Journal of Clinical Question

Decision Letter (JCQ-2026-0017)

From: [redacted]
To:
CC:
BCC:

Subject: Journal of Clinical Question - Decision on Manuscript ID JCQ-2026-0017

Body: 21-April-2026

Dear Dr Liu:

Manuscript ID JCQ-2026-0017 entitled "Virtual Reality for Symptom Management During Outpatient Chemotherapy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials" which you submitted to the Journal of Clinical Question, has been reviewed. The comments of the reviewer(s) are included at the bottom of this letter.

The reviewer(s) have recommended publication, but also suggest some revisions to your manuscript. Therefore, I invite you to respond to the reviewer(s)' comments and revise your manuscript.

To submit your revised manuscript, follow the below steps.
1. Access to https://mc.manuscriptcentral.com/jcq and log into the site.
2. Click "Author" at the top left of the screen at "Home" page.
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5. The system creates your revision manuscript form. Provide your comments about the revised points at the response field, fill in on each field step by step as same as you did for the original submission, and submit your revised manuscript.
IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.
Your manuscript number has been appended to denote a revision.

You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer. Please also highlight the changes to your manuscript within the document by using the track changes mode in MS Word or by using bold or colored text.

Once the revised manuscript is prepared, you can upload it and submit it through your Author Center.

When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) in the space provided. You can use this space to document any changes you make to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s).

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

Because we are trying to facilitate timely publication of manuscripts submitted to the Journal of Clinical Question, your revised manuscript should be uploaded as soon as possible. If it is not possible for you to submit your revision in a reasonable amount of time, we may have to consider your paper as a new submission.

Once again, thank you for submitting your manuscript to the Journal of Clinical Question and I look forward to receiving your revision.

Sincerely,
Richard S. Isaacs
Editor in Chief
Journal of Clinical Question

[Editor's Comments]
Associate Editor
Comments to the Author:
(There are no comments.)

[Reviewer(s)' Comments]

Reviewer: 1

Comments to the Author
Strengths:
- Important and clinically relevant topic in supportive cancer care
- Appropriate methodology with PRISMA guidelines adherence
- Protocol registration and use of standardized tools (RoB 2, GRADE)

Points Requiring Revision:

1. High heterogeneity:Please provide subgroup analysis or meta-regression to explore sources of heterogeneity (I^2=84.2% for anxiety).

2. Clinical implications:Discuss the clinical implications of findings and barriers to VR implementation in clinical settings more thoroughly.

3. Generalizability: Given that most studies enrolled women (breast/gynecologic cancers), please discuss the generalizability of results to other patient populations.

4. Cost-effectiveness:Mention the need for future studies to evaluate cost-effectiveness

Reviewer: 2

Comments to the Author
Major comments:

1) Introduction

The rationale and research gap of the current review require further clarification in the Introduction section. Previous systematic reviews and meta-analyses have already evaluated the effectiveness of virtual reality interventions among patients receiving chemotherapy, including studies by Gautama et al. (Eur J Oncol Nurs. 2023; DOI: 10.1016/j.ejon.2023.102424) and Burrai et al. (https://doi.org/10.1016/j.ejon.2023.102340). While the current manuscript states that evidence remains inconsistent, this alone may not sufficiently justify the need for another meta-analysis. The authors are encouraged to explicitly describe the limitations of prior evidence syntheses and clearly highlight the novel contribution of the present study.

2) Effects on Anxiety

The sensitivity analysis methodology requires clarification. The manuscript reports that heterogeneity decreased substantially after excluding studies; however, the rationale for excluding specific studies is not clearly described. Please specify the predefined criteria used for study exclusion during sensitivity analysis. In addition, consideration may be given to performing a leave-one-out sensitivity analysis to systematically assess whether any individual study disproportionately influenced the pooled estimate and observed heterogeneity.

3)Effects on Pain

Please clarify the approach used for pooling pain outcomes across studies. Different pain assessment instruments (e.g., Visual Analog Scale [VAS] and Numeric Rating Scale [NRS]) may have been used among the included trials. If outcomes were measured using different scales, please specify whether scores were transformed to a common metric before analysis or justify the use of mean difference (MD). Consider whether standardized mean difference (SMD) would be more appropriate when pooling outcomes assessed using different measurement scales.

4) certainty of the evidence

The certainty-of-evidence assessment requires greater transparency. Although the manuscript reports overall GRADE ratings (e.g., low or very low certainty), the rationale for individual downgrading decisions is insufficiently detailed. Consider providing a GRADE Summary of Findings table describing the assessment across domains (risk of bias, inconsistency, indirectness, imprecision, and publication bias) for each outcome to improve transparency and reproducibility.

4) Discussion

The Discussion section would benefit from a more comprehensive comparison with previously published systematic reviews and meta-analyses evaluating virtual reality interventions during chemotherapy, including those by Burrai et al. and Gautama et al. The current manuscript does not adequately explain how its findings differ from or add to existing evidence. Since prior meta-analyses have already assessed multiple patient-reported outcomes such as anxiety, pain, and quality of life, the novel contribution of the present study remains unclear. The authors are encouraged to explicitly discuss the similarities and differences between previous evidence syntheses and clarify the added value of the current review.

Minor comments:
1) Data Synthesis and Statistical Analysis

Please modify the interpretation of the I^2 statistic according to the Cochrane Handbook guidance rather than using rigid cut-off values.

2) Risk of Bias and Publication Bias

The conclusion that funnel plots were "relatively symmetrical" may be overstated given the limited number of included studies. Visual assessment of funnel plot symmetry with fewer than 10 studies is inherently unreliable. Consider using more cautious wording and explicitly acknowledging the limitations in interpreting publication bias.

Date Sent: 21-April-2026

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Journal of Clinical Question

Author's Response to Decision Letter for (JCQ-2026-0017)

Virtual Reality for Symptom Management During Outpatient Chemotherapy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Response Letter

Dear Editor and Reviewers,
We sincerely thank the reviewers for their thoughtful and constructive comments. We have carefully revised the manuscript accordingly. Below, we provide a point-by-point response to each comment. All changes have been incorporated into the revised manuscript.

Response to Reviewer 1
Comment 1. High heterogeneity:Please provide subgroup analysis or meta-regression to explore sources of heterogeneity (I^2=84.2% for anxiety).
Response: Thank you for this important suggestion. We agree that the substantial heterogeneity observed for anxiety requires further exploration. In the revised manuscript, we added subgroup analyses to explore potential sources of heterogeneity, including cancer type, with breast cancer compared against other cancers. We found that heterogeneity remained high in studies involving patients with breast cancer only, whereas it was lower in studies involving other cancer types.
Revision made:
We added a description of subgroup analyses in the and reported the results in the Results section. As follows "Subgroup analysis was conducted to compare breast cancer with other cancer types. For breast cancer, the pooled estimate revealed an anxiety reduction, with an MD of 10.71 (95% CI [−1.61, 23.03]); however, high heterogeneity was observed (I^2 = 92.9%). For other cancer types, the pooled estimate revealed an anxiety reduction, with an MD of 7.06 (95% CI [3.06, 11.01]), with lower heterogeneity (I^2 = 5.25%)."

Comment 2. Clinical implications:Discuss the clinical implications of findings and barriers to VR implementation in clinical settings more thoroughly.
Response:Thank you for this helpful comment. We have expanded the Discussion section to address the clinical implications of our findings. Specifically, we now discuss the potential role of VR as a non-pharmacological supportive care intervention for reducing anxiety and pain during chemotherapy. We also added discussion of implementation barriers, including equipment costs, infection control, staff training, patient acceptability, cybersickness, technical support, and integration into busy oncology workflows.
Revision made as follow "From a clinical perspective, these findings suggest that VR may be considered as a nonpharmacological supportive care intervention to help reduce anxiety during outpatient chemotherapy. Its potential value lies in offering an immersive, low-risk, and patient-centered approach that may complement existing supportive care strategies without adding pharmacological burden. However, implementation in routine oncology practice requires careful consideration of practical barriers. These include the initial costs of VR equipment and software, infection control procedures for shared devices, staff training, patient acceptability, risk of cybersickness, availability of technical support, and integration into busy chemotherapy workflows. Establishing standardized protocols for patient selection, device cleaning, session timing, and staff responsibilities may help improve feasibility and support the safe adoption of VR in outpatient chemotherapy settings."

Comment 3. Generalizability: Given that most studies enrolled women (breast/gynecologic cancers), please discuss the generalizability of results to other patient populations.
Response: We agree with the reviewer. In the revised Discussion, we have added a paragraph acknowledging that most included studies enrolled female patients with breast or gynecologic cancers. Therefore, the findings may not be fully generalizable to male patients, patients with other cancer types, pediatric or older populations, or patients receiving other treatment modalities. We also emphasized the need for future studies in more diverse oncology populations.
Revision made as follows "The generalizability of these findings should be interpreted with caution given the characteristics of the included study populations. Most studies enrolled predominantly female patients, particularly those with breast or gynecologic cancers; therefore, the findings may not be fully generalizable to male patients, patients with other cancer types, pediatric or older populations, or patients receiving other treatment modalities. In addition, differences in baseline symptom burden, treatment context, digital literacy, and acceptability of VR may influence its effectiveness and feasibility across diverse oncology settings. Future studies should include more heterogeneous oncology populations to clarify whether the benefits of VR are consistent across broader clinical groups."

Comment 4. Cost-effectiveness:Mention the need for future studies to evaluate cost-effectiveness
Response: Thank you for this suggestion. We have added a statement in the Discussion and Future Research sections noting that future trials should include economic evaluations to determine the cost-effectiveness, resource requirements, and scalability of VR interventions in routine oncology practice.

A statement on the need for cost-effectiveness studies has been added as follows "Future studies should include larger and more diverse oncology populations, standardized intervention protocols, longer follow-up periods, and economic evaluations to clarify the generalizability, durability, cost-effectiveness, resource requirements, and scalability of VR interventions in routine oncology practice."

Response to Reviewer 2
Major Comment 1. The rationale and research gap of the current review require further clarification in the Introduction section. Previous systematic reviews and meta-analyses have already evaluated the effectiveness of virtual reality interventions among patients receiving chemotherapy, including studies by Gautama et al. (Eur J Oncol Nurs. 2023; DOI: 10.1016/j.ejon.2023.102424) and Burrai et al. (https://doi.org/10.1016/j.ejon.2023.102340). While the current manuscript states that evidence remains inconsistent, this alone may not sufficiently justify the need for another meta-analysis. The authors are encouraged to explicitly describe the limitations of prior evidence syntheses and clearly highlight the novel contribution of the present study.
Response: Thank you for this important comment. We agree that the rationale and research gap required further clarification. We have revised the Introduction to explicitly acknowledge previous systematic reviews and meta-analyses, including those by Gautama et al. and Burrai et al., and to clarify the novel contribution of the present study. Specifically, we now state that prior reviews included broader populations and study designs, including adult and pediatric patients and crossover studies, whereas the present review focuses specifically on RCTs conducted in outpatient chemotherapy settings. We also highlight that several recently published RCTs have expanded the evidence base, supporting the need for an updated and clinically focused synthesis.
Revision made:
Although previous systematic reviews and meta-analyses have examined VR interventions among patients receiving chemotherapy, important evidence gaps remain.14,17 Earlier reviews included broader populations and study designs, such as adult and pediatric patients or both randomized and crossover studies, which may limit the applicability of their findings to routine outpatient chemotherapy settings. Moreover, the publication of additional RCTs in recent years provides an opportunity to update and refine the evidence base. To address these gaps, the present meta-analysis focused specifically on RCTs evaluating VR interventions in patients receiving outpatient chemotherapy. This study aimed to provide a more rigorous and clinically relevant synthesis of the effects of VR on treatment-related anxiety, pain, psychological distress, and overall treatment experience among patients receiving outpatient chemotherapy.

Major Comment 2. Effects on Anxiety
The sensitivity analysis methodology requires clarification. The manuscript reports that heterogeneity decreased substantially after excluding studies; however, the rationale for excluding specific studies is not clearly described. Please specify the predefined criteria used for study exclusion during sensitivity analysis. In addition, consideration may be given to performing a leave-one-out sensitivity analysis to systematically assess whether any individual study disproportionately influenced the pooled estimate and observed heterogeneity.
Response: Thank you for this important suggestion. We agree that the methodology and rationale for the sensitivity analysis required clarification. In the revised manuscript, we clarified that sensitivity analysis was conducted to assess the robustness of the anxiety outcome and to explore whether specific studies with clinical or methodological differences contributed to the observed heterogeneity. The criteria considered for sensitivity analysis included differences in cancer type, VR intervention protocol, comparator condition, outcome assessment timing, and risk of bias. In addition, as suggested, we conducted subgroup analysis by cancer type to further explore potential sources of heterogeneity. The subgroup analysis showed that heterogeneity remained high among studies involving patients with breast cancer only, whereas heterogeneity was substantially lower among studies involving other cancer types. These findings suggest that differences in study populations may partly explain the heterogeneity observed in the anxiety outcome. We also added a statement acknowledging that leave-one-out sensitivity analysis can further clarify whether any individual study disproportionately influences the pooled estimate and heterogeneity.
Revision made:
We clarified the sensitivity analysis methodology and added subgroup analysis results in the Methods and Results sections. "Sensitivity analyses were conducted to assess the robustness of the pooled estimates and explore potential sources of heterogeneity. Studies were considered for exclusion in sensitivity analyses when they differed substantially from the other included trials in terms of cancer type, VR intervention protocol, comparator condition, timing of outcome assessment, or risk of bias. In addition, subgroup analyses were performed to explore potential sources of heterogeneity, including cancer type. A leave-one-out sensitivity analysis was also considered to assess whether any individual study disproportionately influenced the pooled estimate or heterogeneity."
"Subgroup analysis was conducted to compare breast cancer with other cancer types. For breast cancer, the pooled estimate revealed an anxiety reduction, with an MD of 10.71 (95% CI [−1.61, 23.03]); however, high heterogeneity was observed (I^2 = 92.9%). For other cancer types, the pooled estimate revealed an anxiety reduction, with an MD of 7.06 (95% CI [3.06, 11.01]), with lower heterogeneity (I^2 = 5.25%)."

Major Comment 3. Effects on Pain
Please clarify the approach used for pooling pain outcomes across studies. Different pain assessment instruments (e.g., Visual Analog Scale [VAS] and Numeric Rating Scale [NRS]) may have been used among the included trials. If outcomes were measured using different scales, please specify whether scores were transformed to a common metric before analysis or justify the use of mean difference (MD). Consider whether standardized mean difference (SMD) would be more appropriate when pooling outcomes

assessed using different measurement scales.
Response: Thank you for this helpful comment. We have clarified the approach used for pooling pain outcomes. Although different pain instruments such as the VAS and NRS are commonly used in clinical studies, all trials included in the pain analysis in the present meta-analysis used the VAS to assess pain intensity. Therefore, the outcomes were measured on the same scale, and transformation to a common metric was not required. Accordingly, we used the MD rather than the SMD for pooling pain outcomes.
Revision made: "For pain outcomes, all included studies assessed pain intensity using the Visual Analog Scale (VAS)."

Major Comment 4. Certainty of the evidence
The certainty-of-evidence assessment requires greater transparency. Although the manuscript reports overall GRADE ratings (e.g., low or very low certainty), the rationale for individual downgrading decisions is insufficiently detailed. Consider providing a GRADE Summary of Findings table describing the assessment across domains (risk of bias, inconsistency, indirectness, imprecision, and publication bias) for each outcome to improve transparency and reproducibility.
Response: Thank you for this helpful comment. We agree that the certainty-of-evidence assessment required greater transparency. In the revised manuscript, we expanded the description of the GRADE assessment to provide the rationale for downgrading decisions across the relevant domains, including risk of bias, inconsistency, indirectness, imprecision, and publication bias. We also added a GRADE Summary of Findings table as Table S2 to improve transparency and reproducibility.
Revision made: "The certainty of the evidence was rated as very low for anxiety and pain because of concerns regarding risk of bias, imprecision, and heterogeneity. For QOL, the certainty of the evidence was rated as low owing to concerns regarding risk of bias and imprecision (Table S2)."

Major Comment 5. Discussion
The Discussion section would benefit from a more comprehensive comparison with previously published systematic reviews and meta-analyses evaluating virtual reality interventions during chemotherapy, including those by Burrai et al. and Gautama et al. The current manuscript does not adequately explain how its findings differ from or add to existing evidence. Since prior meta-analyses have already assessed multiple patient-reported outcomes such as anxiety, pain, and quality of life, the novel contribution of the present study remains unclear. The authors are encouraged to explicitly discuss the similarities and differences between previous evidence syntheses and clarify the added value of the current review.
Response: Thank you for this important suggestion. We have expanded the Discussion section to compare our findings with those of Burrai et al. and Gautama et al. We now discuss areas of consistency, such as the potential benefits of VR for anxiety and pain during chemotherapy, as well as differences related to study eligibility, included outcomes, analytical approach, risk-of-bias assessment, and certainty-of-evidence evaluation. We also clarified the added value of the current review, particularly its updated synthesis, use of standardized methodological appraisal tools, and explicit assessment of evidence certainty.
Revision made:
"This pattern is broadly consistent with previous reviews by Burrai et al. and Gautama et al., which also suggested that VR may be more effective for reducing psychological distress than for improving pain or broader patient-reported outcomes. The present review adds to existing evidence by focusing specifically on RCTs conducted in outpatient chemotherapy settings and incorporating recently published trials, thereby providing an updated and clinically focused synthesis."

Minor Comments
Minor Comment 1. Data Synthesis and Statistical Analysis. Please modify the interpretation of the I^2 statistic according to the Cochrane Handbook guidance rather than using rigid cut-off values.
Response: Thank you for this helpful comment. We have revised the Methods section to avoid rigid interpretation of I^2 values. The revised text now follows the Cochrane Handbook guidance and presents I^2 thresholds as a rough guide rather than fixed cut-off values.
Revision made: "Statistical heterogeneity among studies was evaluated using the I^2 statistic and interpreted using the Cochrane Handbook's rough guide: 0%–40% might not be important, 30%–60% may represent moderate heterogeneity, 50%–90% may represent substantial heterogeneity, and 75%–100% may represent considerable heterogeneity."

Minor Comment 2. Risk of Bias and Publication Bias. The conclusion that funnel plots were "relatively symmetrical" may be overstated given the limited number of included studies. Visual assessment of funnel plot symmetry with fewer than 10 studies is inherently unreliable. Consider using more cautious wording and explicitly acknowledging the limitations in interpreting publication bias.
Response: Thank you for this helpful comment. We agree that interpretation of funnel plot symmetry is limited when the number of included studies is small. We have revised the relevant text to use more cautious wording and added this issue to the limitations section, noting that publication bias could not be reliably assessed because visual inspection of funnel plots is inherently unreliable with fewer than 10 studies.Revision made: "Assessment of publication bias was also limited because visual interpretation of funnel plot asymmetry is unreliable when fewer than 10 studies are included; therefore, publication bias could not be reliably excluded."

We again thank the editor and reviewers for their valuable comments, which have helped us improve the clarity, methodological transparency, and clinical relevance of the manuscript.

Best Regards
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