PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Comparative Effectiveness of Interventions for Improving Adherence to Ocular Hypotensive Therapy in Patients with Glaucoma or Ocular Hypertension: Protocol for Network Meta-Analysis
AUTHORS	Jang, Mirinae; Shim, Sung-Ryul; Ha, Ahnul; Kim, Young Kook

VERSION 1 – REVIEW

REVIEWER	Hiroshi Yokomichi University of Yamanashi, Department of Health Sciences
REVIEW RETURNED	24-Jun-2021

GENERAL COMMENTS	Doctor Mirinae J et al wrote a protocol of network meta-analysis of effectiveness of ways to increase adherence to ocular hypertensive therapy. I would like to provide comment to increase the study impact. [Minor] 1. Title: Is the analysis conducted in patients with ocular hypertension, not ocular hypotensive therapy? 2. I would like to request them to write concrete primary outcome. Is it difference in difference of ocular pressure? 3. I wonder how the researchers determine and unify the control group in this meta-analysis. 4. I wonder if network meta-analysis could function fully, when there are many studies that show one-to-one pairs of intervention-outcome in literature database. I mean that network meta-analysis would perform when there are conjugated pleural exposures that correlate one another. Overall, the protocol paper covers rationale and detailed methodologies. I hope that they would answer to my questions for increase in readability.

REVIEWER	Maria Achilleos Cyprus University of Technology
REVIEW RETURNED	13-Jul-2021

GENERAL COMMENTS	i) First sentence on strengths and limitations needs change, it doesn't give any information why this study is important. Also you need to mentioned at least one-two limitations of the study. ii) Introduction. First of all you should explain what is 'therapy adherence'. Secondly, why you choose that term? In literature I think is more often the term medication adherence. Additionally, what is the accepted level of medication adherence to these patients? You need more references especially in first paragraph of your introduction.

	iii) As far as the eligibility criteria I think you need to explain better the last sentence: 'and where they were assessed as having a high bias risk'. Why is important the location where the patients were assessed? iv) Outcomes and prioritization. Explain better the secondary outcome measure. Why do you want to asses the relative risk on non-adherence as a binary outcome? Your primary outcome isn't enough to assess adherence?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
Doctor Mirinae J et al wrote a protocol of network meta-analysis of effectiveness of ways to increase adherence to ocular hypertensive therapy. I would like to provide comment to increase the study impact.

1. Title: Is the analysis conducted in patients with ocular hypertension, not ocular hypotensive therapy?

The current analysis was conducted for patients diagnosed with glaucoma or ocular hypertension and treated by ocular hypotensive therapy. We have revised the title to clearly deliver this point.
Title, page 1 “Comparative Effectiveness of Interventions for Improving Adherence to Ocular Hypotensive Therapy in Patients with Glaucoma or Ocular Hypertension: Protocol for Network Meta-Analysis”

2. I would like to request them to write concrete primary outcome. Is it difference in difference of ocular pressure?

As the reviewer correctly pointed out, greater adherence to ocular hypotensive therapy (i.e., intraocular pressure-lowering medication) is expected to further reduce intraocular pressure, but this may not always be the case. Thus, we designated the degree of medication adherence to ocular hypotensive therapy as the primary outcome for this analysis. Adherence degree was assessed as defined in each study, including but not limited to patient interviews, questionnaires, patient diaries or electronic monitoring devices. The data on the effectiveness of intervention to improve adherence includes dichotomous (success/failure), nominal (reasons for non/poor adherence) and discrete (proportions of missed doses over a specific time period) forms. Since individual studies are likely to provide different types of data, we planned to perform both combined and separate analyses according to the data form. We have revised the Methods and Analysis section to clearly deliver these points.

Methods and Analysis, page 8 “The primary outcome is degree of adherence to ocular hypotensive therapy, measured as defined in each study, including but not limited to patient interviews, questionnaires, patient diaries or electronic monitoring devices. This includes dichotomous (success/failure), nominal (reasons for non/poor adherence) and discrete data (proportions of missed doses over a specific time period). The secondary outcome measure is the persistence with therapy as measured by repeat prescriptions (prescription refill) or dispensing counts, or both. This includes dichotomous (success/failure) and discrete data (proportions of uncollected prescriptions over a specific time period).”

3. I wonder how the researchers determine and unify the control group in this meta-analysis.
In order to improve interpretability and support decision making thereby, we planned to group the intervention arms using the categories. The control arm will be standard of care, that is, cases if only

the instructions by the health-care provider at treatment initiation regarding how to take ocular hypotensive medication is provided without any intervention for improving adherence to the medication. In addition, we modified the group of intervention arms to a more granular categorization: (A) standard of care, (B) enhanced standard of care, (C) interacting education, (D) motivational interview and behavior change counselling, (E) multimedia education, (F) tailored care, (G) physician education, (H) printed material, (I) short message service, (J) provision of the patient's own medical records, (K) incentives, and (L) telephone call.

Methods and Analysis, page 6 "To improve interpretability and thereby support decision making, we will group the intervention arms using categories. By an iterative process entailing review of relevant RCTs and discussion, 12 categories for the present NMA were identified: (A) standard of care, (B) enhanced standard of care, (C) interacting education, (D) motivational interview and behavior change counselling, (E) multimedia education, (F) tailored care, (G) physician education, (H) printed material, (I) short message service, (J) provision of the patient's own medical records, (K) incentives, and (L) telephone call. The control arm will be the standard of care (i.e., if only the instructions by the health-care provider at treatment initiation regarding how to take ocular hypotensive medication are provided, without any intervention for improving adherence to the medication)."

4. I wonder if network meta-analysis could function fully, when there are many studies that show one-to-one pairs of intervention-outcome in literature database. I mean that network meta-analysis would perform when there are conjugated pleural exposures that correlate one another.
We agree with the reviewer's concerns regarding the network formation in this analysis. Although many studies have performed one-to-one comparisons, since most have a common control group (i.e., standard of care), we expect that it will be possible to construct the network across different intervention arms. However, this point was added to the Strengths and limitations of this study as an important possible study limitation.
Strengths and limitations of this study, page 3 "5. The sample size and the number of included studies may be inadequate, and as a result, the network of intervention arms may not be formed."

Reviewer 2

1. First sentence on strengths and limitations needs change, it doesn't give any information why this study is important. Also you need to mention at least one-two limitations of the study.
We have added the information on why this study is important (#3 on the Strengths and limitations of this study) and its potential limitations (#4 and #5 on the Strengths and limitations of this study).
Strengths and limitations of this study, page 3

3. This NMA will allow for generation of a hierarchy of interventions for improving ocular hypotensive therapy adherence that is clinically meaningful.

4. This work could not exclude the potential influence of different trial-defined adherence criteria.

5. The sample size and the number of included studies may be inadequate, and as a result, the network of intervention arms may not be formed.

2. Introduction. First of all you should explain what is 'therapy adherence'. Secondly, why you choose that term? In literature I think is more often the term medication adherence. Additionally, what is the accepted level of medication adherence to these patients? You need more references especially in first paragraph of your introduction.

Based on the reviewer's suggestion, we have revised the expression "therapy adherence" to "medication adherence" throughout the manuscript. Additionally, the first paragraph of the Introduction has been rewritten by (1) adding a sentence on the accepted level of medication adherence in glaucoma patients and (2) adding references.

Introduction, page 4 "Poor medication adherence most often leads to increased resource utilization, owing to a reduction in effectiveness and an associated increase in the risk of therapeutic failure.1 Treatment failure may necessitate waste of unfinished pharmaceutical supplies, increased healthcare expenditure and risk to the patient if subsequent surgical intervention is required. Medication adherence is a significant healthcare issue, particularly for patients with chronic diseases such as glaucoma or ocular hypertension (OHT). The treatment for glaucoma or OHT entails the lowering of intraocular pressure (IOP) to prevent disease progression. Patients with glaucoma or OHT have been deemed to be adherent if they had ≥ 292 days with an IOP-lowering medication (i.e., ocular hypotensive therapy) supply over the 365-day assessment period (equivalent to the proportion of days covered ≥ 0.80).2,3 Research from a systematic review indicates that the prevalence of non-adherence to ocular hypotensive therapy ranges from 23 to 60% over 12 months.4 Simplifying eye drop regimes, providing adequate information, teaching drop instillation techniques and ongoing support according to patient need have been getting attention for their potential positive effects on improving adherence to ocular hypotensive therapy."

Abstract, page 2 "Introduction: Poor medication adherence is an important issue in healthcare."

3. As far as the eligibility criteria I think you need to explain better the last sentence: 'and where they were assessed as having a high bias risk'. Why is important the location where the patients were assessed?

The meaning of the sentence was conveyed incorrectly due to a typo. We have now revised the above-mentioned sentence for clarity.

Methods and Analysis, page 6 "Studies reporting on subjects younger than 18 years of age or non-human subjects, along with those assessed as high risk of bias, will be excluded."

4. Outcomes and prioritization. Explain better the secondary outcome measure. Why do you want to assess the relative risk on non-adherence as a binary outcome? Your primary outcome isn't enough to assess adherence?

The authors would like to thank the reviewer for the thoughtful comments. Adherence degree was assessed as defined in each study; including, but not limited to patient interviews, questionnaires, patient diaries or electronic monitoring devices. The data on the effectiveness of intervention to improve adherence includes dichotomous (success/failure), nominal (reasons for non/poor adherence) and discrete (proportions of missed doses over a specific time period) forms. Since individual studies are likely to provide different types of data, we planned to perform both combined and separate analyses according to the data form as a primary outcome. The secondary outcome measure will be the persistence with therapy as measured by repeat prescriptions (prescription refill) or dispensing counts, or both. This includes dichotomous (success/failure) and discrete data (proportions of uncollected prescriptions over a specific time period). We have revised the Methods and Analysis section accordingly.

Methods and Analysis, page 6 "The primary outcome is degree of adherence to ocular hypotensive therapy, measured as defined in each study, including but not limited to patient interviews, questionnaires, patient diaries or electronic monitoring devices. This includes dichotomous (success/failure), nominal (reasons for non/poor adherence) and discrete data (proportions of missed

doses over a specific time period). The secondary outcome measure is the persistence with therapy measured by repeat prescriptions (prescription refill) or dispensing counts, or both. This includes dichotomous (success/failure) and discrete data (proportions of uncollected prescriptions over a specific time period).”