


# BMJ Open Efficacy and safety of phacotrabeculectomy versus phacogoniotomy in advanced primary angle-closure glaucoma: study protocol for a multicentre non-inferiority randomised controlled trial (PVP Study)

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## ABSTRACT

**Introduction** Primary angle-closure glaucoma (PACG) has a high prevalence and blinding rate across Asia. The first-line treatment of PACG is surgery, and phacotrabeculectomy remains the mainstream surgery for advanced PACG. However, it may cause vision-threatening complications with long learning curve. Minimally invasive glaucoma surgery has been gradually used in PACG combined with cataract surgery and achieved efficacy without excessive injury, of which goniotomy is the most commonly performed. Therefore, this study aimed to conduct a multicentre, non-inferiority randomised controlled clinical trial to compare the efficacy and safety of phacotrabeculectomy versus phacogoniotomy in advanced PACG.

**Methods and analysis** This is a non-inferiority multicentre randomised controlled trial and will be conducted at eight ophthalmic departments and institutes in China. 124 patients with advanced PACG will be enrolled and randomised to undergo phacotrabeculectomy or phacogoniotomy. Comprehensive ophthalmic examinations will be performed before and after the surgery. The primary outcome is the change of intraocular pressure at 12 months after surgery compared with the baseline intraocular pressure. An extended follow-up period of 36 months will be required. Cumulative success rate of surgery, intraoperative and postoperative complications, and number of anti-glaucomatous medications will also be compared between the groups as secondary outcomes.

**Ethics and dissemination** Ethical approval has been obtained from the ethical committee of Zhongshan Ophthalmic Center, Sun Yat-sen University, China (ID: 2021KYPJ090) and all subcentres. All the participants will be required to provide written informed consent. The results will be disseminated through scientific meetings and published in peer-reviewed journals.

**Trial registration number** NCT04878458.

## Strengths and limitations of this study

- In this non-inferiority trial, we aim to assess a novel intervention that could have clinical advantages in terms of availability, cost and complications compared with standard treatment.
- This study is a multicentre study that will speed up enrolment and the conclusions will be of wide applicability.
- The study is limited by only including Asian ethnicity and advanced stage of primary angle-closure glaucoma.
- An extended follow-up will provide more valuable evidence, while it will be a big challenge to keep a low attrition rate during such a long-term follow-up.

## INTRODUCTION

Glaucoma is the leading irreversible blinding disease worldwide.<sup>1 2</sup> Primary angle-closure glaucoma (PACG), accounting for only 25% of all glaucoma cases, caused nearly half of glaucoma blindness worldwide. In Asia, it was estimated that PACG had affected 21 million people by the year 2020. In China, patients with PACG account for approximately 50% of all glaucoma cases.<sup>3</sup> The main pathophysiological process of PACG is the formation of peripheral anterior synechia (PAS), causing permanent dysfunction of the trabecular meshwork by chronic adhesion, inflammation, and iris or fibrous tissue hyperplasia,<sup>4</sup> finally blocking the outflow channel of aqueous humour, leading to intraocular pressure (IOP) elevation,<sup>4</sup> which causes irreversible optic nerve damage.

The first-line treatment of PACG is surgery, and a preferred option for advanced PACG is trabeculectomy or phacotrabeculectomy, which combines phacoemulsification with intraocular lens implantation (PEI).<sup>5,6</sup> Phacotrabeculectomy has been successfully performed and has achieved positive results for decades.<sup>7,8</sup> However, there are obvious complications of traditional trabeculectomy, such as excessive conjunctival injury, shallow anterior chamber, hyphema, persistent hypotony, corneal endothelial decompensation, endophthemia and other bleb-related complications.<sup>9–11</sup> Additionally, with the long learning curve for ophthalmologists and the troublesome postoperative care, it is not an ideal surgical method. To reduce complications of trabeculectomy, some surgeons have performed PEI alone or in combination with goniosynechialysis (GSL) to treat advanced PACG. Evidence showed that the PEI alone or PEI+GSL could achieve a satisfactory IOP-lowering effect with fewer complications.<sup>12,13</sup> However, a randomised controlled trial (RCT) showed no difference between PEI alone and PEI+GSL in the treatment of PACG.<sup>14</sup> Adjunctive surgical interventions are needed.

Minimally invasive glaucoma surgery (MIGS) has been widely performed and has started to play an important role in PACG,<sup>15,16</sup> usually combined with PEI. For instance, there are surgeries on Schlemm's canal, implantation of bypass and endocycloplasty.<sup>17,18</sup> Among patients with PACG, the goniotomy ab interno (GT), one kind of Schlemm's canal incision, was the most common MIGS, highlighted by few complications, minimal injury, quick recovery, effective IOP reduction and simplicity of procedure.<sup>19</sup> Currently, the effects of various GTs with PEI have been verified in PACG, for instance, GT assisted by Kahook dual blade<sup>20–22</sup> or Tanito microhook (TMH)<sup>23,24</sup> and other microhooks.<sup>25,26</sup> However, the evidence was mainly retrospective.<sup>27</sup> The above proof indicates that goniotomy could be an adjunct to PEI in the treatment of advanced PACG.<sup>25</sup> However, high-quality RCTs to validate the efficacy and safety of MIGS compared with phacotrabeculectomy are still lacking.

Therefore, this study intends to conduct a joint collaboration of eight top ranked ophthalmic departments and institutes in China and perform a non-inferiority RCT to compare the efficacy and safety of phacotrabeculectomy versus phacogoniotomy (PEI+GSL+GT) in advanced PACG.

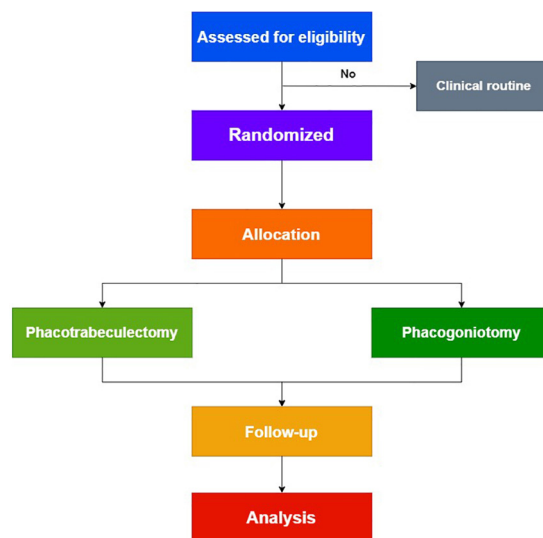
## METHODS AND ANALYSIS

### Objectives

The trial aims to compare the efficacy and safety of phacotrabeculectomy versus phacogoniotomy in the treatment of advanced PACG, in order to provide more options for this blinding disease.

### Design and setting

This is a multicentre, parallel assignment, open-label, non-inferiority RCT. The study will be conducted at Zhongshan



**Figure 1** Study flow chart.

Ophthalmic Center (ZOC), Sun Yat-sen University as the principal centre, in joint partnership with seven other hospitals and eye institutes, including the Department of Ophthalmology, the Second Affiliated Hospital, Harbin Medical University; Department of Ophthalmology, West China Hospital of Sichuan University; Department of Ophthalmology, Shijiazhuang People's Hospital; Department of Ophthalmology, Fujian Medical University Union Hospital; Department of Ophthalmology, Shanghai General Hospital, Shanghai Jiao Tong University; Handan City Eye Hospital (the Third Hospital of Handan); and Department of Ophthalmology, the Third Affiliated Hospital of Chongqing Medical University, as subcentres. The trial settings are presented in [figure 1](#).

### Eligibility

#### Inclusion criteria

1. Aged 40–80 years.
2. Diagnosed with advanced PACG<sup>28,29</sup>: met a, b, c; or a, b, d criteria below.
  - a. At least 180° PAS under gonioscopy and it should cover the nasal and inferior quadrants for surgical purposes.
  - b. IOP >21 mm Hg with or without anti-glaucoma medication.
  - c. Obvious glaucomatous optic neuropathy (cup-to-disc (C/D) ratio  $\geq 0.7$ , or C/D asymmetry  $> 0.2$ , or the rim width at the superior and inferior temporal  $< 0.1$  vertical diameters of optic disc).
  - d. With glaucomatous visual field defects, such as nasal step, arcuate scotoma and paracentral scotoma on a reliable Humphrey analyser using Swedish interactive threshold algorithm (SITA) standard 24-2 or 30-2 algorithm; mean deviation (MD)  $\leq -12$  dB.
3. Clinically obvious cataract and uncorrected visual acuity (UCVA)  $< 0.63$  (Early Treatment Diabetic Retinopathy Study (ETDRS) chart), or needed lens extraction assessed by a clinician.

4. Voluntarily participate in the study and provide signed informed consent.

#### Exclusion criteria

1. History of ocular surgery (other than laser iridotomy or laser iridoplasty) or trauma.
2. With other types of glaucoma (ie, open-angle glaucoma, secondary angle-closure glaucoma, steroid-induced glaucoma, angle regression glaucoma, neovascular glaucoma, nanophthalmos, pseudoexfoliation syndrome).
3. The International Standardized Ratio >3.0 for patients receiving warfarin or anticoagulant therapy before surgery.
4. With retinal disease that affects the collection of ocular parameters.
5. Monophthalmia (best-corrected visual acuity (BCVA) <0.01 in the non-study eye).
6. With other serious systemic diseases.
7. Pregnant or lactating women.

If both eyes of the subject are eligible for the study, the subject's eye with the worse UCVA will be considered.

#### Recruitment

This trial is a multicentre study. All subcentres are tertiary hospitals in China and could ensure adequate participants. First screening will be conducted in the outpatient clinics at all subcentres. After confirming the eligibility, the trial will then proceed.

#### Allocation of interventions

A central randomisation system will be used to generate a random allocation sequence with block size of 4 for each subcentre. The subjects in each block unit will be evenly assigned (1:1) to the control group (phacotrabeculectomy) and the experimental group (phacogoniotomy). The random sequence will be generated by the main centre using electronic data capture (EDC) system.

#### Masking

This study will adopt an open design, since the experimental group and the control group are different surgical interventions, and masking cannot be implemented for surgeons and participants. Technicians are unaware of the grouping during the screening, allocation and the follow-up. The trial statisticians will be blinded to the randomisation results until the completion of statistical analysis.

#### Intervention methods

All surgeries will be performed by professors or experienced senior attending doctors at each subcentre.

#### Anaesthesia

All surgeries will be performed under general anaesthesia or topical anaesthesia according to the standard clinical routine.

#### Control group (phacotrabeculectomy)

All patients in the control group will undergo a standard phacotrabeculectomy. A fornix-based conjunctival flap will be dissected. Electrocautery will be used to control episcleral bleeding. A rectangular 4×3 mm size superficial scleral flap with a 1/2 or 2/3 scleral thickness at 12 o'clock will be made. Mitomycin-soaked sponges (0.2–0.5 mg/mL) will be applied under the scleral flap and the conjunctiva for 1–5 min, and the area will then be washed thoroughly with 200 mL of balanced salt solution. A superior or temporal clear corneal incision will be made with a 1.8–3.2 mm clear corneal incision, and a small limbal paracentesis will be performed at the 90° from the main incision. A viscoelastic agent will be used to maintain the anterior chamber. After the continuous curvilinear capsulorhexis, the nucleus will be removed using the phacoemulsification technique. The cortical remnants will then be removed, and the intraocular lens will be placed in the capsular bag. Then the viscoelastic agent will be completely aspirated. Carbachol will be used for myopsis. Trabeculectomy will be performed by using a 1×2 mm deep scleral flap, followed by a peripheral iridectomy. The scleral flap and conjunctiva will then be tightly sutured with 10-0 nylon sutures (with or without adjustable sutures). Finally, the anterior chamber will be reformed with a balanced salt solution at the end of the surgery.

#### Intervention group (phacogoniotomy)

PEI will be performed as described above. An additional viscoelastic agent will be used to provide clearance and maintenance of the anterior chamber. Goniotomy will be performed at either the nasal or inferior quadrant according to the surgeon's choice. For instance, in nasal procedure, the surgeon can choose the temporal position and make the corneal incision, and the patient's head should be rotated by 35°–40° away from the surgeon. The surgical microscope is tilted 30° towards the operator. Then the viscoelastic agent is applied to the surface of the cornea. A surgical gonioscope is placed on the cornea to observe the angle and focus on the trabecular meshwork. GSL will be performed by gently pressing all the PAS with a chopper. A TMH will be then inserted into the anterior chamber through the main incision of the cornea. The tip of the TMH will then be inserted into the Schlemm's canal and advanced along to incise the inner wall and trabecular meshwork with a 120° range. After the viscoelastic agents and bleeding are aspirated, the corneal incisions will be closed by corneal stromal hydration.

#### Postoperative management

1. Topical 1% prednisone acetate eye drops will be administered four times per day for 1 month for the phacotrabeculectomy group and then switched to non-steroidal anti-inflammatory eye drops if needed; 1 week prednisone acetate eye drops for phacogoniotomy switched to non-steroidal anti-inflammatory drug

- for continued 3 weeks, plus 1% pilocarpine eye drops will be administered four times per day for 1 month.
- On the day of surgery and before and after surgery, subjects in both groups will be routinely administered an intramuscular injection of 2 kU haemocoagulase to reduce bleeding. Other haemostatic agents will not be routinely administered after surgery to reduce bias.
  - If glucocorticoids are considered to be the cause of postoperative IOP spike according to previous study,<sup>30</sup> the patients would be re-evaluated and treatment would be replaced with non-steroidal anti-inflammatory eye drops for 7 days after withdrawal of the steroidal drugs. If IOP remained uncontrolled after 7 days, the patients will be excluded.
  - If an IOP reduction of lower than 18 mm Hg is achieved, topical anti-glaucoma medication will not be prescribed. If IOP was found higher than 18 mm Hg after surgery, topical anti-glaucoma medication will be administered in both arms of the study. In the control group, postoperative care such as eyeball massage, releasable suture lysis or laser suture lysis will be performed as necessary by the attending ophthalmologist. Timolol eye drops (0.5%) will be the first choice. Brinzolamide eye drops or brimonidine tartrate eye drops (or mixed combination) will be added if single timolol solution is not enough. The maximum medications used will be three drugs with different mechanisms.
  - If an IOP is >40 mm Hg, a 250 mL intravenous drip of 20% mannitol could be used.
  - The individual will be excluded from the study and repeated surgery will be performed if the IOP is >18 mm Hg on maximum anti-glaucoma medications at the end of 3 months.

The flow chart of postoperative management is shown in [figure 2](#).

## Outcome measurement

### Primary outcome

The primary outcome measure is the change of IOP at 12 months after surgery compared with the baseline IOP.

### Secondary outcomes

- Cumulative success rate of surgery: (1) complete success is defined as the postoperative IOP between 5 and

18 mm Hg, and 20% reduction from baseline with no need for IOP-lowering medication; (2) qualified success is defined as the postoperative IOP between 5 and 18 mm Hg, and 20% reduction from baseline with or without IOP-lowering medication.

- Intraoperative and postoperative complications—for example, shallow anterior chamber, hyphema, persistent hypotony, corneal endothelium decompensation, endophthalmitis and other filtering bleb-related complications.
- Number of anti-glaucomatous medications.

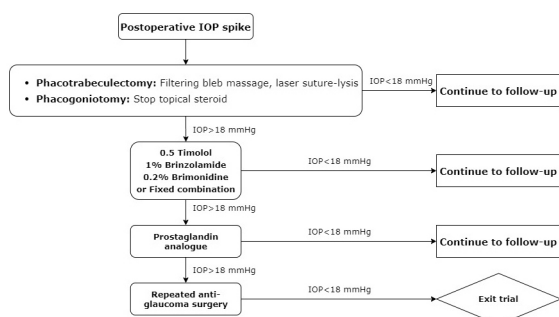
Other prespecified and exploratory outcomes:

- Visual acuity.
- Degree of peripheral anterior synechia.
- Corneal endothelial cell counting.
- Visual field.
- Optic nerve head morphology and retinal parameters based on optical coherence tomography (OCT).
- Measurement of quality of life.
- Filtering bleb classification based on Indiana Bleb Appearance Grading Scale.<sup>31</sup>
- Time consumed of operation and the surgery cost.

## Examinations

Baseline data and follow-up examination items are as follows:

- Demographic data: including name, ID number, sex and education level.
- Medical history, surgical history and medications in use.
- Vital signs, height and weight.
- Optometry and visual acuity: using an ETDRS LogMAR visual acuity chart (Precision Vision, Villa Park, Illinois, USA), in accordance with the refractive error study in children (RESC) research protocol;<sup>32</sup> at a test distance of 4 m, the naked eye and BCVA will be evaluated and recorded in the sitting position.
- Slit-lamp examination: the ophthalmological examination includes slit-lamp examination (BQ-900, Haag Streit, Switzerland) and fundus examination.
- Fundus photography: a fundus camera will be used (model can be defined according to the subcentre) to take a photo of the fundus.
- IOP measurement: each visit requires an IOP evaluation in both eyes of the patient and the average of the two measurements will be taken using Goldmann applanation tonometry (AT900, Haag Streit, Koeniz, Switzerland).
- Endothelial cell counting using endokeratoscope (SP-2000P, Topcon, Japan).
- Gonioscope: a single-mirror gonioscope (Ocular Instruments, Bellevue, Washington, USA) will be used to grade according to the Shaffer classification method.
- Ultrasound biomicroscopy inspection to observe the morphology of the anterior segment.
- Posterior segment spectral-domain OCT (Cirrus 5000, Carl Zeiss Meditec, USA; or Heidelberg OCT



**Figure 2** Schematic of medical treatment postoperatively. IOP, intraocular pressure.

SPECTRALIS OCT, Heidelberg, Germany) will be used (each subcentre can choose the instrument model).

12. Visual field examination will be performed using SITA standard 24-2 program by Humphrey Field Analyzer Mark 2/3 (Carl Zeiss Meditec, Dublin, California, USA). It is required to report false positive rate <15%, false negative rate <15% and fixation loss <20%. The reliability of visual field inspection, and MD and pattern standard deviation (PSD) values will be recorded.
13. Quality of life assessment using EQ-5D-5L (simplified Chinese, EuroQol Research Foundation, the Netherlands; registered).
14. Adverse events are collected at each visit.
15. Anterior OCT examination will be performed using a CASIA OCT (Tomey, Tokyo, Japan) to examine the patient's angle structure.
16. Pentacam examination by Pentacam AXL (Oculus, Germany) to measure the biological parameters of the patient's corneal curvature, corneal spherical aberration, corneal astigmatism, etc.

### Subject schedule

Table 1 shows the schedule for subject follow-up.

### Sample size calculation

This is a non-inferiority trial. The sample size is estimated based on the primary outcome, that is, the change in IOP at 12 months after surgical treatment compared with baseline. Previous studies have reported that phacotrabeculectomy for PACG reduces IOP by an average of 10–18.8 mm Hg,<sup>33 34</sup> PEI+GSL for PACG reduces IOP by an average of 7.1 mm Hg,<sup>14</sup> phacogoniotomy treatment in PACG reduces IOP by approximately 12 mm Hg.<sup>26</sup> It is reasonable to assume that the difference between the two study groups in reducing IOP is 4 mm Hg. Thus, the non-inferiority margin ( $\Delta$ ) was specified as 4.0 mm Hg with a common SD ( $\sigma$ ) of 6 mm Hg for both treatment groups, at one-sided significant level ( $\alpha$ ) of 2.5%, to achieve a power ( $1-\beta$ ) of 90%, the sample size of 49 eyes from 49 participants per group will be required. Allowing for a 20% loss to follow-up, a sample size of 62 eyes from 62 participants per group will be necessary.

### Monitoring

#### Data monitoring

The data monitoring will be performed by professional data administrators in clinical research centre of ZOC and will be independent of the researchers, who have no competing interests.

#### Interim analysis

Interim analysis will not be conducted.

### Harms

The risks include uncontrollable IOP, general anaesthesia adverse effects and adverse drug reactions, which are common risks in clinical diagnosis and treatment. The

surgical operations in this project are mature methods and do not pose major risks.

### Auditing

The trial will not involve new drugs or new devices, and will be conducted under the guidance of the ethics committee of all subcentres.

### Data collection and management

All the original data will be stored in the EDC system. The principal centre is eligible to view the data of all subcentres, but revision will not be allowed. The data will be directly entered into the database by researchers and used as raw data. All raw data information must be kept by the researcher in the subject's file. Any changes from the raw data will be documented in the EDC system.

### Statistical plan

Normality of continuous data will be checked using the Shapiro-Wilk test and histogram. Continuous data are to be described as mean (SD) or median (IQR). Analysis of the primary and secondary outcomes will follow the intent-to-treat (ITT) principles. All participants who are randomised and receive surgery will be included in the ITT analysis, and missing data will be imputed by multiple imputation. Comparison between two treatment groups will be performed using two-sample t-test for normally distributed continuous measures, Mann-Whitney U test for non-normally distributed continuous measures, and  $X^2$  test or Fisher's exact test for categorical outcomes. The between-treatment difference in cumulative rate of surgical success and complications will be assessed using  $X^2$  test or Fisher's exact test. The stratified Kaplan-Meier survival curves will be constructed to show the cumulative probability over time in each group, and log-rank test is used to compare the time with the incidence of unsuccessful surgery. Unsuccessful was defined as an IOP of more than 18 mm Hg or less than 20% reduction below baseline on two consecutive follow-up visits after 3 months, IOP of 5 mm Hg or less on two consecutive follow-up visits after 3 months, reoperation for glaucoma or loss of light perception vision.<sup>35</sup> Unadjusted and adjusted mean treatment difference in reduction of IOP at 12 months and 95% CIs will be estimated by univariable and multivariable linear regression model, respectively, with adjustment of baseline IOP for both regression analyses. Study group and other baseline variables with  $p < 0.20$  in the univariable analysis will be included in the multivariable model. For the non-inferiority test, it will reject the hypothesis of inferiority (in favour of non-inferiority) when the upper limit of the two-sided 95% CI of the difference in IOP changes between treatment groups is less than the prespecified non-inferiority margin (4 mm Hg). A two-sided  $p < 0.05$  is considered to be statistically significant. All statistical analyses will be performed using Stata V.16 (StataCorp, College Station, Texas, USA) and other appropriate software.

Table 1 Follow-up schedule

Visit number	0	1	2	3	4	5	6	7	8	9
Inspection items	-7 to 1 day	7 days	1 month	3 months	6 months	12 months*	18 months	24 months	30 months	36 months
Informed consent	X									
Demographic data and medical history	X									
Vital signs	X					X	X	X	X	X
Medication record	X	X	X	X	X	X	X	X	X	X
Optometry	X					X				
Visual acuity	X	X	X	X	X	X	X	X	X	X
Slit-lamp biomicroscopy	X	X	X	X	X	X	X	X	X	X
Fundus photo	X					X		X		X
Intraocular pressure	X	X	X	X	X	X	X	X	X	X
Endokeratoscope	X					X		X		X
Gonioscopy	X			X		X		X		X
UBM	X									
Anterior segment OCT†	X					X		X		X
Posterior segment OCT	X					X		X		X
Visual field	X					X		X		X
Pentacam‡	X					X		X		X
Quality of life questionnaire	X					X		X		X
Adverse events	X	X	X	X	X	X	X	X	X	X

X indicates that data need to be collected during the visit.

\*End of study (EOS) follow-up showed that the main study outcome had been achieved; from the second visit, the time window of each visit was  $\pm 7$  days.

†These examinations can be selected by subcentres.

OCT, optical coherence tomography; UBM, ultrasound biomicroscopy.

## Study completion and termination

### Study completion

When the study is completed, the investigator will hold a clinical study report meeting, revise and sign the final clinical study report. The investigator will report the completion of the study to the ethics committee.

### Discontinuation and early termination of the study

Subjects will be withdrawn from the study if: they do not comply with protocol or for safety reasons; female patients who intend to become pregnant or who have been confirmed to be pregnant; they participate in other clinical trials; adverse events occurred during the study or there was surgical failure. If a subject decides to withdraw from the study, the subject will be advised to complete the last follow-up and required tests prior to withdrawal.

### Patient and public involvement

No patient or public involvement.

### Ethics and dissemination

#### Ethics approval

Ethical approval has been obtained from the Ethical Committee of the ZOC, Sun Yat-sen University, China (ID: 2021KYPJ090; V.20210824) and all subcentres. The registration identifiers of other centres are listed as follows: the Second Affiliated Hospital, Harbin Medical University (KY2021-206); West China Hospital of Sichuan University (2021(772)); Shijiazhuang People's Hospital (2021(79)); Fujian Medical University Union Hospital (2021YF026-01); Shanghai General Hospital, Shanghai Jiao Tong University (2021(109)); Handan City Eye Hospital (the Third Hospital of Handan) (2021(2)); the Third Affiliated Hospital of Chongqing Medical University (2021(30)).

#### Informed consent

Researchers must obtain signed informed consent to confirm that the subjects fully understand the content of the study and participate voluntarily before the trial starts.

#### Confidentiality

The content of this clinical study is confidential information. Any information about this study, including the study design, methods, results, etc, is within the scope of confidentiality which cannot be discussed with persons outside the study.

#### Dissemination policy

The results will be disseminated through scientific meetings and published in peer-reviewed journals.

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**Contributors** XiulZ, HY, LT, GT, LL, SF, MZ and LX participated in the study design. YS, WS and YIZ co-wrote the protocol draft. LJ helped with sample size calculation and statistical consultation. HZ, MX, XiaoZ, AL, XY, PL, XZhu, XG, KH, YinZ and XL helped to review the protocol draft. XiZ was responsible for the data collection. The authors from all centres agreed to publish the protocol in the name of 'Phacotrabeculectomy versus Phacogoniotomy (PVP) Study group.'

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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