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Comparative Effectiveness of Interventions for Improving Adherence to Ocular Hypotensive Therapy: Protocol for Network Meta-Analysis

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Comparative Effectiveness of Interventions for Improving Adherence to Ocular Hypotensive Therapy: Protocol for Network Meta-Analysis

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ABSTRACT

Introduction: Poor therapy adherence is an important issue in healthcare. Various types of intervention for improved adherence to ocular hypotensive therapy have been proposed, though evidence on the effectiveness of any isolated intervention remains limited. The protocol proposed herein is an ongoing network meta-analysis (NMA) design that enables comparative investigation of any and all interventions for which there are available randomized controlled trials (RCTs). Our aim is the systematic comparison of the efficacy of different types of adherence interventions for patients suffering glaucoma or ocular hypertension.

Methods and analysis: Four electronic databases (Cochrane Central Register of Controlled Trials, Embase, MEDLINE, and Scopus) will be searched for RCTs without any time limitation. First titles and abstracts, and then full-text papers, will be screened by two reviewers, who will extract the useful data. The primary outcome measure is an intervention's impact on adherence. The two reviewers will also assess, using the relevant domain-based risk-of-bias assessment tool, the internal validity of the studies. The overall quality of the evidence will be assessed by the Confidence in Network Meta-Analysis approach, and will be summarized with network diagrams. To allow for assessment of both direct and indirect evidence, a contribution matrix will be utilized. For visualization of the effects of all of the included interventions on adherence, forest plots will be constructed. Pairwise effect sizes will be calculated according to all of the evidence available in the network. The effect measures for treatments not yet compared by pairwise RCT can be indirectly compared by using a common comparator to contrast comparisons' effect sizes.

Ethics and dissemination: This work will synthesize evidence from already published studies and as such, will not require an ethics review or approval. A manuscript presenting the findings will be submitted to a peer-reviewed scientific journal for publication.

PROSPERO registration number: CRD42021253145

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. This protocol describes a network meta-analysis (NMA) design for investigation of the effects of different types of intervention for improved adherence to ocular hypotensive therapy among adult patients diagnosed with glaucoma or ocular hypertension (OHT).
2. NMA enables comparative investigation of all available adherence interventions for which randomized controlled trials are available.
3. The overall quality of the evidence and its certainty for the purposes of the NMA will be assessed by the Confidence in Network Meta-Analysis (CINeMA) approach.
4. This NMA design enables ranking of available interventions' efficacy for improving ocular hypotensive therapy adherence.
5. The NMA will provide evidence that is directly clinically applicable.

INTRODUCTION

Therapy adherence is a significant healthcare issue, particularly for patients with chronic diseases (e.g., glaucoma). Failure of treatment might necessitate unwarranted medication changes, increased healthcare expenditure, and indeed, could incur additional patient risk in cases where surgical intervention is necessary.

Two systematic reviews already have examined the effectiveness of adherence interventions for patients with glaucoma or ocular hypertension (OHT).[1 2] They indicate that whereas complex interventions in the form of patient education combined with personalized behavioral change (e.g., tailoring of daily routines for promotion of adherence to eye drops) may improve glaucoma medication adherence, overall there is still insufficient evidence for recommendation of any particular intervention. Traditional (meta-analytic) pairwise investigation of those isolated interventions proved impossible, as they varied by study, and randomized controlled trials (RCTs) were insufficient in number to evaluate each of the different intervention types.

Drawing conclusions on the comparative effectiveness of different adherence interventions based on individual RCTs and systematic review is difficult. Traditional meta-analyses, moreover, are limited by the relative unavailability of pairwise comparisons of interventions.[3] It is difficult, therefore, to interpret the entire body of evidence available, many RCTs being available for only some interventions, and the evidence being limited for some others. Furthermore, for many types of adherence interventions, there are no available direct comparisons.

Network meta-analysis (NMA) is a study design that allows for investigation of the efficacy of different interventions.[4 5] Creation of a network of pairwise RCTs enables use of all direct and indirect evidence for determination of such efficacy.[6] NMA makes possible the comparative analysis of all adherence interventions for which there are available RCTs, unlike traditional systematic review and meta-analysis, which can analyze only two. Furthermore, with this design, the efficacies of available interventions can be ranked.

The protocol presented in these pages describes an ongoing NMA design for systematic

comparison of the effectiveness of different intervention types for improved adherence to ocular hypotensive therapy among adult patients with glaucoma or OHT. The main research question was: What are the efficacies of different types of interventions for adherence? The above-alluded-to objective — to evaluate the efficacies of different types of interventions — will allow for generation of a hierarchy of interventions that is clinically meaningful.

METHODS AND ANALYSIS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for protocols (PRISMA-P) is followed by this protocol.[7] The NMA results will be reported in accordance with the PRISMA statement and the PRISMA extension for network meta-analyses (PRISMA-NMA).[8 9] The research has been registered on PROSPERO (CRD 42021253145, online supplementary file 1 for PRISMA-P checklist).

Eligibility criteria

Studies eligible for inclusion in the NMA are those that are RCTs indicating the effects of any interventions on adherence to ocular hypotensive therapy by adults (age ≥ 18 years) with either glaucoma or OHT. Any intervention, control-treatment, or no-treatment group will be included as a comparator. Studies reporting secondary results (e.g., intraocular pressure and visual field test results) other than adherence also will be included. Any studies for inclusion need to be available in the full-text format. Studies will be excluded in cases where they report on subjects younger than 18 or non-human subjects, and where they were assessed as having a high bias risk.

Categorization of studies

By an iterative process entailing review of relevant RCTs and discussion, 8 categories for the present NMA were identified: (A) standard of care, (B) printed material, (C) device reminder, (D) short message service, (E) telephone call, (F) motivational interview and behavior change counselling, (G) interacting education, (H) multimedia education, (I) provision of the patient's own medical records, (J) tailored care, (K) incentives, (L) physician education.

Information sources

Four electronic databases (Cochrane Central Register of Controlled Trials, Embase, MEDLINE and Scopus) were searched for RCTs, with no time limitation.

Search strategy

With the assistance of a medical librarian, a six-part search strategy including terms by which to identify studies relevant to (i) glaucoma, (ii) OHT, (iii) OHT therapy, (iv) intervention, (v) adherence, and (vi) RCTs was developed. The search terms were based on the established terminology, and the extensive MESH and EMBASE search terms were employed when

available. The search strategy was developed for the MEDLINE database and then adjusted to meet the conditions of the other databases. For prospectively identified systematic reviews and meta-analyses, the reference lists of which may include potentially relevant studies, manual searches will be conducted to identify any of those missed by the electronic searches. The studies that are analyzed will include data on types of intervention and improved adherence to OHT therapy, regardless of the language, publication date, country or study design.

Selection process

Two reviewers will each independently screen titles as well as abstracts so as to identify potentially eligible studies. For each identified study, the two reviewers will then independently review the full-text papers. In either of these two stages, a third reviewer will be brought in to resolve any disagreements. The inter-rater agreements will be reported in terms of Cohen's kappa coefficient (κ). For studies that have been reported in multiple papers, the paper that reports the most complete effectiveness analysis will be selected (i.e., reports on either subgroup or secondary analyses will be excluded). The entire stepwise process will be presented using a PRISMA flow chart (Figure 1).

Data collection and management

The two reviewers will use a standardized extraction table agreed to by all of the authors to extract and record study data.

Data items

The extracted data will include study characteristics (author, year), participant characteristics (sample sizes, age, sex, type of glaucoma, proportion of open-angle glaucoma), types of intervention on adherence, duration, frequency and intensity, and timing of follow-up assessment. Means and standard deviations (SDs) of primary outcome measures at baseline, as well as the time points after and closest to the end of the treatment will be extracted, so as to accommodate predicted treatment-duration variation across studies. Although there is no current consensus on the appropriate duration of adherence interventions, it is expected that most interventions will fall somewhere between 4 and 12 weeks. Given the potential differences in the treatment durations, this second time point will allow for an investigation that ensures completion of the treatment regimen, and will likely be the point of maximal

therapeutic effect.

Where studies have reported more than two adherence interventions (or control groups) that independently could have been included in this NMA, data will be extracted from all of the study arms. For example, if one RCT encompasses three treatment arms (A, B, and C), data from all three will be extracted.

For primary outcomes where mean ± SE are reported, SDs will be calculated using the formula: SD = SE ∗ √n. Where medians and interquartile ranges are reported, the methods described by Wan *et al* will be used for computation of means and SDs.[10] Where means and 95% CIs are reported, SDs will be calculated according to the formula: SD = √ n ∗ (upper 95% CI limit − lower 95% CI limit) / t, t being the value from a t-distribution for a 95% CI for a sample distribution having degrees of freedom equal to the group sample size −1. If a paper does not provide sufficient data, they will be obtained from the corresponding author if possible. Extracted data will be tabulated.

Outcomes and prioritization

The primary outcome measure is the effectiveness of the intervention on adherence as a continuous outcome, which is measured as the adherence score change between the baseline and the end-point. The secondary outcome measure is the relative risk on non-adherence as a binary outcome, which is measured as the non-adherent proportion change between the baseline and the end-point. The third outcome measure is the acceptability of the intervention on adherence as a binary outcome, which is measured as the drop-out rate during the study period. For each outcome measure, three separate analyses will be performed.

Risk of bias in individual studies

The two reviewers will assess the internal validity (i.e., risk of bias) of the included studies according to the relevant domain-based risk-of-bias assessment tool, and the results will be presented in a graphical format further to the The Cochrane Handbook recommendation. A third reviewer will be brought in to resolve any disagreements. The inter-rater agreement will be reported based on Cohen's kappa coefficient (κ).

Data synthesis

The included trials' characteristics (i.e., type of glaucoma, details of intervention on

adherence, outcomes) will be both summarized and tabulated. The summarization will entail the use of a network diagram, each node in which will represent an intervention class (as categorized in the inclusion criteria), the node size being proportional to the number of patients who are receiving the treatment. The effects of the pairwise comparisons of the two interventions will be shown as edges that interconnect the nodes, the thickness of the edge lines representing the pairwise comparison weight. A contribution matrix will be included to indicate the influence of the individual comparisons as well as the influence of the direct and indirect evidence on the overall effects summary. If quantitative synthesis is not appropriate, we will conduct a narrative synthesis.

Assessment of transitivity and meta-biases

It is expected that all of the interventions on adherence that are identified in the preliminary search will be in-principle jointly randomizable, which attribute will meet the transitivity assumption. For all of the comparisons between interventions in the network, the inferences will be based on direct evidence (pairwise RCTs), indirect evidence (effect B–C derived from A–B and A–C comparisons), or a mixture of both direct and indirect evidence. And, to meet the transitivity assumption, measures that potentially could modify effects such as sex, age, glaucoma type, and the distributions of these variables will be inspected.

Network meta-analysis

Assuming that the distribution of the effect modifiers is similar across studies, a frequentist NMA will be performed (see the proposed closed network geometry in Figure 2). Pairwise effect sizes will be calculated after including all of the evidence available in the network.[11] If outcome data on the different intervention durations and frequencies are available, their effectiveness for adherence will be investigated. Effect measures for treatments not already compared in a pairwise RCT can be indirectly compared by using a common comparator to contrast the comparisons' effect sizes.[3 12 13] Considering that interventions may vary for certain characteristics, the sample used in each study might slightly differ; thus, a random effects model will be employed to generate pooled standardized effect sizes. Corrected effect size (Hedges' g) will be used in order to allow for inclusion of smaller studies.[14] Network forest plots, interval plots, and league tables will be used to rank the mixed (direct and indirect) effect sizes and 95% CIs for all treatment combinations in the network.

Detection of heterogeneity and assessment of inconsistency

Heterogeneity will be reported using 95% prediction intervals and I^2. Forest plots will be visually examined so as to identify any obvious inconsistency existing between direct and indirect treatment effects (loop consistency); any observed inconsistency might indicate non-satisfaction of the transitivity assumption. In cases where significant heterogeneity is detected, inconsistency will be evaluated one comparison at a time using the node-splitting approach.[15] Also, comparison-adjusted funnel plots will be employed for visual inspection and assessment of small-study effects as well as assessment of potential publication bias.[16]

Confidence in cumulative evidence

Based on study limitations, imprecision, heterogeneity indirectness, and publication bias,[17] the overall quality of evidence will be assessed by the Confidence in Network Meta-Analysis (CINeMA) approach, which is broadly based on the GRADE framework, but with a number of conceptual and semantic differences.[17] It covers 6 domains: (i) within-study bias (impact of risk of bias in included studies), (ii) reporting bias (publication and other reporting bias), (iii) indirectness, (iv) imprecision, (v) heterogeneity, and (vi) incoherence.[18] The reviewer's input is required at the study level for within-study bias and indirectness. Then, by applying user-defined rules, CINeMA assigns, to each domain, judgments at 3 levels (no concerns, some concerns, major concerns). Such judgments across domains are summarized in order to obtain 4 levels of confidence for each relative treatment effect, which levels will correspond to the standard GRADE assessments (very low, low, moderate, high).

Statistical analyses

Statistical package R will be used in all of the statistical analyses.[19] The netmeta R-package will be utilized to perform and report the NMA. P scores will enable the treatment efficacy ranking. The netmeta package function forest. netmeta will be employed to create the visual network of nodes and connections.

Patient and public involvement

No patients and members of the public will be directly involved. Only data already existent in the literature and the aforementioned sources will be used for this study.

ETHICS AND DISSEMINATION

This work will synthesize evidence from already published studies, and as such, will not require an ethics review or approval. A manuscript presenting the findings will be submitted to a peer-reviewed scientific journal for publication; the results will be reported in accordance with the PRIMSA statement and the PRIMSA extension for network meta-analyses (PRISMA-NMA) guidelines. We will update this protocol required in the future and the date of amendments and description of changes will be presented as a supplement. Also, important protocol amendments will be documented and updated on PROSPERO.

FIGURE LEGENDS

Figure 1. PRISA flow diagram of the study selection process.

Figure 2. All possible network connections (pairwise comparisons, lines) with 12 nodes [interventions, A–L: (A) standard of care, (B) printed material, (C) device reminder, (D) short message service, (E) telephone call, (F) motivational interview and behavior change counselling, (G) interacting education, (H) multimedia education, (I) provision of the patient's own medical records, (J) tailored care, (K) incentives, (L) physician education].

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AUTHORS' CONTRIBUTIONS

MJ conceived the content and wrote the paper. SRS and AH developed the search strategy and evaluated the protocol. YKK designed the study and revised the protocol. All the authors read the protocol and have given the final approval for publication.

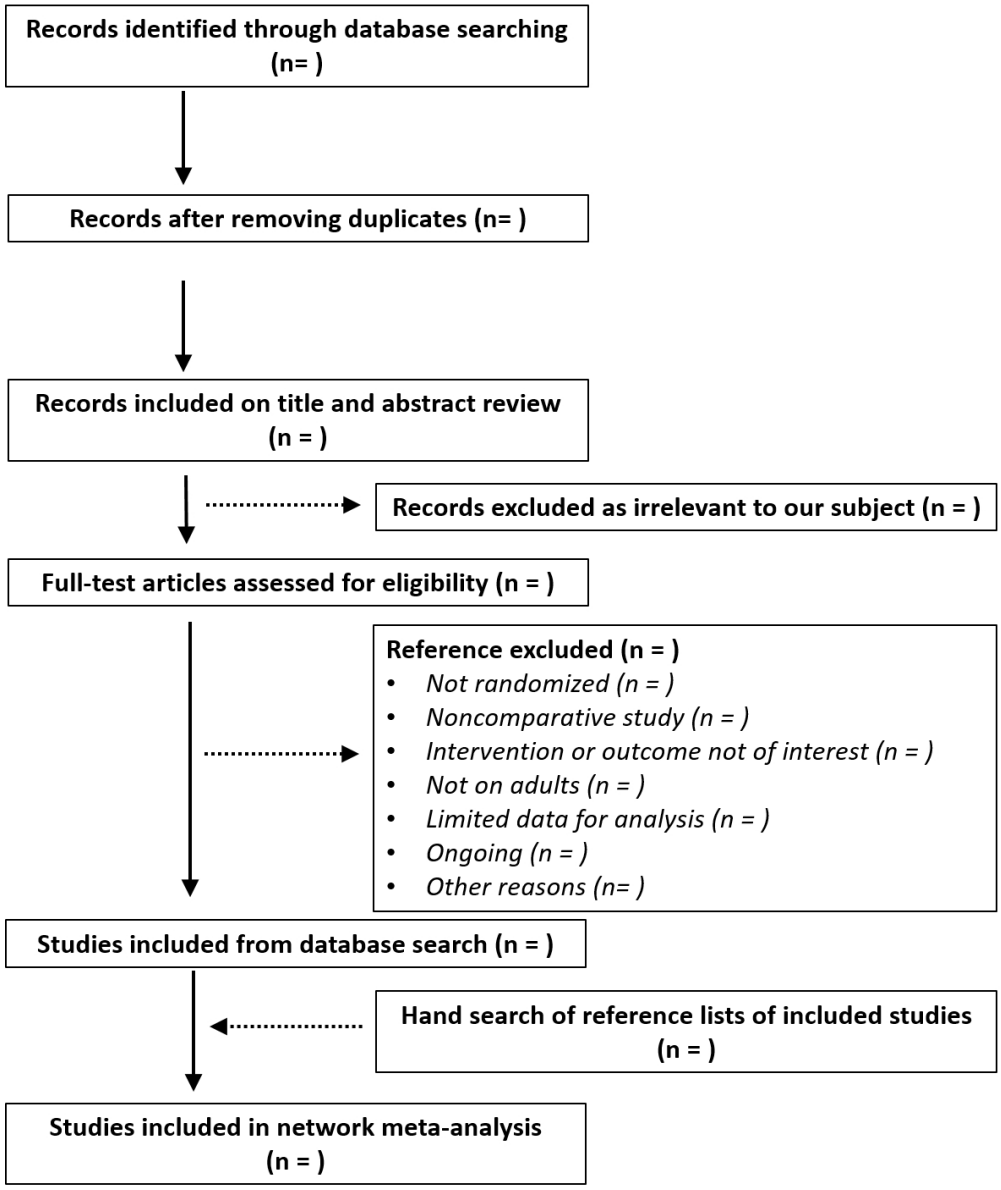

Figure 1. PRISA flow diagram of the study selection process.

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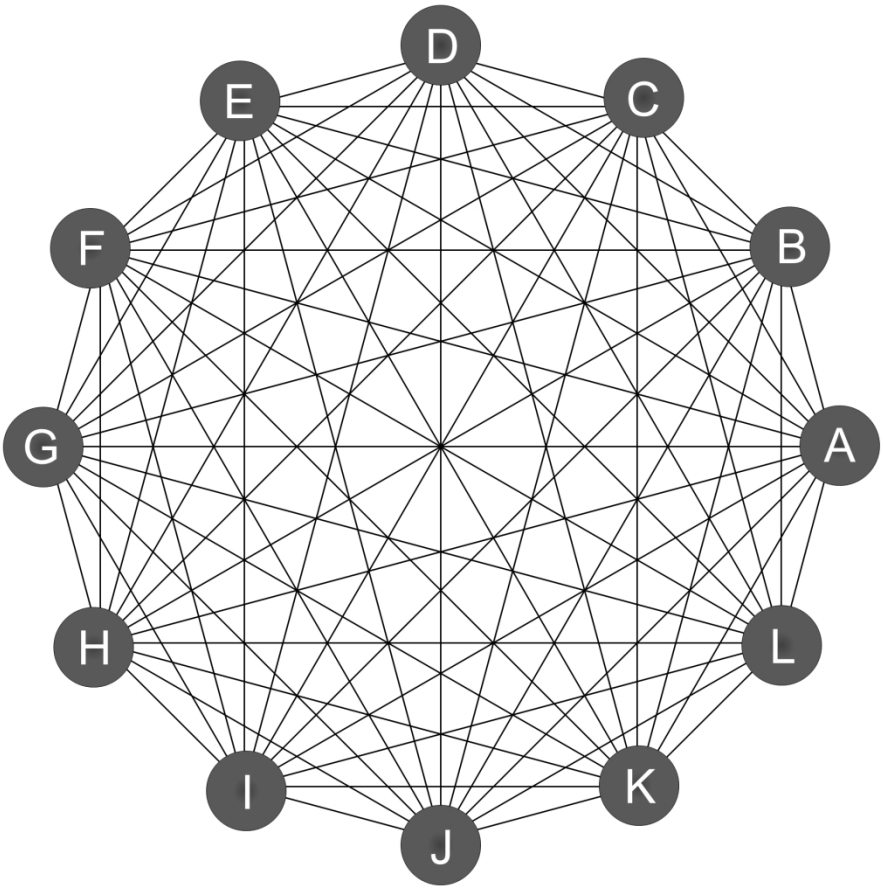

Figure 2. All possible network connections (pairwise comparisons, lines) with 12 nodes [interventions, A–L: (A) standard of care, (B) enhanced standard of care, (C) interacting education, (D) motivational interview and behavior change counselling, (E) multimedia education, (F) tailored care, (G) physician education, (H) printed material, (I) short message service, (J) provision of the patient's own medical records, (K) incentives, and (L) telephone call].

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number Page 2
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review Page 10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments Page 1
Support:		
Sources	5a	Indicate sources of financial or other support for the review Page 1
Sponsor	5b	Provide name for the review funder and/or sponsor Page 1
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol Page 1
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known Page 3-4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) Page 3-4
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review Page 5-6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage Page 6

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated Page 6-7
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review Page 7-8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) Page 7-8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators Page 7-8
Data items	12	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators Page 7-8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale Page 8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis Page 8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised Page 9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2 , Kendall's τ) Page 9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) NA
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned Page 9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) Page 9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) Page 9-10

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Keywords:	Glaucoma < OPHTHALMOLOGY, Medical ophthalmology < OPHTHALMOLOGY, Clinical trials < THERAPEUTICS

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Comparative Effectiveness of Interventions for Improving Adherence to Ocular Hypotensive Therapy in Patients with Glaucoma or Ocular Hypertension: Protocol for Network Meta-Analysis

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ABSTRACT

Introduction: Poor medication adherence is an important issue in healthcare. Various types of intervention for improved adherence to ocular hypotensive therapy have been proposed, though evidence on the effectiveness of any isolated intervention remains limited. The current protocol is an ongoing network meta-analysis (NMA) design that enables comparative investigation of any and all interventions for which there are available randomized controlled trials (RCTs). Our aim is the systematic comparison of the efficacy of different types of adherence interventions for patients suffering glaucoma or ocular hypertension (OHT).

Methods and analysis: Studies of interest will assess the effects of any interventions on medication adherence in adults (age ≥ 18 years) with either glaucoma or OHT. Four electronic databases (Cochrane Central Register of Controlled Trials, Embase, MEDLINE, and Scopus) will be searched for RCTs published in any language, without any time limitation. First titles and abstracts, and then full-text papers, will be screened by two reviewers, who will extract the useful data. The primary outcome measure is an intervention's impact on adherence. The two reviewers will also assess, using the relevant domain-based risk-of-bias assessment tool, the internal validity of the studies. The overall quality of the evidence will be assessed by the Confidence in Network Meta-Analysis approach, and will be summarized with network diagrams. To allow for assessment of both direct and indirect evidence, a contribution matrix will be utilized. For visualization of the effects of all of the included interventions, forest plots will be constructed. Pairwise effect sizes will be calculated according to all of the evidence available in the network.

Ethics and dissemination: This work will synthesize evidence from already published studies and as such, will not require an ethics review or approval. A manuscript presenting the findings will be submitted to a peer-reviewed scientific journal for publication.

PROSPERO registration number: CRD42021253145

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. This protocol describes a network meta-analysis (NMA) design for investigation of the effects of different types of intervention for improved adherence to ocular hypotensive therapy among adult patients diagnosed with glaucoma or ocular hypertension (OHT).
2. NMA enables comparative investigation of all available adherence interventions for which randomized controlled trials are available.
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.

INTRODUCTION

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.

Two systematic reviews already have examined the effectiveness of adherence interventions for patients with glaucoma or ocular hypertension (OHT).[5 6] They indicate that whereas complex interventions in the form of patient education combined with personalized behavioral change (e.g., tailoring of daily routines for promotion of adherence to eye drops) may improve glaucoma medication adherence, overall there is still insufficient evidence for recommendation of any particular intervention. Traditional (meta-analytic) pairwise investigation of those isolated interventions proved impossible, as they varied by study, and randomized controlled trials (RCTs) were insufficient in number to evaluate each of the different intervention types.

Drawing conclusions on the comparative effectiveness of different adherence interventions based on individual RCTs and systematic review is difficult. Traditional meta-analyses, moreover, are limited by the relative unavailability of pairwise comparisons of interventions.[7] It is difficult, therefore, to interpret the entire body of evidence available, many RCTs being available for only some interventions, and the evidence being limited for some others.

Furthermore, for many types of adherence interventions, there are no available direct comparisons.

Network meta-analysis (NMA) is a study design that allows for investigation of the efficacy of different interventions.[8 9] Creation of a network of pairwise RCTs enables use of all direct and indirect evidence for determination of such efficacy.[10] NMA makes possible the comparative analysis of all adherence interventions for which there are available RCTs, unlike traditional systematic review and meta-analysis, which can analyze only two. Furthermore, with this design, the efficacies of available interventions can be ranked.

The protocol presented in these pages describes an ongoing NMA design for systematic comparison of the effectiveness of different intervention types for improved adherence to ocular hypotensive therapy among adult patients with glaucoma or OHT. The main research question was: What are the efficacies of different types of interventions for adherence? The above-alluded-to objective — to evaluate the efficacies of different types of interventions — will allow for generation of a hierarchy of interventions that is clinically meaningful.

METHODS AND ANALYSIS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for protocols (PRISMA-P) is followed by this protocol.[11] The NMA results will be reported in accordance with the PRISMA statement and the PRISMA extension for network meta-analyses (PRISMA-NMA).[12 13] The research has been registered on PROSPERO (CRD 42021253145, online supplementary file 1 for PRISMA-P checklist).

Eligibility criteria

Studies eligible for inclusion in the NMA are those that are RCTs indicating the effects of any interventions on adherence to ocular hypotensive therapy by adults (age ≥ 18 years) with either glaucoma or OHT. Any intervention, control-treatment, or no-treatment group will be included as a comparator. Studies reporting secondary results (e.g., intraocular pressure and visual field test results) other than adherence also will be included. Any studies for inclusion need to be available in the full-text format. 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.

Categorization of studies

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).

Information sources

Four electronic databases (Cochrane Central Register of Controlled Trials, Embase, MEDLINE and Scopus) were searched for RCTs, with no time limitation.

Search strategy

With the assistance of a medical librarian, a six-part search strategy including terms by which to identify studies relevant to (i) glaucoma, (ii) OHT, (iii) OHT therapy, (iv) intervention, (v) adherence, and (vi) RCTs was developed. The keywords included were *glaucoma, ocular hypertension, medication, adherence, and compliance.* The search terms were based on the established terminology, and the extensive MESH and EMBASE search terms were employed when available. The search strategy was developed for the MEDLINE database and then adjusted to meet the conditions of the other databases. The full search strategies are provided in online supplemental file 2.

For prospectively identified systematic reviews and meta-analyses, the reference lists of which may include potentially relevant studies, manual searches will be conducted to identify any of those missed by the electronic searches. The studies that are analyzed will include data on types of intervention and improved adherence to OHT therapy, regardless of the language, publication date, country or study design.

Selection process

Two reviewers will each independently screen titles as well as abstracts so as to identify potentially eligible studies. For each identified study, the two reviewers will then independently review the full-text papers. In either of these two stages, a third reviewer will be brought in to resolve any disagreements. The inter-rater agreements will be reported in terms of Cohen's kappa coefficient (κ). For studies that have been reported in multiple papers, the paper that reports the most complete effectiveness analysis will be selected (i.e., reports on either subgroup or secondary analyses will be excluded). The entire stepwise process will be presented using a PRISMA flow chart (Figure 1).

Data collection and management

The two reviewers will use a standardized extraction table agreed to by all of the authors to extract and record study data.

Data items

The extracted data will include study characteristics (author, year), participant characteristics (sample sizes, age, sex, type of glaucoma, proportion of open-angle glaucoma), types of intervention on adherence, duration, frequency and intensity, and timing of follow-up

assessment. Means and standard deviations (SDs) of primary outcome measures at baseline, as well as the time points after and closest to the end of the treatment will be extracted, so as to accommodate predicted treatment-duration variation across studies. Although there is no current consensus on the appropriate duration of adherence interventions, it is expected that most interventions will fall somewhere between 4 and 12 weeks. Given the potential differences in the treatment durations, this second time point will allow for an investigation that ensures completion of the treatment regimen, and will likely be the point of maximal therapeutic effect.

Where studies have reported more than two adherence interventions (or control groups) that independently could have been included in this NMA, data will be extracted from all of the study arms. For example, if one RCT encompasses three treatment arms (A, B, and C), data from all three will be extracted.

For primary outcomes where mean ± SE are reported, SDs will be calculated using the formula: $SD = SE * \sqrt{n}$. Where medians and interquartile ranges are reported, the methods described by Wan *et al* will be used for computation of means and SDs.[14] Where means and 95% CIs are reported, SDs will be calculated according to the formula: $SD = \sqrt{n} * (\text{upper 95\% CI limit} - \text{lower 95\% CI limit}) / t$, t being the value from a t-distribution for a 95% CI for a sample distribution having degrees of freedom equal to the group sample size −1. If a paper does not provide sufficient data, they will be obtained from the corresponding author if possible. Extracted data will be tabulated.

Outcomes and prioritization

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).

Risk of bias in individual studies

The two reviewers will assess the internal validity (i.e., risk of bias) of the included studies according to the relevant domain-based risk-of-bias assessment tool, and the results will be presented in a graphical format further to the The Cochrane Handbook recommendation. A third reviewer will be brought in to resolve any disagreements. The inter-rater agreement will be reported based on Cohen's kappa coefficient (κ).

Data synthesis

The included trials' characteristics (i.e., type of glaucoma, details of intervention on adherence, outcomes) will be both summarized and tabulated. The summarization will entail the use of a network diagram, each node in which will represent an intervention class (as categorized in the inclusion criteria), the node size being proportional to the number of patients who are receiving the treatment. The effects of the pairwise comparisons of the two interventions will be shown as edges that interconnect the nodes, the thickness of the edge lines representing the pairwise comparison weight. A contribution matrix will be included to indicate the influence of the individual comparisons as well as the influence of the direct and indirect evidence on the overall effects summary. If quantitative synthesis is not appropriate, we will conduct a narrative synthesis.

Assessment of transitivity and meta-biases

It is expected that all of the interventions on adherence that are identified in the preliminary search will be in-principle jointly randomizable, which attribute will meet the transitivity assumption. For all of the comparisons between interventions in the network, the inferences will be based on direct evidence (pairwise RCTs), indirect evidence (effect B–C derived from A–B and A–C comparisons), or a mixture of both direct and indirect evidence. And, to meet the transitivity assumption, measures that potentially could modify effects such as sex, age, glaucoma type, and the distributions of these variables will be inspected.

Network meta-analysis

Assuming that the distribution of the effect modifiers is similar across studies, a frequentist NMA will be performed (see the proposed closed network geometry in Figure 2). Pairwise effect sizes will be calculated after including all of the evidence available in the network.[15] If outcome data on the different intervention durations and frequencies are available, their effectiveness for adherence will be investigated. Effect measures for treatments not already

compared in a pairwise RCT can be indirectly compared by using a common comparator to contrast the comparisons' effect sizes.[7 16 17] Considering that interventions may vary for certain characteristics, the sample used in each study might slightly differ; thus, a random effects model will be employed to generate pooled standardized effect sizes. Corrected effect size (Hedges' g) will be used in order to allow for inclusion of smaller studies.[18] Network forest plots, interval plots, and league tables will be used to rank the mixed (direct and indirect) effect sizes and 95% CIs for all treatment combinations in the network.

Detection of heterogeneity and assessment of inconsistency

Heterogeneity will be reported using 95% prediction intervals and I^2. Forest plots will be visually examined so as to identify any obvious inconsistency existing between direct and indirect treatment effects (loop consistency); any observed inconsistency might indicate non-satisfaction of the transitivity assumption. In cases where significant heterogeneity is detected, inconsistency will be evaluated one comparison at a time using the node-splitting approach.[19] Also, comparison-adjusted funnel plots will be employed for visual inspection and assessment of small-study effects as well as assessment of potential publication bias.[20]

Confidence in cumulative evidence

Based on study limitations, imprecision, heterogeneity indirectness, and publication bias,[21] the overall quality of evidence will be assessed by the Confidence in Network Meta-Analysis (CINeMA) approach, which is broadly based on the GRADE framework, but with a number of conceptual and semantic differences.[21] It covers 6 domains: (i) within-study bias (impact of risk of bias in included studies), (ii) reporting bias (publication and other reporting bias), (iii) indirectness, (iv) imprecision, (v) heterogeneity, and (vi) incoherence.[22] The reviewer's input is required at the study level for within-study bias and indirectness. Then, by applying user-defined rules, CINeMA assigns, to each domain, judgments at 3 levels (no concerns, some concerns, major concerns). Such judgments across domains are summarized in order to obtain 4 levels of confidence for each relative treatment effect, which levels will correspond to the standard GRADE assessments (very low, low, moderate, high).

Statistical analyses

Statistical package R will be used in all of the statistical analyses.[23] The netmeta R-package will be utilized to perform and report the NMA. P scores will enable the treatment efficacy

ranking. The netmeta package function forest. netmeta will be employed to create the visual network of nodes and connections.

Patient and public involvement

No patients and members of the public will be directly involved. Only data already existent in the literature and the aforementioned sources will be used for this study.

ETHICS AND DISSEMINATION

This work will synthesize evidence from already published studies, and as such, will not require an ethics review or approval. A manuscript presenting the findings will be submitted to a peer-reviewed scientific journal for publication; the results will be reported in accordance with the PRIMSA statement and the PRIMSA extension for network meta-analyses (PRISMA-NMA) guidelines. We will update this protocol required in the future and the date of amendments and description of changes will be presented as a supplement. Also, important protocol amendments will be documented and updated on PROSPERO.

FIGURE LEGENDS

Figure 1. PRISA flow diagram of the study selection process.

Figure 2. All possible network connections (pairwise comparisons, lines) with 12 nodes [interventions, A–L: (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].

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AUTHORS' CONTRIBUTIONS

MJ conceived the content and wrote the paper. SRS and AH developed the search strategy and evaluated the protocol. YKK designed the study and revised the protocol. All the authors read the protocol and have given the final approval for publication.

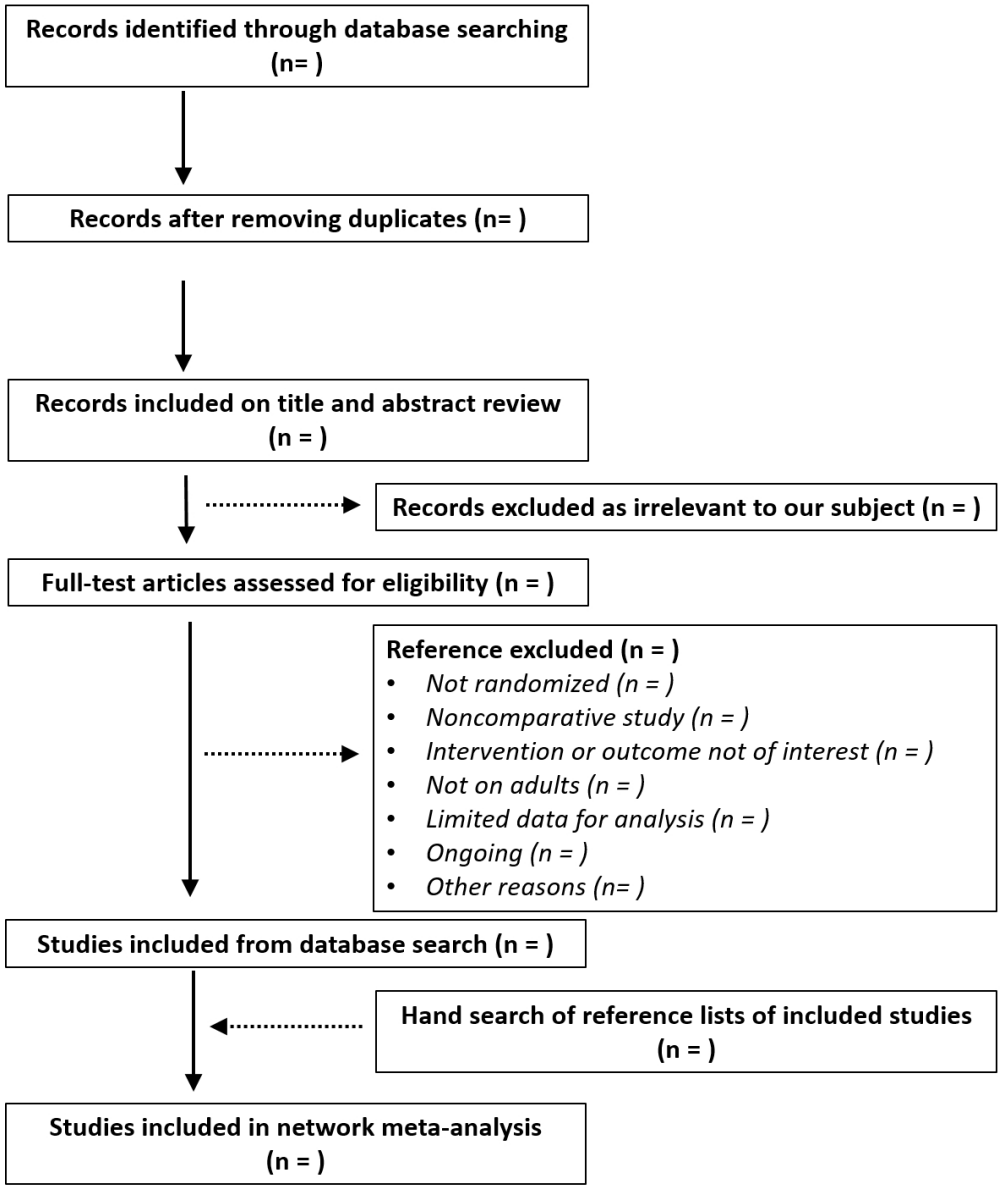

Figure 1. PRISA flow diagram of the study selection process.

100x119mm (300 x 300 DPI)

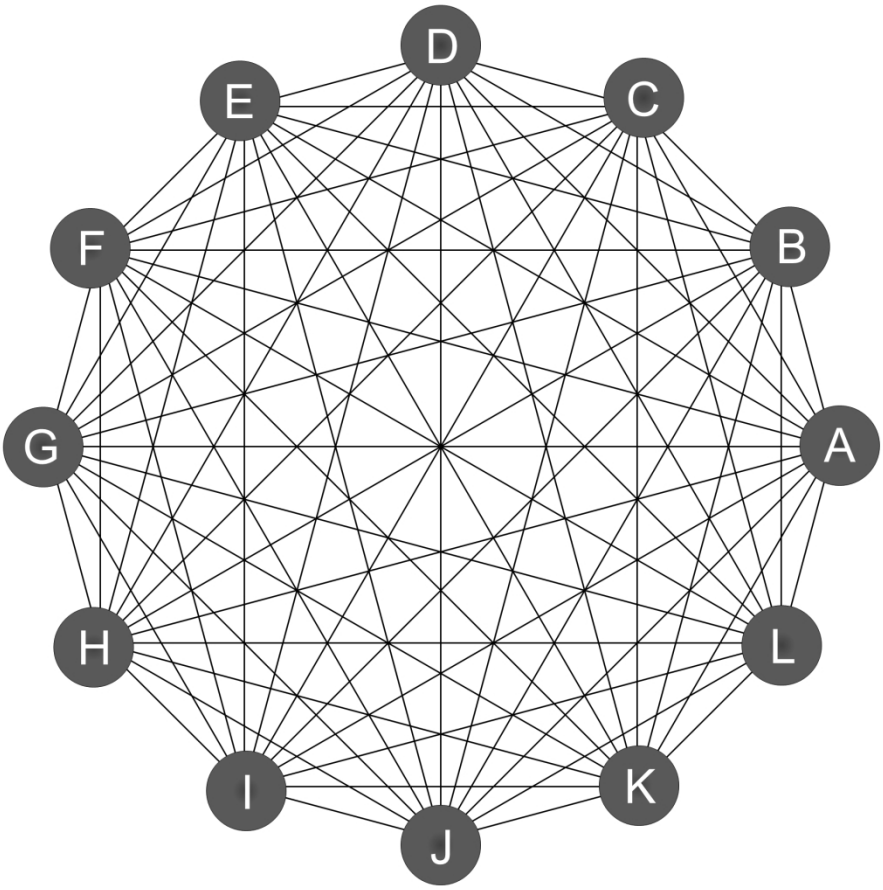

Figure 2. All possible network connections (pairwise comparisons, lines) with 12 nodes [interventions, A–L: (A) standard of care, (B) enhanced standard of care, (C) interacting education, (D) motivational interview and behavior change counselling, (E) multimedia education, (F) tailored care, (G) physician education, (H) printed material, (I) short message service, (J) provision of the patient's own medical records, (K) incentives, and (L) telephone call].

Search Terms

MEDLINE (Pubmed)

(Glaucoma[Mesh] OR Glaucoma[Tiab] OR "Ocular Hypertension"[Mesh] OR "Ocular Hypertension"[Tiab] OR "Intraocular Pressure"[Mesh] OR "Intraocular Pressure"[Tiab]) AND (Antiglaucoma* OR Therap* OR Drug* OR Drop* OR Treat* OR Medicat*) AND ("Medication Adherence"[Mesh] OR "Medication Adherence"[Tiab] OR "Patient Compliance"[Mesh] OR Adhere* OR Non-adhere* OR Nonadhere* OR Complian* OR Noncomplian* OR Non-complian*)

Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (Wiley)

#1 MeSH descriptor Glaucoma
#2 MeSH descriptor Ocular Hypertension
#3 MeSH descriptor Intraocular Pressure
#4 Glaucoma*
#5 Ocular hypertensi*
#6 (#1 OR #2 OR #3 OR #4 OR #5)
#7 Antiglaucoma*
#8 Therap* OR Drug* OR Drop* OR Treat* OR Medicat*
#9 (#7 OR #8)
#10 MeSH descriptor Medication Adherence
#11 MeSH descriptor Patient Compliance
#12 Adhere* OR Non-adhere* OR Nonadhere*
#13 Complian* OR Noncomplian* OR Non-complian*
#14 (#10 OR #11 OR #12 OR #13)
#15 (#6 AND #9 AND #14)

EMBASE (Ovid)

(Glaucoma/exp OR Intraocular hypertension/exp OR Intraocular pressure/exp OR Glaucom* OR Ocular hypertensi*) AND ('Antiglaucoma agent'/exp OR Antiglaucoma* OR Therap* OR Drug* OR Drop* OR Treat* OR Medicat*) AND ('Patient Compliance'/exp OR

‘Medication Compliance’/exp OR Adhere* OR Non-adhere* OR Nonadhere* OR Complian* OR Noncomplian* OR Non-complian*)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number Page 2
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review Page 10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments Page 1
Support:		
Sources	5a	Indicate sources of financial or other support for the review Page 1
Sponsor	5b	Provide name for the review funder and/or sponsor Page 1
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol Page 1
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known Page 3-4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) Page 3-4
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review Page 5-6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage Page 6

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated Page 6-7
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review Page 7-8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) Page 7-8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators Page 7-8
Data items	12	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators Page 7-8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale Page 8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis Page 8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised Page 9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2 , Kendall's τ) Page 9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) NA
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned Page 9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) Page 9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) Page 9-10

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Comparative Effectiveness of Interventions for Improving Adherence to Ocular Hypotensive Therapy in Patients with Glaucoma or Ocular Hypertension: Protocol for Network Meta-Analysis

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Comparative Effectiveness of Interventions for Improving Adherence to Ocular Hypotensive Therapy in Patients with Glaucoma or Ocular Hypertension: Protocol for Network Meta-Analysis

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ABSTRACT

Introduction: Poor medication adherence is an important issue in healthcare. Various types of intervention for improved adherence to ocular hypotensive therapy have been proposed, though evidence on the effectiveness of any isolated intervention remains limited. The current protocol is an ongoing network meta-analysis (NMA) design that enables comparative investigation of any and all interventions for which there are available randomized controlled trials (RCTs). Our aim is the systematic comparison of the efficacy of different types of adherence interventions for patients suffering glaucoma or ocular hypertension (OHT).

Methods and analysis: Studies of interest will assess the effects of any interventions on medication adherence in adults (age ≥ 18 years) with either glaucoma or OHT. Four electronic databases (Cochrane Central Register of Controlled Trials, Embase, MEDLINE, and Scopus) will be searched for RCTs published in any language, without any time limitation. First titles and abstracts, and then full-text papers, will be screened by two reviewers, who will extract the useful data. The primary outcome measure is an intervention's impact on adherence. The two reviewers will also assess, using the relevant domain-based risk-of-bias assessment tool, the internal validity of the studies. The overall quality of the evidence will be assessed by the Confidence in Network Meta-Analysis approach, and will be summarized with network diagrams. To allow for assessment of both direct and indirect evidence, a contribution matrix will be utilized. For visualization of the effects of all of the included interventions, forest plots will be constructed. Pairwise effect sizes will be calculated according to all of the evidence available in the network.

Ethics and dissemination: This work will synthesize evidence from already published studies and as such, will not require an ethics review or approval. A manuscript presenting the findings will be submitted to a peer-reviewed scientific journal for publication.

PROSPERO registration number: CRD42021253145

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The use of a network meta-analyses (NMA) design should enable comparative investigation of all available adherence interventions for which randomized controlled trials are available.
- This NMA could potentially allow for generation of a hierarchy of interventions for improving ocular hypotensive therapy adherence that is clinically meaningful.
- This work could not exclude the potential influence of different trial-defined adherence criteria.
- 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.

INTRODUCTION

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.

Two systematic reviews already have examined the effectiveness of adherence interventions for patients with glaucoma or ocular hypertension (OHT).[5 6] They indicate that whereas complex interventions in the form of patient education combined with personalized behavioral change (e.g., tailoring of daily routines for promotion of adherence to eye drops) may improve glaucoma medication adherence, overall there is still insufficient evidence for recommendation of any particular intervention. Traditional (meta-analytic) pairwise investigation of those isolated interventions proved impossible, as they varied by study, and randomized controlled trials (RCTs) were insufficient in number to evaluate each of the different intervention types.

Drawing conclusions on the comparative effectiveness of different adherence interventions based on individual RCTs and systematic review is difficult. Traditional meta-analyses, moreover, are limited by the relative unavailability of pairwise comparisons of interventions.[7] It is difficult, therefore, to interpret the entire body of evidence available, many RCTs being available for only some interventions, and the evidence being limited for some others.

Furthermore, for many types of adherence interventions, there are no available direct comparisons.

Network meta-analysis (NMA) is a study design that allows for investigation of the efficacy of different interventions.[8 9] Creation of a network of pairwise RCTs enables use of all direct and indirect evidence for determination of such efficacy.[10] NMA makes possible the comparative analysis of all adherence interventions for which there are available RCTs, unlike traditional systematic review and meta-analysis, which can analyze only two. Furthermore, with this design, the efficacies of available interventions can be ranked.

The protocol presented in these pages describes an ongoing NMA design for systematic comparison of the effectiveness of different intervention types for improved adherence to ocular hypotensive therapy among adult patients with glaucoma or OHT. The main research question was: What are the efficacies of different types of interventions for adherence? The above-alluded-to objective — to evaluate the efficacies of different types of interventions — will allow for generation of a hierarchy of interventions that is clinically meaningful.

METHODS AND ANALYSIS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for protocols (PRISMA-P) is followed by this protocol.[11] The NMA results will be reported in accordance with the PRISMA statement and the PRISMA extension for network meta-analyses (PRISMA-NMA).[12 13] The research has been registered on PROSPERO (CRD 42021253145).

Eligibility criteria

Studies eligible for inclusion in the NMA are those that are RCTs indicating the effects of any interventions on adherence to ocular hypotensive therapy by adults (age ≥ 18 years) with either glaucoma or OHT. Any intervention, control-treatment, or no-treatment group will be included as a comparator. Studies reporting secondary results (e.g., intraocular pressure and visual field test results) other than adherence also will be included. Any studies for inclusion need to be available in the full-text format. 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.

Categorization of studies

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).

Information sources

Four electronic databases (Cochrane Central Register of Controlled Trials, Embase, MEDLINE and Scopus) were searched for RCTs, with no time limitation.

Search strategy

With the assistance of a medical librarian, a six-part search strategy including terms by which to identify studies relevant to (i) glaucoma, (ii) OHT, (iii) OHT therapy, (iv) intervention, (v) adherence, and (vi) RCTs was developed. The keywords included were *glaucoma, ocular hypertension, medication, adherence, and compliance.* The search terms were based on the established terminology, and the extensive MESH and EMBASE search terms were employed when available. The search strategy was developed for the MEDLINE database and then adjusted to meet the conditions of the other databases. The full search strategies are provided in online supplemental file.

For prospectively identified systematic reviews and meta-analyses, the reference lists of which may include potentially relevant studies, manual searches will be conducted to identify any of those missed by the electronic searches. The studies that are analyzed will include data on types of intervention and improved adherence to OHT therapy, regardless of the language, publication date, country or study design.

Selection process

Two reviewers will each independently screen titles as well as abstracts so as to identify potentially eligible studies. For each identified study, the two reviewers will then independently review the full-text papers. In either of these two stages, a third reviewer will be brought in to resolve any disagreements. The inter-rater agreements will be reported in terms of Cohen's kappa coefficient (κ). For studies that have been reported in multiple papers, the paper that reports the most complete effectiveness analysis will be selected (i.e., reports on either subgroup or secondary analyses will be excluded). The entire stepwise process will be presented using a PRISMA flow chart (Figure 1).

Data collection and management

The two reviewers will use a standardized extraction table agreed to by all of the authors to extract and record study data.

Data items

The extracted data will include study characteristics (author, year), participant characteristics (sample sizes, age, sex, type of glaucoma, proportion of open-angle glaucoma), types of intervention on adherence, duration, frequency and intensity, and timing of follow-up

assessment. Means and standard deviations (SDs) of primary outcome measures at baseline, as well as the time points after and closest to the end of the treatment will be extracted, so as to accommodate predicted treatment-duration variation across studies. Although there is no current consensus on the appropriate duration of adherence interventions, it is expected that most interventions will fall somewhere between 4 and 12 weeks. Given the potential differences in the treatment durations, this second time point will allow for an investigation that ensures completion of the treatment regimen, and will likely be the point of maximal therapeutic effect.

Where studies have reported more than two adherence interventions (or control groups) that independently could have been included in this NMA, data will be extracted from all of the study arms. For example, if one RCT encompasses three treatment arms (A, B, and C), data from all three will be extracted.

For primary outcomes where mean ± SE are reported, SDs will be calculated using the formula: $SD = SE * \sqrt{n}$. Where medians and interquartile ranges are reported, the methods described by Wan *et al* will be used for computation of means and SDs.[14] Where means and 95% CIs are reported, SDs will be calculated according to the formula: $SD = \sqrt{n} * (\text{upper 95\% CI limit} - \text{lower 95\% CI limit}) / t$, t being the value from a t-distribution for a 95% CI for a sample distribution having degrees of freedom equal to the group sample size −1. If a paper does not provide sufficient data, they will be obtained from the corresponding author if possible. Extracted data will be tabulated.

Outcomes and prioritization

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).

Risk of bias in individual studies

The two reviewers will assess the internal validity (i.e., risk of bias) of the included studies according to the relevant domain-based risk-of-bias assessment tool, and the results will be presented in a graphical format further to the The Cochrane Handbook recommendation. A third reviewer will be brought in to resolve any disagreements. The inter-rater agreement will be reported based on Cohen's kappa coefficient (κ).

Data synthesis

The included trials' characteristics (i.e., type of glaucoma, details of intervention on adherence, outcomes) will be both summarized and tabulated. The summarization will entail the use of a network diagram, each node in which will represent an intervention class (as categorized in the inclusion criteria), the node size being proportional to the number of patients who are receiving the treatment. The effects of the pairwise comparisons of the two interventions will be shown as edges that interconnect the nodes, the thickness of the edge lines representing the pairwise comparison weight. A contribution matrix will be included to indicate the influence of the individual comparisons as well as the influence of the direct and indirect evidence on the overall effects summary. If quantitative synthesis is not appropriate, we will conduct a narrative synthesis.

Assessment of transitivity and meta-biases

It is expected that all of the interventions on adherence that are identified in the preliminary search will be in-principle jointly randomizable, which attribute will meet the transitivity assumption. For all of the comparisons between interventions in the network, the inferences will be based on direct evidence (pairwise RCTs), indirect evidence (effect B–C derived from A–B and A–C comparisons), or a mixture of both direct and indirect evidence. And, to meet the transitivity assumption, measures that potentially could modify effects such as sex, age, glaucoma type, and the distributions of these variables will be inspected.

Network meta-analysis

Assuming that the distribution of the effect modifiers is similar across studies, a frequentist NMA will be performed (see the proposed closed network geometry in Figure 2). Pairwise effect sizes will be calculated after including all of the evidence available in the network.[15] If outcome data on the different intervention durations and frequencies are available, their effectiveness for adherence will be investigated. Effect measures for treatments not already

compared in a pairwise RCT can be indirectly compared by using a common comparator to contrast the comparisons' effect sizes.[7 16 17] Considering that interventions may vary for certain characteristics, the sample used in each study might slightly differ; thus, a random effects model will be employed to generate pooled standardized effect sizes. Corrected effect size (Hedges' g) will be used in order to allow for inclusion of smaller studies.[18] Network forest plots, interval plots, and league tables will be used to rank the mixed (direct and indirect) effect sizes and 95% CIs for all treatment combinations in the network.

Detection of heterogeneity and assessment of inconsistency

Heterogeneity will be reported using 95% prediction intervals and I^2. Forest plots will be visually examined so as to identify any obvious inconsistency existing between direct and indirect treatment effects (loop consistency); any observed inconsistency might indicate non-satisfaction of the transitivity assumption. In cases where significant heterogeneity is detected, inconsistency will be evaluated one comparison at a time using the node-splitting approach.[19] Also, comparison-adjusted funnel plots will be employed for visual inspection and assessment of small-study effects as well as assessment of potential publication bias.[20]

Confidence in cumulative evidence

Based on study limitations, imprecision, heterogeneity indirectness, and publication bias,[21] the overall quality of evidence will be assessed by the Confidence in Network Meta-Analysis (CINeMA) approach, which is broadly based on the GRADE framework, but with a number of conceptual and semantic differences.[21] It covers 6 domains: (i) within-study bias (impact of risk of bias in included studies), (ii) reporting bias (publication and other reporting bias), (iii) indirectness, (iv) imprecision, (v) heterogeneity, and (vi) incoherence.[22] The reviewer's input is required at the study level for within-study bias and indirectness. Then, by applying user-defined rules, CINeMA assigns, to each domain, judgments at 3 levels (no concerns, some concerns, major concerns). Such judgments across domains are summarized in order to obtain 4 levels of confidence for each relative treatment effect, which levels will correspond to the standard GRADE assessments (very low, low, moderate, high).

Statistical analyses

Statistical package R will be used in all of the statistical analyses.[23] The netmeta R-package will be utilized to perform and report the NMA. P scores will enable the treatment efficacy

ranking. The netmeta package function forest. netmeta will be employed to create the visual network of nodes and connections.

Patient and public involvement

No patients and members of the public will be directly involved. Only data already existent in the literature and the aforementioned sources will be used for this study.

ETHICS AND DISSEMINATION

This work will synthesize evidence from already published studies, and as such, will not require an ethics review or approval. A manuscript presenting the findings will be submitted to a peer-reviewed scientific journal for publication; the results will be reported in accordance with the PRIMSA statement and the PRIMSA extension for network meta-analyses (PRISMA-NMA) guidelines. We will update this protocol required in the future and the date of amendments and description of changes will be presented as a supplement. Also, important protocol amendments will be documented and updated on PROSPERO.

FIGURE LEGENDS

Figure 1. PRISMA flow diagram of the study selection process.

Figure 2. All possible network connections (pairwise comparisons, lines) with 12 nodes [interventions, A–L: (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].

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AUTHORS' CONTRIBUTIONS

MJ conceived the content and wrote the paper. SRS and AH developed the search strategy and evaluated the protocol. YKK designed the study and revised the protocol. All the authors read the protocol and have given the final approval for publication.

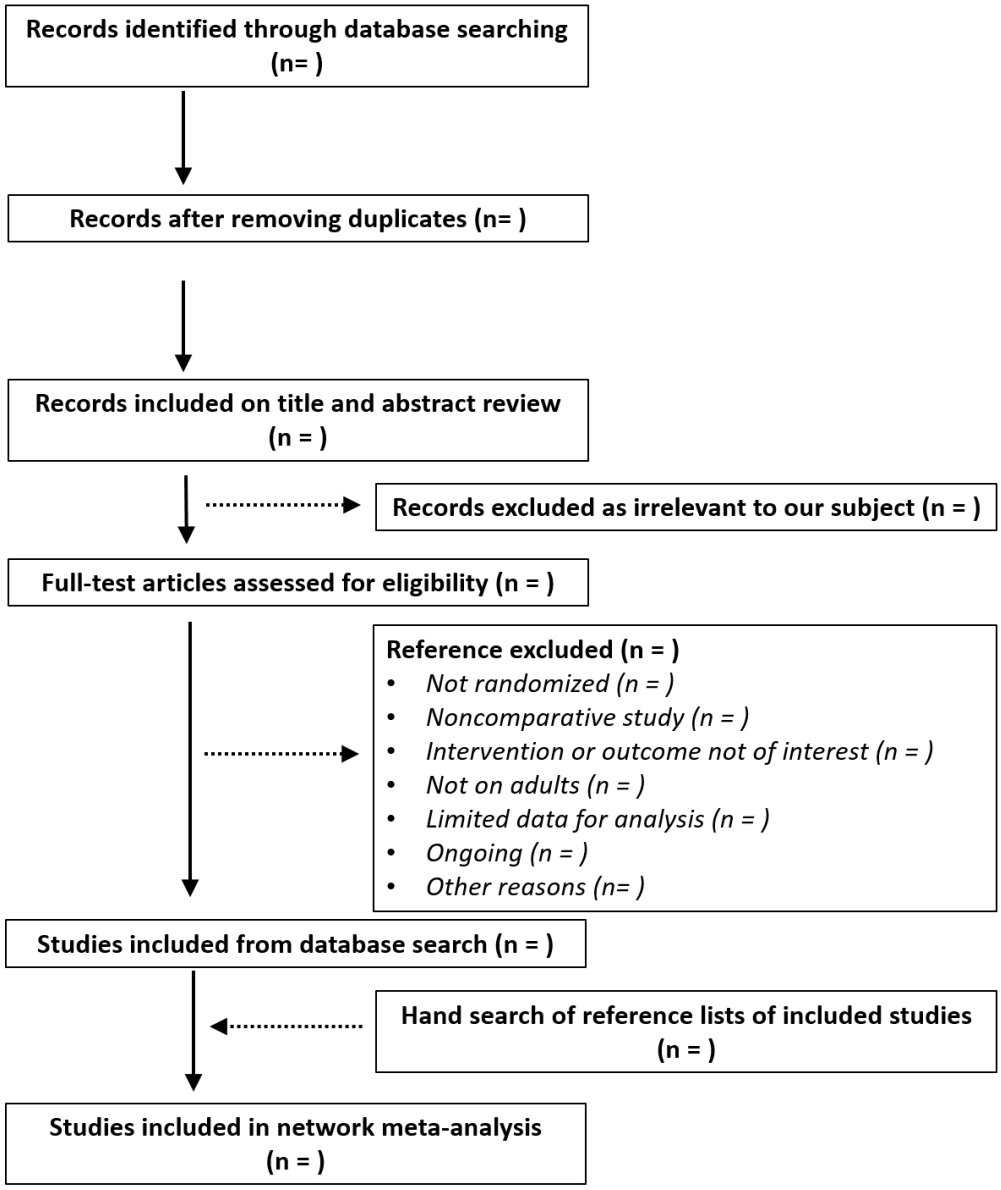

Figure 1. PRISA flow diagram of the study selection process.

100x119mm (300 x 300 DPI)

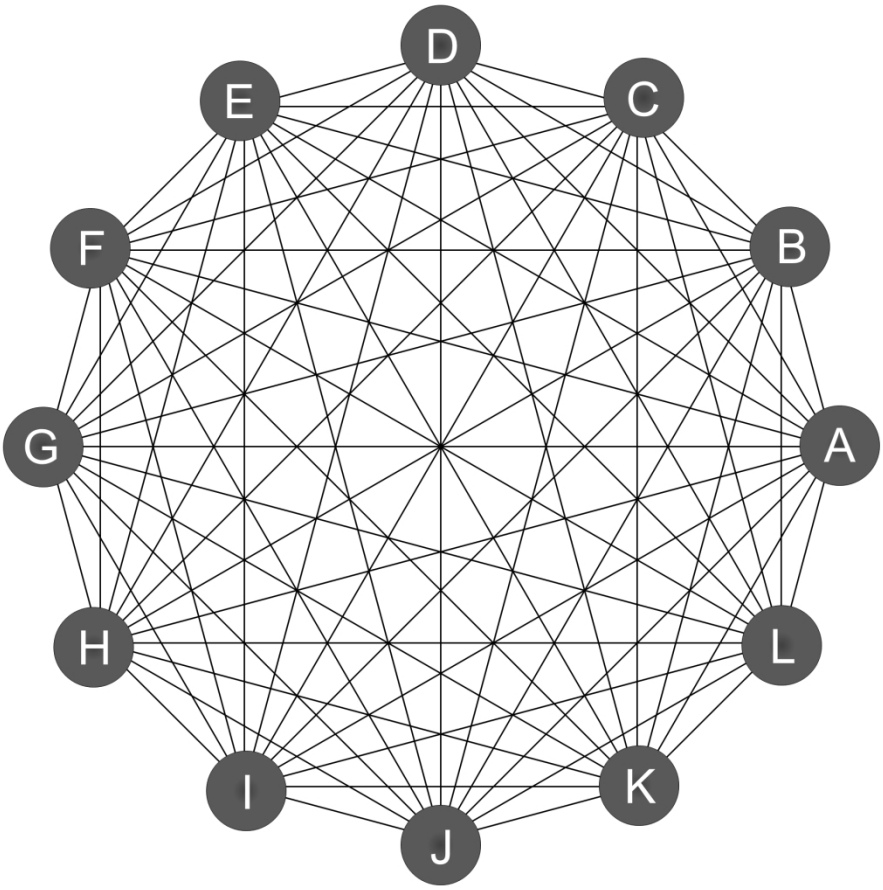

Figure 2. All possible network connections (pairwise comparisons, lines) with 12 nodes [interventions, A–L: (A) standard of care, (B) enhanced standard of care, (C) interacting education, (D) motivational interview and behavior change counselling, (E) multimedia education, (F) tailored care, (G) physician education, (H) printed material, (I) short message service, (J) provision of the patient's own medical records, (K) incentives, and (L) telephone call].

Search Terms

MEDLINE (Pubmed)

(Glaucoma[Mesh] OR Glaucoma[Tiab] OR "Ocular Hypertension"[Mesh] OR "Ocular Hypertension"[Tiab] OR "Intraocular Pressure"[Mesh] OR "Intraocular Pressure"[Tiab]) AND (Antiglaucoma* OR Therap* OR Drug* OR Drop* OR Treat* OR Medicat*) AND ("Medication Adherence"[Mesh] OR "Medication Adherence"[Tiab] OR "Patient Compliance"[Mesh] OR Adhere* OR Non-adhere* OR Nonadhere* OR Complian* OR Noncomplian* OR Non-complian*)

Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (Wiley)

#1 MeSH descriptor Glaucoma
#2 MeSH descriptor Ocular Hypertension
#3 MeSH descriptor Intraocular Pressure
#4 Glaucoma*
#5 Ocular hypertensi*
#6 (#1 OR #2 OR #3 OR #4 OR #5)
#7 Antiglaucoma*
#8 Therap* OR Drug* OR Drop* OR Treat* OR Medicat*
#9 (#7 OR #8)
#10 MeSH descriptor Medication Adherence
#11 MeSH descriptor Patient Compliance
#12 Adhere* OR Non-adhere* OR Nonadhere*
#13 Complian* OR Noncomplian* OR Non-complian*
#14 (#10 OR #11 OR #12 OR #13)
#15 (#6 AND #9 AND #14)

EMBASE (Ovid)

(Glaucoma/exp OR Intraocular hypertension/exp OR Intraocular pressure/exp OR Glaucom* OR Ocular hypertensi*) AND ('Antiglaucoma agent'/exp OR Antiglaucoma* OR Therap*

OR Drug* OR Drop* OR Treat* OR Medicat*) AND ('Patient Compliance'/exp OR 'Medication Compliance'/exp OR Adhere* OR Non-adhere* OR Nonadhere* OR Complian* OR Noncomplian* OR Non-complian*)

Scopus

#1. [All fields] glaucoma* OR "Ocular hypertensi*" OR "Intraocular Pressure"

#2. [All fields] Antiglaucoma* OR Therap* OR Drug* OR Drop* OR Treat* OR Medicat*

#3 [All fields] Adhere* OR Non-adhere* OR Nonadhere* OR Complian* OR Noncomplian* OR Non-complian*

#4. (#1 AND #2 AND #3)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number Page 2
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review Page 10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments Page 1
Support:		
Sources	5a	Indicate sources of financial or other support for the review Page 1
Sponsor	5b	Provide name for the review funder and/or sponsor Page 1
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol Page 1
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known Page 3-4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) Page 3-4
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review Page 5-6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage Page 6

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated Page 6-7
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review Page 7-8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) Page 7-8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators Page 7-8
Data items	12	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators Page 7-8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale Page 8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis Page 8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised Page 9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2 , Kendall's τ) Page 9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) NA
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned Page 9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) Page 9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) Page 9-10

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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