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Iridotomy to slow progression of angle-closure glaucoma (Protocol)

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[Intervention Protocol]

Iridotomy to slow progression of angle-closure glaucoma

Jimmy T Le[1a], Benjamin Rouse[1b], Gus Gazzard[2]

[1]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA. [2]Moorfields Eye Hospital NHS Foundation Trust, London, UK

[a]Joint first author. [b]Joint first author

Contact address: Jimmy T Le, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe Street, Baltimore, Maryland, 21205, USA. jle6@jhu.edu.

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

The primary objective is to assess the role of iridotomy-compared with observation-in the prevention of visual field loss for individuals who have primary angle closure or primary angle-closure glaucoma in at least one eye. We will also examine the role of iridotomy in the prevention of elevated intraocular pressure (IOP) in individuals with narrow angles (primary angle-closure suspect) in at least one eye.

BACKGROUND

Introduction

Glaucoma characterizes a group of similar diseases defined by progressive damage to the optic nerve (optic neuropathy) that occurs in a characteristic pattern with associated changes in appearance and visual field (Foster 2002). High intraocular pressure (IOP) is associated with glaucomatous optic nerve damage. IOP can elevate when aqueous humor, a clear fluid that continuously flows in and out of the anterior chamber to nourish the eye, does not drain properly (Mapstone 1968; EGS 2014; AAO 2015). When impairment of aqueous drainage occurs at the trabecular meshwork by the iris, this is referred to as angle closure (Emanuel 2014). Optic nerve damage resulting from angle closure commonly is described as primary angle-closure glaucoma (PACG), while optic nerve damage without the angle closure is known as primary open-angle glaucoma (POAG). Both open-angle and angle-closure glaucoma also can be classified as secondary when the condition is traced to an identifiable concomitant cause such as an eye injury, eye inflammation, or other eye illnesses (Law 2013). A further manifestation of angle closure is an acute 'attack' or crisis, in which sudden blockage to the drainage is associated with very high intraocular pressures and symptoms including headache, blurred vision and a severe dull eye pain.

Currently, there is increasing interest in examining the efficacy of interventions for preventing PACG (Yu 2015). These include medical or surgical treatments that aim to equalize the pressures across the anterior and posterior chambers of the eye by allowing the iris to fall back, away from the trabecular meshwork, in an attempt to open the angles and lower IOP. Two common techniques used to accomplish this objective are iridectomy-which involves surgical removal of parts of the iris-and iridotomy-which involves

the use of a laser to create a hole in the iris. Early studies examining angle-closure disease in the 1950s documented that when the contralateral eye of a patient with angle-closure was given no treatment or pilocarpine (once or twice daily), there was a 50% chance over a period of 25 year sthat the patient would develop acute attacks or a sudden rise in IOP (Lowe 1962; Lowe 1966). Conversely, only 1 out of 54 patients treated with surgical iridectomy during this same period of time developed an acute attack in the untreated contralateral eye (Ang 2000; Edwards 1982; Snow 1977). Iridotomy is a less invasive and more common procedure than iridectomy (Ramulu 2007). While both achieve the same purpose, there are approximately 51 iridotomies for every iridectomy performed.

For patients and their providers, a better understanding of an intervention that addresses angle-closure glaucoma would assist in deciding the most appropriate prevention modality; for researchers and decision makers, this information facilitates the design and implementation of global screening programs and may be useful for identifying persons at risk.

Epidemiology

Glaucoma is among the leading causes of blindness and, particularly due to the irreversible nature of the disease, a pressing public health challenge (Kingman 2004; Resnikoff 2004; Bourne 2013). The World Health Organization characterizes glaucoma as one of its priority eye diseases, and researchers have approximated that about five million people today are blind as a consequence of glaucoma (Osborne 2003; Quigley 2006). A recent systematic review found a global prevalence of glaucoma in the 40 to 80 years age group of 3.54%, and estimated that prevalence will reach 76 million by 2020 and 111.8 million by 2040 (Tham 2014). The prevalence of angle-closure glaucoma in particular is estimated to rise to 21 million by 2020 (Quigley 2006).

PACG is less common among Caucasians, with pooled prevalence of PACG for people aged 40 years or older from European ancestry estimated to be 0.4% (Day 2012). PACG, however, is more prevalent in Asians of Mongolian descent (Bonomi 2002; Tham 2014). Among the 64.26 million people with glaucoma aged 40 to 80 years, 20.17 million are estimated to have PACG in 2013; among this sub-population, 14.47 million are estimated to be living in Asia (Quigley 2006; Tham 2014). For example, in China, 91% of the 1.7 million cases of bilateral blindness are attributable to PACG (Foster 2001; Ng 2012). The prevalence also appears to be greater among older women, compared with their male and younger counterparts in all ethnic populations (Bonomi 2002; Day 2012). There is substantial variation in the data on the incidence rates for PACG, ranging from 4 per 100,000 person-years to 58.7 per 100,000 person-years (Erie 1997; Lai 2001; Ivanisevic 2002).

Description of the condition

The consensus view regarding the mechanism of elevation in IOP in angle-closure glaucoma has identified pupillary block as the major mechanism, which limits the flow of aqueous fluid from the posterior to the anterior chamber of the eye (Friedman 2001; Foster 2002; AAO 2015). The pressure differential created by the build-up of fluid causes the iris to bulge forward and come into iridotrabecular contact (ITC) with the trabecular meshwork and peripheral cornea (Mapstone 1968; AAO 2015). This contact causes a rise in the IOP by reducing the outflow of aqueous fluids. Another important mechanism that is often associated with the development of angle closure is a plateau iris configuration. A plateau iris is the result of narrowing of the anterior chamber, pushing peripheral parts of the iris forward by displacement of the ciliary body anteriorly, leading to continuation of ITC (AAO 2015).

For this review, we follow a recently proposed classification of angle-closure glaucoma (Foster 2000; Aung 2001; Foster 2002; Ng 2012; AAO 2015). This definition rests on the idea of describing an 'occludable' angle, using terms such as 'narrow' to specify the anatomical predisposition to angle closure, further qualified by degrees of ITC and whether or not the patient has peripheral anterior synechiae (PAS). The drainage angle is easily and painlessly assessable through a gonioscopy during an eye exam.

- Primary angle-closure suspects (PACS) are patients described as having narrow angles, where there is appositional or synechial contact 180 degrees or more, as observed on gonioscopy, between the peripheral iris and the posterior trabecular meshwork; however, there is no evidence of permanent aqueous outflow obstruction or damage to the angle. In other words, there is neither elevated IOP nor PAS. Accordingly, there are also no signs of elevated IOP or glaucomatous optic disc neuropathy.

- Patients with primary angle-closure (PAC) are those showing signs of chronic angle damage beyond narrow angles with iridotrabecular contact in three or more quadrants at least 180 degrees, therefore obstruction by the peripheral iris has occurred and there is elevated IOP and/or PAS but no signs of glaucomatous optic disc neuropathy.

- Primary angle-closure glaucoma (PACG) patients are those with 180 degrees of angle or greater in which the posterior (usually pigmented) and presumed functional trabecular meshwork is not visible and there is the presence of glaucomatous optic nerve damage in addition to elevated eye pressure and/or PAS as described for PAC.

The American Academy of Ophthalmology in its 2015 Preferred Practice Patterns for Primary Angle Closure summarizes clinical findings defining patients seen with angle-closure disease (AAO 2015) (Table 1). This classification for the progression from PACS to PAC to PACG suggests potential for preventing the conse-

quences of narrow angles and angle closure through early detection and treatment. More traditional definitions of PACG and angle-closure disease were based on whether nor not symptoms occur acutely or chronically (e.g., having acute angle-closure crisis or AACC). For this review, we are treating acute angle-crisis or attacks as separate clinical conditions, despite similar mechanisms, and will not consider AACC for this review.

Description of the intervention

Iridotomy is a laser-assisted surgical procedure aimed at creating an opening in the peripheral part of the iris and is conducted as an outpatient procedure involving the use of a laser (e.g., neodymium-doped yttrium aluminium garnet or Nd:YAG laser, argon laser) and slit lamp biomicroscope (AAO 2015; Nolan 2000).

While iridotomy is also the standard of care for treating PAC and PACG (AAO 2015), there are some limitations and risks to using this procedure. By disrupting the natural flow of aqueous fluids in the eye, which may in turn result in significant increase in contact between the lens and the iris, there is a theoretical risk of more rapid development of cataracts (Caronia 1996). Other potential risks include rare occurrence of corneal endothelial damage localized to the surgery site, stray light symptoms, and the development of posterior synechiae (Pollack 1981; Quigley 1981; Robin 1984). Posterior synechiae potentially can limit vision in dimly-lit environments and complicate cataract surgery or pan retinal photocoagulation.

How the intervention might work

Iridotomy removes pupillary block by making an opening in the peripheral iris; this hole-created through the use of a laser-provides for free circulation of aqueous from posterior to anterior chambers even if the pupil becomes blocked (Fleck 1997; Friedman 2001; Ng 2012). This opening prevents IOP from rising further, which in theory should minimize subsequent optic nerve damage and progression of visual field loss.

Why it is important to do this review

Understanding the preventative effects of laser iridotomy in primary angle-closure suspects and patients with iridotrabecular contact are high-priority clinical questions that reflect the American Academy of Ophthalmology's Preferred Practice Patterns recommendations for management of primary angle-closure (AAO 2015). Epidemiologists have pointed out this topic area as an evidence gap for the management of PAC (Yu 2015).

While there is some evidence that a prophylactic iridotomy significantly reduces the risk of angle closure (i.e., PAC or PACG) in the contralateral eye of an individual who has previously been diagnosed with angle closure or PACG, there is much confusion regarding the need for a prophylactic iridotomy in eyes of patients with asymptomatic narrow angles noted through gonioscopy, i.e., PAC suspects (Snow 1977; Edwards 1982; Ang 2000). Similarly, some research findings suggest that iridotomy may be insufficient for long-term control of IOP (See 2011). Lastly, while complications of laser-assisted iridotomy seem minor relative to the risk and burden of angle closure, they are of significant concern for patients considering these procedures, particularly in East Asia and India (Dandona 2000; Foster 2000; Ramakrishnan 2003). For instance, if iridotomy hastens the progression of cataracts significantly, these procedures may cause more cataract-related blindness with widespread screening and usage of iridotomy treatment, especially in an environment such as a low- and middle-income country where cataract services are not universally available.

OBJECTIVES

The primary objective is to assess the role of iridotomy-compared with observation-in the prevention of visual field loss for individuals who have primary angle closure or primary angle-closure glaucoma in at least one eye. We will also examine the role of iridotomy in the prevention of elevated intraocular pressure (IOP) in individuals with narrow angles (primary angle-closure suspect) in at least one eye.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials (RCTs). Given that there may be few RCTs on this intervention, we also will include quasi-randomized trials and will address potential selection bias in the analysis and discussion. We define quasi-randomized trials as studies that employed a method of allocating patients to a treatment arm that is not strictly random (e.g., by date of birth, hospital record number, in alternation, etc).

Types of participants

We will include studies of participants with gonioscopically-narrow angles-i.e. primary angle-closure suspects (PACS), those with primary angle closure (PAC), or those with primary angle-closure glaucoma in one or both eyes. We will not restrict by age, gender or ethnicity.

Types of interventions

We will include only trials that compared iridotomy versus observation (i.e., no surgical treatment) or sham treatment with or without IOP-lowering medication.

Types of outcome measures

Primary outcomes

- Progressive visual field loss at one year, defined as the proportion of participants with evidence of progression of visual field loss, measured using a validated method, at one year of follow up. These methods include, but are not limited to automated Humphrey Field Analyzer, Heidelberg Edge Perimeter, or Oculus. We also will consider other time points during follow-up as reported in the included studies. We will only assess this outcome for studies involving patients with PAC or PACG.

Secondary outcomes

The secondary outcomes for comparison of interventions include the following.

1. Mean change in IOP from baseline to one year, measured by any method of applanation tonometry, e.g. Goldmann or Perkins.
2. Gonioscopic findings in the participant, including angle width and presence of PAS, as reported by the investigators.
3. Need for additional surgery, as defined by the proportion of participants who received additional surgery to control IOP within one year after iridotomy.
4. Number of medications used to control IOP at one year.
5. Mean change in best corrected visual acuity (BCVA) as measured by logMAR from baseline to one year after iridotomy.
6. Quality of life data will be tabulated as documented.

To improve comparability and consistency, we have adapted some of the above outcomes from previous Cochrane reviews (Friedman 2006; Zhang 2015).

Adverse events

1. Adverse effects, including IOP spikes, persistent IOP elevation, hyphema and other adverse effects will be reported as documented.

Search methods for identification of studies

Electronic searches

We will search CENTRAL (which contains the Cochrane Eyes and Vision Trials Register) (latest issue), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to present), EMBASE (January 1980 to present), PubMed (January 1948 to present), Latin American and Caribbean Health Sciences Literature Database (LILACS) (1982 to present), ClinicalTrials.gov (www.clinicaltrials.gov), and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We will not use any date or language restrictions in the electronic searches.

See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), PubMed (Appendix 4), LILACS (Appendix 5), ClinicalTrials.gov (Appendix 6) and the ICTRP (Appendix 7).

Searching other resources

We intend to search the references of included studies for information about further trials. We do not intend to handsearch journals and conference proceedings.

Data collection and analysis

Selection of studies

Two review authors independently will screen titles and abstracts of all records identified in the searches. We will classify each record as either 'relevant' or 'not relevant' for full-text review. The full-text copies of all studies that we identify for full-text review will be assessed by two review authors independently to determine if they meet the inclusion criteria ('Yes' or 'No'). We will contact the trial authors to clarify any details necessary to make a complete assessment of the relevance or design of the study. We will document reasons for exclusion for each study assessed as not eligible after review of the full-text reports. We will resolve discrepancies between review authors by discussion at each stage of the selection process.

Data extraction and management

Two review authors independently will extract data for the primary and secondary outcomes using a web-based electronic data collection form (Appendix 8). We will extract information on the study design (e.g., study setting, countries where recruitment took place, sample size, study duration and follow-up time, study design, analysis choice, sources of funding, and potential conflicts of interests), characteristics of the participants (e.g., inclusion/exclusion criteria, underlying disease conditions, and medical history, including visual acuity and other vision-related characteristics), interventions and comparators (e.g., type of laser, duration

and timing), and outcomes (e.g., domain, specific measurement, specific metric, method of aggregation, and the time frame).
The two authors will then compare the extracted data and resolve discrepancies by discussion, and when necessary, through consultation with the third author. One review author will complete data entry into RevMan 5.3 (RevMan 2014) and a second author will verify the data entered.

Assessment of risk of bias in included studies

Two review authors independently will assess the risk of bias in included studies following the guidance enumerated in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Specific items to consider will include random sequence generation and allocation concealment (selection bias), masking of participants and study personnel (performance bias), masking of outcome assessors (detection bias), missing data and intention-to-treat analysis (attrition bias), selective outcome reporting (reporting bias) and other potential sources of bias. We will assign each item as having 'low risk', 'high risk', or, if the information provided is insufficient to make an assessment, 'unclear risk' . We will document reasons for those assessments.
Any discrepancy will be resolved through discussion, and when necessary, through consultation with a third author or by contacting the study investigators as appropriate. In the event of the latter, if the study investigator does not respond within two weeks, the review authors will use the information available in published reports to judge risk of bias. We will present the overall assessments as the 'Risk of bias summary' figure and graph (Higgins 2011).

Measures of treatment effect

We will report risk ratios with 95% confidence intervals (CIs) for any dichotomous outcomes and mean differences in change from baseline with 95% CIs for continuous outcomes (i.e., mean change in IOP, progressive field loss, number of medications used, and mean change in BCVA). We will conduct separate analyses for outcomes in the eyes of participants with angle-closure glaucoma, for outcomes in the eyes of participants with angle closure, and for outcomes in the eyes with only narrow angles but no obstructions (i.e. PACS). If any trials on eyes with narrow angles compared eyes within individuals (e.g., one eye was randomized to the treatment while the other was randomized to observation), then we will note whether or not the study investigators included statistical methods accounting for the correlation between eyes belonging to the same individual.

Unit of analysis issues

Our unit of analysis is one study eye per individual participant, therefore accounting for non-independence of eyes is not necessary.

We also will consider studies that included two eyes per participant. In this situation, if both eyes of the same participant received the same treatment assignment and if both eyes were treated as a single unit, then our unit of analysis is the participant. However, if both eyes of participants either received different treatment assignments or were treated as two distinct units, then we will review the publication to see if the study investigators properly accounted for the non-independence of eyes. If they did not account for this potential correlation, then we will seek the expertise of a statistical consultant and account for this in the discussion of the review.

Dealing with missing data

We will address any missing study data for the outcomes of interest or any unclear information by writing to the authors. Should there be no response within two weeks, we will analyze the data using the best available information. We also will consider multiple imputation or other imputation approaches for missing data. In the event that the quality of the available data prevents any meaningful analysis, we will omit the study from the analyses and note this decision in the discussion.

Assessment of heterogeneity

We will assess clinical and methodological heterogeneity by examining participant characteristics, iridotomy procedures, and outcomes by carefully reviewing the study publication and taking into consideration potential risk of bias. This heterogeneity also will manifest as statistical heterogeneity which we will examine by assessing forest plots and examining the I^2 value and its confidence interval (Deeks 2011). An I^2 value that is greater than 70% will suggest substantial statistical heterogeneity, therefore a meta-analysis might not be appropriate; however, we will give consideration to the consistency of the effect estimates. For example, if we find that all effect estimates are in the same direction, we may report a meta-analysis even though there may be substantial statistical heterogeneity.

Assessment of reporting biases

We will assess publication bias through constructing a funnel plot when there are 10 or more trials included in our review. We will assess for selective outcome reporting as part of the 'Risk of bias' assessment.

Data synthesis

We will follow Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* for data analysis (Deeks 2011). In the absence of substantial clinical and methodological heterogeneity, we will use a random-effects model to compute a quantitative synthesis. When the number of studies is less than 3 and there is no evidence of substantial statistical heterogeneity, we may consider

fixed-effect meta-analysis. We also will provide a descriptive, qualitative synthesis of studies and their results.

Subgroup analysis and investigation of heterogeneity

We will consider the following subgroups: a) with or without use of IOP-lowering medications, and b) by ethnic/racial groups.

Sensitivity analysis

We will conduct two sensitivity analyses to determine the effect of excluding studies at high risk of bias for incomplete outcome data and the effect of excluding studies that were quasi-randomized trials. If appropriate, we also will conduct additional sensitivity analyses to determine the impact of any post-hoc decisions made during the review process.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. AAO summary of clinical findings defining angle-closure diseases

	Primary angle-closure suspect (PACS)	Primary angle closure (PAC)	Primary angle-closure glaucoma (PACG)
ITC greater than or equal to 180 degrees	X	X	X
Elevated intraocular pressure OR peripheral anterior synechiae		X	X
Optic nerve damage			X

ITC: iridotrabecular contact

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Glaucoma, Angle-Closure] explode all trees
#2 (angle* near/3 closure*)
#3 (angle* near/3 close*)
#4 (Uncompensat* near/2 glaucoma*)
#5 (Narrow* near/2 angle*)
#6 (occlude* near/3 angle*)
#7 Acute glaucoma*
#8 (APAC or AACG or PACG or PACS)
#9 pupillary block glaucoma*
#10 {or #1-#9}
#11 MeSH descriptor: [Laser Therapy] explode all trees
#12 MeSH descriptor: [Lasers] explode all trees
#13 Laser*
#14 (iridotom* or LPI)
#15 {or #11-#14}
#16 #10 AND #15

Appendix 2. MEDLINE (Ovid) search strategy

1. exp Glaucoma, Angle-Closure/
2. (angle* adj3 closure*).tw.
3. (angle* adj3 close*).tw.
4. (Uncompensat* adj2 glaucoma*).tw.
5. (Narrow* adj2 angle*).tw.
6. (occlude* adj3 angle*).tw.
7. Acute glaucoma*.tw.
8. (APAC or AACG or PACG or PACS).tw.
9. pupillary block glaucoma.tw.
10. or/1-9
11. exp Laser Therapy/
12. exp Lasers/
13. Laser*.tw.
14. (iridotom* or LPI).tw.
15. or/11-14
16. 10 and 15

Appendix 3. EMBASE.com search strategy

#1 'closed angle glaucoma'/exp
#2 (angle* NEAR/3 closure*):ab,ti
#3 (angle* NEAR/3 close*):ab,ti
#4 (uncompensat* NEAR/2 glaucoma*):ab,ti
#5 (narrow* NEAR/2 angle*):ab,ti
#6 (occlude* NEAR/3 angle*):ab,ti
#7 (acute NEAR/1 glaucoma*):ab,ti
#8 apac:ab,ti OR aacg:ab,ti OR pacg:ab,ti OR pacs:ab,ti
#9 ('pupillary block' NEAR/2 glaucoma):ab,ti

#10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
#11 'low level laser therapy'/exp
#12 'laser'/exp
#13 laser*:ab,ti
#14 'iridotomy'/exp
#15 iridotom*:ab,ti OR lpi:ab,ti
#16 #11 OR #12 OR #13 OR #14 OR #15
#17 #10 AND #16

Appendix 4. LILACS search strategy

("Glaucoma de Ángulo Cerrado" OR "Glaucoma de ngulo Fechado" OR MH:C11.525.381.056$ OR (angle$ AND (closure$ OR close$ OR narrow$ OR occlude$)) OR (Uncompensat$ glaucoma$) OR (Acute glaucoma$) OR (pupillary block glaucoma$) OR APAC OR AACG OR PACG OR PACS) AND (Laser$ OR iridotom$ or LPI OR MH:E02.594$ OR MH:E04.014.520$ OR MH:E07.632.490$ OR MH:E07.710.520$ OR MH:SP4.011.087.698.384.075.166.027$ OR MH:VS2.006.002.009$)

Appendix 5. PubMed search strategy

1. (angle*[tw] AND closure*[tw]) NOT Medline[sb]
2. (angle*[tw] AND close*[tw]) NOT Medline[sb]
3. (Uncompensat*[tw] AND glaucoma*[tw]) NOT Medline[sb]
4. (Narrow*[tw] AND angle*[tw]) NOT Medline[sb]
5. (occlude*[tw] AND angle*[tw]) NOT Medline[sb]
6. Acute glaucoma*[tw] NOT Medline[sb]
7. (APAC[tw] or AACG[tw] or PACG[tw] or PACS[tw]) NOT Medline[sb]
8. pupillary block glaucoma[tw] NOT Medline[sb]
9. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
10. Laser*[tw] NOT Medline[sb]
11. (iridotom*[tw] OR LPI[tw]) NOT Medline[sb]
12. #10 OR #11
13. #9 AND #12

Appendix 6. ClinicalTrials.gov search strategy

Angle closure glaucoma OR Acute glaucoma OR pupillary block glaucoma

Appendix 7. ICTRP search strategy

Angle closure glaucoma OR Acute glaucoma OR pupillary block glaucoma OR narrow-angle glaucoma OR uncompensated glaucoma OR uncompensative glaucoma

Appendix 8. Data on study characteristics

Mandatory items		Optional items
Methods		
Study design	· **Parallel group RCT** *i.e. people randomized to treatment* · **Within-person RCT** *i.e. eyes randomized to treatment* · **Cluster RCT** *i.e. communities randomized to treatment* · **Cross-over RCT** · Other, specify	Exclusions after randomization Losses to follow up Number randomized/analyzed How were missing data handled? *e.g., available case analysis, imputation methods* Reported power calculation (Y/N*), if yes, sample size and power* Unusual study design/issues
Eyes *or* Unit of randomization/ unit of analysis	· **One eye included in study**, *specify how eye selected* · **Two eyes included in study, both eyes received same treatment**, *briefly specify how* analyzed*(best/worst/average/both and adjusted for within person correlation/both and not adjusted for within person correlation) and specify if mixture one eye and two eye* · **Two eyes included in study, eyes received different treatments,** *specify if correct pair-matched analysis done*	
Participants		
Country		Setting Ethnic group Equivalence of baseline characteristics (Y/
Total number of participants	*This information should be collected for total study population recruited into the study. If these data are only reported for the people who were followed up only, please indicate.*	
Number (%) of men and women		
Average age and age range		
Inclusion criteria		
Exclusion criteria		
Interventions		
Intervention (n=) Comparator (n=) ***See MECIR 65 and 70***	· Number of people randomized to this group · Drug (or intervention) name · Dose · Frequency · Route of administration	

(*Continued*)

Outcomes		
Primary and secondary outcomes *as defined in study reports* ***See MECIR R70***	List outcomes Adverse events reported (Y/N) Length of follow up and intervals at which outcomes assessed	Planned/actual length of follow up

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JL, BR, and GG designed and wrote this protocol.

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