adults with childhood trauma experiences: Study protocol for a feasibility trial within the German Center for Mental Health

Authors

Seitz, Katja Isabell I.; Schouler, Niklas; Hundertmark, Jan; Wilhelm, Maximilian; Franz, Svea; Bauer, Stephanie; Taubner, Svenja; Korn, Christoph W.; Haun, Markus W.; Ditzen, Beate; Zimmermann, Hanna; Enning, Frank; Vonderlin, Ruben; Schmahl, Christian; Schramm, Elisabeth; Aguilar-Raab, Corina; Vonderlin, Eva; Bailer, Josef; Bopp, Elias; Berner-Rodoreda, Astrid; Bärnighausen, Till; Calvano, Claudio; Feisst, Manuel; von Stockert, Sophia; Kristalis, Laura Tabea; Friederich, Hans-Christoph; Herpertz, Sabine C.

VERSION 1 - REVIEW

Reviewer **1**

Name **Burkhardt, Gerrit**

Affiliation **University Hospital Munich, Psychiatry and Psychotherapy**

Date **21-Oct-2024**

COI **I currently lead a clinical trial on theta burst stimulation for adolescents and young adults with depressive disorders (DRKS00033313), which is supported within the initial phase of the German Center for Mental Health (Deutsches Zentrum für Psychische Gesundheit [DZPG], grant 01EE2303A) at the Munich-Augsburg site.**

This study protocol outlines a well-conceived feasibility trial comparing a modular psychotherapy program (MeMoPsy) with cognitive-behavioral therapy (CBT) for adolescents and young adults with a history of childhood trauma across a range of psychiatric diagnoses. In addition to a core module on trauma history, MeMoPsy incorporates specialized modules targeting rejection sensitivity, emotion regulation, and relationship difficulties—key areas of impairment associated with childhood trauma. These modules are selected based on participant scores that meet empirically derived cut-off values on self-report measures. The trial addresses a clear clinical need and is grounded in contemporary research on trauma

mechanisms. Notable strengths include the use of an active control group (non-manualized CBT with regular supervision), blinding of clinical raters, state-of-the-art data management and monitoring procedures, and a strong emphasis on patient and public involvement. The manuscript adheres to the SPIRIT 2013 Checklist and is both well-written and comprehensive. Overall, the manuscript is highly relevant to a broad medical and psychological readership. However, there are a few design elements that would benefit from further clarification:

- The treatment selection algorithm is based on empirical cut-off values from adult, general population samples. It would be helpful if the authors could elaborate on the clinical relevance of these thresholds, particularly in the adolescent population. Additionally, further clarification is needed regarding how potential misclassifications, especially in diagnostic subgroups, will be identified and managed.

- Categorical diagnoses are established using the Mini-DIPS, which provides comprehensive assessment for anxiety and mood disorders but includes only basic screening for conditions like psychotic disorders. The rationale behind the decision to include more detailed assessments for ADHD but not for other conditions, such as psychosis, should be explained. The author might also consider repeating diagnostic assessments later in the trial to evaluate the stability of diagnoses over time.

- The trial allows changes in psychotropic medications two weeks before inclusion (three weeks for fluoxetine), which generally ensures steady-state plasma levels. However, the timeline for therapeutic effects can vary between disorders (e.g., delayed response to antidepressants in OCD compared to depression). The authors should discuss how such variations might affect the interpretation of results across different diagnostic groups.

- The trial does not exclude participants based on prior psychotherapy experience. Participants with extensive previous therapy exposure might be familiar with techniques in both MeMoPsy and CBT, potentially reducing their responsiveness to the interventions. Are there guidelines in place for MeMoPsy therapists on how to adapt in such cases, especially since the control group may offer more flexibility?

- While clinical outcomes will be assessed by blinded raters, self-reported outcomes could be influenced by factors such as treatment expectancy and health beliefs. Have the authors considered adding measures to account for these potential mediators?

- In the “Strengths and limitations of this study” section, the authors mention that the trial includes “difficult to treat adolescents and young adults” (p.6 l.8). Since prior treatment-resistance or non-response is not a criterion for inclusion, this claim might be misleading and should be revised.

- It is encouraging that the authors intend to provide access to participant-level data and statistical code upon request, greatly enhancing the reproducibility of their findings. To further support transparency and facilitate broader research collaboration, have the authors

considered openly sharing anonymized data via a dedicated repository, such as a publicly accessible database?

VERSION 1 - AUTHOR RESPONSE

The following paragraph addresses the comments and suggestions of Reviewer #1, Dr. Gerrit Burkhardt, University Hospital Munich:

This study protocol outlines a well-conceived feasibility trial comparing a modular psychotherapy program (MeMoPsy) with cognitive-behavioral therapy (CBT) for adolescents and young adults with a history of childhood trauma across a range of psychiatric diagnoses. In addition to a core module on trauma history, MeMoPsy incorporates specialized modules targeting rejection sensitivity, emotion regulation, and relationship difficulties—key areas of impairment associated with childhood trauma. These modules are selected based on participant scores that meet empirically derived cut-off values on self-report measures. The trial addresses a clear clinical need and is grounded in contemporary research on trauma mechanisms. Notable strengths include the use of an active control group (non-manualized CBT with regular supervision), blinding of clinical raters, state-of-the-art data management and monitoring procedures, and a strong emphasis on patient and public involvement. The manuscript adheres to the SPIRIT 2013 Checklist and is both well-written and comprehensive. Overall, the manuscript is highly relevant to a broad medical and psychological readership.

We would like to thank Dr. Burkhardt for his positive feedback.

However, there are a few design elements that would benefit from further clarification:

1. **The treatment selection algorithm is based on empirical cut-off values from adult, general population samples. It would be helpful if the authors could elaborate on the clinical relevance of these thresholds, particularly in the adolescent population. Additionally, further clarification is needed regarding how potential misclassifications, especially in diagnostic subgroups, will be identified and managed.**

We thank Dr. Burkhardt for this important comment. We now elaborate on the clinical relevance of the empirical cut-off values of our module-specific questionnaires.

Page 11: "If the cut-off values of the module-specific questionnaires are exceeded, the respective module will be used for that patient. Building on prior experiences (1, 43, 53), the module-specific cut-off values are based on adult general population samples. While validation of our empirical cut-off values in an adolescent clinical sample is still pending, all three module-specific questionnaires have

been tested in adolescent general populations (e.g., 54, 55, 56) and one of them (i.e., Rejection Sensitivity Questionnaire, RSQ, 25) has already been proven to be clinically relevant in a previous trial (1).”

Page 12: “Module 1 is administered if patients score ≥ 9.88 on the Rejection Sensitivity Questionnaire (RSQ) [25] (cut-off defined as one standard deviation above the general population mean, i.e. the upper 16%, as reported in Schramm et al. [1]). […]”

Page 12: “Module 2 is administered if patients score ≥ 46.97 on the State Difficulties in Emotion Regulation Scale (S-DERS) [62] (cut-off defined as one standard deviation above the general population mean as reported in Lavender et al. [62]). […]”.

Page 13: “Module 3 is administered if patients score ≥ 13 on the German version of the Outcome Questionnaire 45 (OQ-45), Interpersonal Relations subscale [53, 64] (cut-off defined as the 80th percentile of the general population as reported in Lambert et al. [53]). […]”

With regard to Dr. Burkhardt’s comment concerning “potential misclassifications, especially in diagnostic subgroups”, we would like to emphasize that MeMoPsy targets transdiagnostic mechanisms of change (i.e., rejection sensitivity, emotion dysregulation, difficulties in (close) interpersonal relationships) closely related to childhood trauma experiences. The reasons for not focusing on diagnostic subgroups lie in large-scale longitudinal studies indicating that individuals with childhood trauma experiences have threefold increased odds of having more than three mental disorders (e.g., Scott et al., 2010, Arch Gen Psychiatry). Our sample is thus transdiagnostic and is not classified into diagnostic subgroups. However, motivated by Dr. Burkhardt’s comment, we now clarify that in the qualitative interviews, therapists will be asked about their experiences with MeMoPsy, also with regard to their experiences with the algorithm-driven selection of therapy modules for a population meeting various clinical diagnoses.

Page 18: “Therapists will be asked about […] their experiences with the algorithm-driven selection of therapy modules for a population meeting different clinical diagnoses.”

2. **Categorical diagnoses are established using the Mini-DIPS, which provides comprehensive assessment for anxiety and mood disorders but includes only basic screening for conditions like psychotic disorders. The rationale behind the decision to include more detailed assessments for ADHD but not for other conditions, such as psychosis, should be explained. The author might also consider repeating diagnostic assessments later in the trial to evaluate the stability of diagnoses over time.**

We thank Dr. Burkhardt for allowing us to explain the rationale behind selecting the diagnostic instruments for our feasibility trial. The Mini-DIPS is a fast and efficient measure to screen for different mental disorders, however, it does not allow to assess ADHD which is why we opted for an additional assessment of this condition using the SCID-5-CV. We have added this information in the section on Data collection (see below). Furthermore, acute psychotic symptoms are an exclusion criterion in our study (see Page 10: "One or more mental disorders requiring diagnosis-specific treatment as assessed by clinical judgement and applying the Mini-DIPS [46] […], including acute psychotic […] symptoms […]). Therefore, we decided that a basic screening for psychotic disorders using the Mini-DIPS is sufficient. Since our treatment targets transdiagnostic mechanisms underlying the connection between early trauma and mental disorders and not diagnoses, we decided to avoid placing an even greater time burden (currently around 3 hours of diagnostics at baseline alone) on our young patients, which could also lead to poor data quality.

Page 23: "(4) ADHD will be assessed with the SCID-5-CV [48] as it cannot be determined by using the Mini-DIPS […]"

We thank Dr. Burkhardt for suggesting to repeat diagnostic assessments to evaluate stability of diagnoses. With our transdiagnostic approach, we focus on assessing the severity of functional impairments and psychopathological symptoms, rather than the stability of categorical diagnoses over time. Thus, we decided against repeating the Mini-DIPS, but rather repeat transdiagnostic assessments in our study (see Table S1 in the Supplement).

3. **The trial allows changes in psychotropic medications two weeks before inclusion (three weeks for fluoxetine), which generally ensures steady-state plasma levels. However, the timeline for therapeutic effects can vary between disorders (e.g., delayed response to antidepressants in OCD compared to depression). The authors should discuss how such variations might affect the interpretation of results across different diagnostic groups.**

We thank Dr. Burkhardt for noting that the timeline for therapeutic effects of psychotropic medications can vary between disorders. We agree with Dr. Burkhardt that these variations might affect the interpretation of results and thus represent a methodological limitation of transdiagnostic studies. Motivated by Dr. Burkhardt's comment, we decided to calculate a standardized composite psychotropic medication score to be able to control for potential medication effects before, during, and at the end of treatment:

Page 18: "Self-designed items to assess medication before, during and at the end of treatment, rated by patients, which will allow to calculate a standardized composite psychotropic medication score following established procedures [87]"

4. **The trial does not exclude participants based on prior psychotherapy experience. Participants with extensive previous therapy exposure might be familiar with techniques in both MeMoPsy and CBT, potentially reducing their responsiveness to the interventions. Are there guidelines in place for MeMoPsy therapists on how to adapt in such cases, especially since the control group may offer more flexibility?**

In accordance with the objectives of the German Center of Mental Health (Deutsches Zentrum für Psychische Gesundheit, DZPG), the clinical study was designed close to the reality of a high-need patient population, excluding as few patients as possible. Motivated by Dr. Burkhardt's comment, we now draw the reader's attention to the fact that prior psychotherapy experience is not an exclusion criterion in the section on eligibility criteria. Due to the young age of the patients, however, we do not assume that they have extensive prior psychotherapy experience, and we expect psychotherapy experience to be evenly distributed across both treatment arms. We now make the reader aware of the fact that we assess prior psychotherapy experiences in detail using online questionnaires, and we will be able to compare prior psychotherapy experiences between both treatment arms.

Page 10: "Please note that prior psychotherapy experience is not an exclusion criterion; however, prior psychotherapy experience will be assessed in detail in both therapy arms to allow for a comparison regarding familiarity with psychotherapeutic interventions."

Concerning the assumption that CBT may offer more flexibility than MeMoPsy, we would like to state that modular treatment is known for its high flexibility (McHugh, Murray, & Barlow, 2009, Behav Res Ther), e.g. MeMoPsy therapists are flexible in when they use which module and determine the dosage of each module depending on the patient's needs. Motivated by Dr. Burkhardt's comment, we now elaborate more on the flexibility of our MeMoPsy approach:

Page 13: "The modules are not simply added as separate and serial components, but therapists will be trained and supervised to integrate them into the dynamic course of the therapeutic process. Consequently, the amount of time spent with a single module will be reduced if more modules are indicated for an individual patient. The therapists are required to use all defined mandatory interventions within the course of a therapy, but beyond that, they will use their clinical judgement and the aid of their supervisors to choose the most effective interventions from the available modules. Therapists will document the time spent with each module and which interventions they use. Altogether, the treatment procedure is algorithm-driven, but allows for a certain degree of flexibility and further personalization necessary in clinical practice."

5. **While clinical outcomes will be assessed by blinded raters, self-reported outcomes could be influenced by factors such as treatment expectancy and health beliefs. Have the authors considered adding measures to account for these potential mediators?**

We thank Dr. Burkhardt for this very valuable suggestion. Due to limited resources in the current feasibility trial, we were unfortunately not able to include additional assessments of clinical outcomes by blinded rates. However, we are planning to include them in the main trial following the current feasibility trial.

6. **In the "Strengths and limitations of this study" section, the authors mention that the trial includes "difficult to treat adolescents and young adults" (p.6 l.8). Since prior treatment-resistance or non-response is not a criterion for inclusion, this claim might be misleading and should be revised.**

We have revised the sentence according to Dr. Burkhardt's suggestion.

Page 4: "This is the first study to investigate the feasibility of a mechanism-based, modular psychotherapy (MeMoPsy) for adolescents and young adults with various, frequently comorbid diagnoses and a history of early trauma, thus, a population known to often show poorer treatment responses to standard psychotherapy compared to non-traumatized patients."

7. **It is encouraging that the authors intend to provide access to participant-level data and statistical code upon request, greatly enhancing the reproducibility of their findings. To further support transparency and facilitate broader research collaboration, have the authors considered openly sharing anonymized data via a dedicated repository, such as a publicly accessible database?**

We thank Dr. Burkhardt for this valuable suggestion. After correspondence with the DZPG data management committee, the general data sharing plans and contracts within the DZPG are currently being developed.

VERSION 2 - REVIEW

Reviewer	**1**
Name	**Burkhardt, Gerrit**
Affiliation	**University Hospital Munich, Psychiatry and Psychotherapy**
Date	**07-Mar-2025**

COI

The authors' revisions have significantly enhanced the clarity, rigor, and overall quality of the manuscript. Readers can now better appreciate the significance of transdiagnostic measurements, the rationale behind decisions regarding the study's eligibility criteria, and procedures conducted during therapy sessions. Additionally, the authors have effectively addressed the issue of heterogeneous psychotropic medication use within the targeted population by calculating a medication score. Based on these substantial improvements, I highly recommend the manuscript for publication in BMJ Open and congratulate the authors for their valuable contribution to the field.