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Trabeculotomy Versus Combined Trabeculotomy-Trabeculectomy for Primary Congenital Glaucoma: Study Protocol of a Randomized Controlled Trial

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4 1 **Trabeculotomy Versus Combined Trabeculotomy-Trabeculectomy for**
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6 2 **Primary Congenital Glaucoma: Study Protocol of a Randomized**
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8 3 **Controlled Trial**
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51 17 **Word count: 3569**
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3
4 20 **Abstract**
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7 21 **Introduction:** Trabeculotomy and combined trabeculotomy-trabeculectomy
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10 22 (CTT) are major surgical options for primary congenital glaucoma (PCG).
11
12 23 However, it is unclear which of the two surgical procedures should be
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14
15 24 recommended as the optimum first-line treatment for PCG. This trial aims to
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17
18 25 determine whether the surgical outcomes of trabeculotomy is not inferior to
19
20 26 that of CTT for PCG with a horizontal corneal diameter (HCD) of 12-14 mm.
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22

23 27 **Methods and analysis:** This is a 3-year, noninferiority, prospective,
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25
26 28 randomized controlled trial. We anticipate recruiting 248 participants (aged ≤ 3
27
28
29 29 years) with PCG with an HCD of 12-14 mm, from the Department of
30
31
32 30 Glaucoma, Zhongshan Ophthalmic Center, Guangzhou, China. One eye per
33
34 31 participant will be randomly (1:1) assigned to receive trabeculotomy or CTT.
35
36
37 32 The primary outcome is the 3-year postoperative success rate, and the
38
39 33 secondary clinical outcomes will include visual acuity (VA), HCD, corneal
40
41
42 34 thickness, axial length, cup-disc ratio, refractive error, and postoperative
43
44 35 complications. Data will be analysed by the intention-to-treat principle.
45
46

47 36 **Ethical approval and dissemination:** The study protocol has been approved
48
49
50 37 by the ethics committee of Zhongshan Ophthalmic Center (2014MEKY023)
51
52
53 38 and the "5010 Plan" evaluation committee at Sun Yat-Sen University,
54
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56 39 Guangzhou, China. The results will be disseminated in international academic
57
58 40 meetings and published in peer-reviewed journals.
59
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4 41 **Trial registration:** Chinese Clinical Trial Registry, ChiCTR-IOR-14005588;

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7 42 Date registered: 20 November 2014.

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9 43 **Keywords:** PCG, Primary congenital glaucoma, Trabeculotomy, Combined
10
11
12 44 trabeculotomy-trabeculectomy, Randomized controlled trial
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14

15 **Article Summary**

16 17 18 46 **Strengths and limitations of this study**

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21 47 ■ The trial design is prospective, randomized and controlled with a relative
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24 48 large sample size, and the follow-up is comparatively long (3 years).

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26
27 49 ■ To date, the study is the first randomized controlled trial that
28
29
30 50 comprehensively evaluate the surgical and visual outcomes of
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33 51 trabeculotomy and CTT in treating PCG patients with an HCD of 12 to 14
34
35 52 mm, and surgical complications.

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38 53 ■ This study includes many important clinical measurements that use
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40
41 54 standardized protocols, such as HCD, axial length, corneal thickness,
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44 55 C/D ratio, refractive errors and VA. Importantly, structural changes can be
45
46 56 observed dynamically in follow-up visits.

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48
49 57 ■ This is a single-center trial, which may induce selection bias.

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52 58 ■ Participants may drop out of the study during the long-term follow-up,
53
54
55 59 which is a potential threat to external validity.
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61 INTRODUCTION

62 Primary congenital glaucoma (PCG) is one of main causes of blindness in
63 children. Liu *et al*¹ reported that congenital glaucoma accounts for 5.1% of all
64 congenital ocular diseases in a Chinese population. It is estimated to accounts
65 for 0.01–0.04% of blindness worldwide.² In India, the disease accounts for
66 4.2% of all childhood blindness.² Haddad *et al*³ evaluated 3210 visually
67 impaired children and found that, PCG was responsible for 10.2% of the visual
68 impairments. Since at least 50% of eyes with PCG presenting at birth will
69 become legally blind, patients with PCG require prompt treatment and
70 follow-up examinations throughout their lives.⁴

71 Among all the treatment options, surgical intervention is the main
72 treatment for PCG. Goniotomy and trabeculotomy have been considered initial
73 procedures because of the high success rates.^{5,6} However, goniotomy can be
74 performed only if the cornea is clear, while trabeculotomy does not require a
75 clear cornea. Trabeculotomy reduces intraocular pressure (IOP) by tearing the
76 trabecular meshwork into the anterior chamber. Regarding complications,
77 hyphema is more common with trabeculotomy but can resolve spontaneously
78 and cause no additional problems.⁷⁻⁹

79 Combined trabeculotomy-trabeculectomy (CTT) has been advocated for
80 treating moderate to severe congenital glaucoma.¹⁰ The rationale for CTT is to
81 gain access to the dual outflow, through Schlemm's canal and the

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4 82 trabeculectomy fistula. The application of Mitomycin-C (MMC) can improve the
5
6 83 surgical success rates of CTT,¹¹ which is, however, disputed by some other
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8
9 84 studies.^{12,13} Complications after CTT surgery, such as hyphema, bleb-related
10
11
12 85 infections, and choroidal detachment, have been reported.¹⁴
13
14

15 86 Although some studies have indicated that trabeculotomy and CTT are
16
17 87 equally effective in lowering IOP,^{7,9,15} their results
18
19
20 88 were inconsistent with others.^{10,16} There is a paucity of randomized controlled
21
22
23 89 trial with large sample size comparing the results of trabeculotomy with CTT for
24
25
26 90 PCG. A randomized trial by Khalil *et al*⁹ which included a cohort of 28 eyes of
27
28 91 28 children younger than 2-year-old with mean follow-up time of 3 years
29
30
31 92 concluded that both trabeculotomy and CTT with MMC had similar outcomes.
32
33
34 93 However, due to limited sample sizes, it was still difficult to determine which
35
36 94 procedure was more preferred.¹⁷
37
38

39 95 The horizontal corneal diameter (HCD) is usually increased in PCG
40
41 96 patients, which indicates the disease severity and can be used as a rough
42
43
44 97 guide for surgery selection.¹⁸ In general, angle surgeries are recommended for
45
46
47 98 PCG with an HCD <12 mm. Huang *et al*⁸ described 21 eyes of 12 patients with
48
49 99 a mean age of 26.1 days (range: 11 – 28 days) who underwent trabeculotomy
50
51
52 100 with a mean follow-up period of 46.9 months (range 12–122 months). Their
53
54
55 101 success rate was 100% regardless of the medications used. Trabeculectomy
56
57
58 102 or CTT with or without the use of MMC is usually chosen for advanced cases
59
60 103 with an HCD exceeding 14 mm, which is consistent with previous studies.^{7,19}

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4 104 However, which surgical procedure for PCG with HCD of 12-14 mm offers
5
6 105 better outcomes and results in fewer complications remains unknown.
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9

106 **Study objectives**

107 The primary aim of our study is to compare the 3-year success rate between
108 trabeculectomy and CTT in patients with PCG with an HCD of 12-14 mm. The
109 secondary aim is to assess the changes in biological parameters of eyeball,
110 visual outcomes and postoperative complications of these two surgical
111 procedures.

112 **METHODS AND ANALYSIS**

113 This protocol is developed in line with the Standard Protocol Items
114 Recommendations for Interventional Trials (SPIRIT). The SPIRIT checklist for
115 the protocol is available as 'supplement'. The trial was registered at Chinese
116 Clinical Trial Registry (www. Chictr. org. cn) on 20, November 2014 with a
117 number of ChiCTR-IOR-14005588. Version identifier 1.4 of this trial protocol
118 was approved on 25 August 2014.

119 **Trial design and setting**

120 This study is a 3-year, prospective, randomized, single-center, noninferiority
121 trial comparing two surgical procedures (trabeculectomy versus CTT) on the
122 surgical and visual outcomes and postoperative complications in the treatment
123 of PCG with an HCD 12- 14 mm. Eligible patients will be enrolled and randomly
124 assigned to receive either trabeculectomy or CTT (figure 1). The trial is being

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4 125 conducted at the Zhongshan Ophthalmic Center, Guangzhou, China.
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7 126 **Participant selection**
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10 127 Inclusion criteria
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13 128 Participants will be included if they meet all of the following criteria: (1)
14 129 diagnosis of PCG in either eye; (2) Under 3 years of age; (3) HCD between 12
15 130 and 14 mm; (4) no previous intraocular surgery or laser treatment.
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22 131 PCG is defined as follows:
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- 25 132 1. Age of onset \leq 3 years old.
26
27
28 133 2. IOP $>$ 21 mmHg.
29
30
31
32 134 3. Absence of other ocular or systemic diseases.
33
34
35 135 4. Combined with one or more of the following clinical signs: (1) corneal
36 136 findings: Haab's striae, corneal edema, corneal diameters $>$ 11 mm in the
37 137 newborns, $>$ 12mm in children younger than 1 year old, and $>$ 13mm in
38 138 children older than 1 year old;²⁰ (2) increased ($>$ 0.3) or asymmetric ($>$ 0.2)
39 139 C/D ratio; and (3) abnormally increased axial length (AL). Normal AL is as
40 140 follows: 3mo-3yrs: 19-22 mm.²¹
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51 141 Only one eye per patient will be enrolled. If both eyes of a patient are eligible
52 142 for the study, the eye with the higher base-line IOP will be selected. The
53 143 treatment for the fellow eye will be determined at the physician's discretion.
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60 144 Exclusion criteria

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4 145 Patients will be excluded if they meet any of the following criteria:
5
6

7 146 ■ Inability of the patients' legal guardian to give informed consent.
8
9

10 147 ■ Inability of the patient to return to the clinic for the scheduled study visits.
11
12

13 148 ■ Contraindications to anesthesia or surgery for ocular disease.
14
15

16 149 ■ An HCD less than 12 mm or greater than 14 mm.
17
18

19 150 ■ Severe corneal cloudiness precluding anterior chamber visualization.
20
21

22 151 ■ Secondary congenital glaucoma.
23
24

25 152 ■ Prior intraocular surgery.
26
27

28 153 ■ Other coexisting ocular diseases such as an abnormal cornea, congenital
29 iris abnormality, congenital cataract, or retinopathy of prematurity.
30
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33
34

35 155 Withdrawal criteria
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37

38 156 1. Failure to locate or dissect Schlemm's canal by 120°.
39
40

41 157 2. Presence of any of the following issues during the operation: severe
42 anesthesia accident, suprachoroidal hemorrhage, vitreous loss, or a
43 change in the operative procedure according to the patient's condition.
44
45
46
47
48
49

50 160 3. Desire to quit the trial.
51
52

53 161 The withdrawal criteria described above have been established to ensure that
54 the outcomes of the two procedures (trabeculotomy and CTT) will be
55 effectively analyzed for the full 3-year duration of the study.
56
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164 **Sample size calculation**

165 The sample calculation is based on the hypothesis that the 3-year success rate
166 of trabeculotomy will not be inferior to that of CTT. Published studies have
167 showed that the success rate at the 3rd year after CTT ranged from 72.6% to
168 87%.^{1,9,22,23} Success is defined as an IOP \leq 21 mmHg with or without
169 glaucoma medication, no requirement for additional glaucoma surgery and no
170 evidence of progression or enlargement of the cup-disc ratio (C/D ratio) or
171 HCD.^{7,8} We assume that the 3-year success rate of CTT will be approximately
172 80%. In this trial, we expect no significant difference in the 3-year success
173 rates between the two groups; therefore, a sample size of 224 will provide a
174 power of 80% and a one-sided test at 2.5% significance. Assuming a 10% loss
175 to follow-up, a sample size of 248 participants is required for this study, with
176 124 participants in each group.

177 **Patient recruitment and baseline data collection**

178 All subjects will first be assessed for potential participation in the study by the
179 primary investigator. Patients identified as eligible for the study in the survey
180 will be invited to undergo enrollment examinations to verify their eligibility for
181 enrollment in the trial.

182 **Examinations**

183 IOP. IOP will be measured with a Tono-Pen Avia (Reichert, Depew, New York,
184 USA) under sedation with chloral hydrate 10% and topical anesthesia.

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4 185 Although anesthetic agents used during examination under anesthesia (EUA)
5
6 186 may influence IOP and affect the accuracy of IOP documentation, chloral
7
8
9 187 hydrate 10% has a minimal effect on IOP in pediatric ophthalmic
10
11
12 188 examination.¹⁸
13

14
15 189 Slit-lamp examination. The condition of the anterior segment, including corneal
16
17 190 clarity, corneal edema, Haab's striae, anterior chamber depth, iris, pupil, and
18
19
20 191 lens, will be evaluated using a hand-held slit lamp (Keeler, Bucks, England).
21

22
23 192 Corneal clarity will be recorded as mild (iris texture clearly seen), moderate (iris
24
25
26 193 seen but texture not clearly visible), and severe (iris not visible).
27

28
29 194 HCD. A caliper will be used to measure the HCD (white to white) by
30
31
32 195 experienced ophthalmologists. Participants with an HCD less than 12 mm or
33
34
35 196 greater than 14 mm will be excluded.
36

37
38 197 Corneal thickness. Corneal thickness will be measured using ultrasound
39
40
41 198 pachymetry (IOPac, Heidelberg Engineering, Heidelberg, Germany).
42

43
44 199 C/D ratio. The C/D ratio will be evaluated using direct ophthalmoscopy (66
45
46 200 Vision, Suzhou, China) as permitted by the media clarity. Images showing of
47
48
49 201 the C/D ratio will be obtained using a hand-held retinal camera (Kowanonmyd
50
51 202 a-D III; KowaOptimedInc, Aichi, Japan) through a dilated a pupil. For children
52
53
54 203 with hazy media, whose fundus cannot be visualized, B-scan ultrasound
55
56
57 204 (Quantel Medical, CF, France) will be used to rule out any intraocular
58
59 205 pathology and to detect excavation of the optic nerve head.
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4 206 Ocular biometry. Ocular biometry, including AL, anterior chamber depth, lens
5
6 207 thickness, and vitreous chamber depth, will be measured using A-scan
7
8
9 208 ultrasound (Quantel Medical, CF, France). Ten repeated measurements will be
10
11
12 209 taken and averaged for analysis.

13
14
15 210 Visual acuity (VA). VA will be measured using suitable procedures. Teller
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17 211 acuity cards (Vistech Consultants, Inc. Dayton, OH, USA) will be utilized at a
18
19
20 212 distance of 55 cm for nonverbal children. The Lea symbols (Precision Vision,
21
22
23 213 La Salle, IL) with a test distance of 3 meters and the Early Treatment of
24
25 214 Diabetic Retinopathy Study (ETDRS) LogMAR E chart (Precision Vision, Villa
26
27
28 215 Park, Illinois, USA) with a test distance of 4 meters will be employed for verbal
29
30
31 216 children. Monocular VA will be assessed in the right eye followed by the left
32
33
34 217 eye. For children who cannot complete the quantified VA examinations
35
36 218 mentioned above, the ability to fix and follow light will be evaluated.

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38
39 219 Refractive error. Refraction will be measured by retinoscopy after cycloplegia.
40
41
42 220 Cycloplegia will be induced with two drops of cyclopentolate 1% instilled 5 min
43
44
45 221 apart, with a third drop administered after 20 min. Cycloplegia will be then
46
47
48 222 evaluated after an additional 15 min. Cycloplegia is considered complete if the
49
50 223 pupil dilates to ≥ 6 mm and a light reflex is absent.²⁴

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53 224 All ophthalmological examinations described above will be performed in both
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56 225 eyes and under sedation using chloral hydrate 10% (0.8 ml/kg, oral or rectal
57
58 226 administration, the maximum dose is 10 ml per day).

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4 227 Written informed consent will be collected from each eligible participant's legal
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6 228 guardian prior to inclusion in the study. For eligible participants, demographic
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9 229 data (sex, date of birth, and laterality), family history of PCG and medical
10
11 230 history (age of onset, initial syndrome, age at diagnosis, and medical
12
13
14 231 treatment) will be recorded. Pregnancy and delivery information (gestational
15
16
17 232 weeks, delivery mode, maternal drug intake and infection during pregnancy)
18
19
20 233 will also be ascertained and recorded.

234 **Randomisation**

235 A random number table was generated by a biostatistician who will not
236 participate in data management with the SAS V 9.3 software package (SAS
237 Institute, Cary, NC, USA). The allocation of patients will be concealed using
238 sequentially numbered, opaque sealed envelopes. A total of 248 envelopes
239 will be prepared by two researchers not involved in the study. For each
240 recruited patient, his/ her group assignment will be revealed in the operating
241 room on the day of surgery. If a patient is deemed ineligible, then the
242 unopened envelope will be returned to the research center, and the patient will
243 not be randomized in the study. A surgeon will be assigned for surgical
244 management and intraoperative data collection. The 1:1 randomization
245 procedure will be performed in blocks of eight.

246 Postoperative follow-up will be performed by investigators who do not
247 participate in patient care and have been trained to follow-up patients prior to

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4 248 the study. Both surgeon(s) and investigator(s) do not communicate with each
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6 249 other while collecting data.
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10 250 **Interventions**

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13 251 All surgeries will be performed under general anesthesia.
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15

16 252 Trabeculotomy

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19 253 This technique has been previously described.⁸ In brief, a superior quadrant
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21
22 254 fornix-based flap will be created. A 3-mm × 3-mm superficial (12 o'clock)
23
24
25 255 scleral flap of three-quarters thickness will be made. A 2-mm radial incision will
26
27
28 256 be made starting from the gray zone up to the white zone, followed by entering
29
30
31 257 Schlemm's canal externally. An incision will be slowly deepened until the outer
32
33
34 258 wall of Schlemm's canal is opened, and seeping aqueous humor is observed.
35
36
37 259 Schlemm's canal will be dissected by 120° using a trabeculotome probe in
38
39
40 260 both directions. The scleral flap will then be replaced with three interrupted
41
42
43 261 10-0 nylon sutures. The conjunctival flap will also be replaced with 8-0
44
45
46 262 absorbable sutures.

47 263 CTT

48
49
50 264 In the superior quadrant, CTT with MMC will be performed. A fornix-based
51
52
53 265 conjunctival flap will be dissected. MMC will be applied at a concentration of
54
55
56 266 0.3mg/ ml and sustained for 3 min. Then, the area where MMC is applied will
57
58
59 267 be irrigated thoroughly with balanced salt solution. A superficial scleral flap
60
268 measuring 4 × 3 mm will be raised at 12 o'clock. Then, trabeculotomy will be

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4 269 performed as described above. Trabeculectomy will be performed by cutting a
5
6 270 1-mm × 2-mm deep scleral flap, followed by a peripheral iridectomy. The
7
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9 271 scleral flap and conjunctiva will then be replaced. Finally, the anterior chamber
10
11
12 272 will be reformed with balanced salt solution.

13
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15 273 Intraoperative data, including the duration of surgery, the doses and duration
16
17 274 of MMC used during the operation, anesthesia accidents, intraoperative
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19 275 complications, such as hyphema, and iris/vitreous damage, and
20
21 276 trabeculotomy-related problems, such as failure to identify Schlemm's canal or
22
23
24
25 277 an inability to dissect Schlemm's canal by 120 degrees, will be collected.

278 **Postoperative treatment and patient follow-up**

279 Patients will be treated with prednisolone acetate 1% (dexamethasone,
280 Allergan, Parsippany-Troy Hills, NJ, USA) 6 times daily in combination with
281 topical antibiotics (tobramycin 0.3%, s.a. ALCON-COUVREUR n.v) and
282 pilocarpine 1% (Bausch & Lomb, Rochester, NY) 4 times daily within the first 4
283 weeks after the surgery.

284 Postoperative follow-up visits will be performed in the pediatric glaucoma clinic
285 at Week 1, Week 2, Week 4, Month 3 and then every 3 months (±1 weeks) for
286 3 years. The scheduled examinations of the follow-up visits are summarized in
287 Table 1. When necessary, chloral hydrate 10% will be applied to patients for
288 examinations.

289
59
60

290 Table 1 Scheduled examinations of follow-up visits.

Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Examination	Base Line ± 7 d	Procedure	1 w ± 2 d	2 w ± 2 d	1 m ± 7 d	3 m ± 7 d	6 m ± 7 d	9 m ± 7 d	12 m ± 7 d	15 m ± 7 d	18 m ± 7 d	21 m ± 7 d	24 m ± 7 d	27 m ± 7 d	30 m ± 7 d	33 m ± 7 d	36 m ± 7 d
Informed content	x																
Demographics data	x																
Medical history	x																
Physical examination	x																
IOP	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
AL	x					x	x		x		x		x		x		x
HCD	x	x				x	x	x	x	x	x	x	x	x	x	x	x
Slit lamp examination	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Fundus photography	x					x	x		x		x		x		x		x
B-scan ultrasound*	x					x	x		x		x		x		x		x
refraction	x					x	x		x		x		x		x		x

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VA	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Corneal transparency	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Corneal thickness	x																x
medications	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Advent event		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Reoperation					x	x	x	x	x	x	x	x	x	x	x	x	x

291 * In the event of nonvisibility of fundus, B-scan ultrasound will be used to measure cupping. IOP, intraocular pressure; AL, axial
 292 length; HCD, horizontal corneal diameter; VA, visual acuity.

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4 297 **Outcome assessment**
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7 298 Primary outcome
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10 299 The primary outcome is the success rate at 3 years after surgery. Complete
11
12
13 300 success is defined as a postoperative IOP measure of ≥ 5 and ≤ 21 mmHg
14
15 301 without the need for antiglaucoma medications. Qualified success is defined as
16
17
18 302 the same IOP criteria with the use of glaucoma medications. Treatment failure
19
20
21 303 is defined as the presence of any of the following:

22
23
24 304 1. IOP >21 mmHg with maximum medications or IOP < 5 mmHg on two
25
26 305 consecutive follow-up visits.

27
28
29
30 306 Maximal medication indicates that the patient was treated with three types
31
32 307 of glaucoma medication or with fewer than three types of medication but
33
34 308 could not tolerate more.

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36
37
38 309 2. The occurrence of severe postoperative complications threatening vision,
39
40
41 310 such as suprachoroidal hemorrhage, retinal detachment or endophthalmitis.

42
43
44 311 3. A need for reoperation to control the IOP.
45
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47 312 Secondary outcomes
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50
51 313 The secondary outcomes are changes in the biological parameters of eyeball
52
53 314 (including HCD, corneal clarity, corneal thickness, C/D ratio, AL), VA, and
54
55 315 refraction. Postoperative complications, including hyphema, shallow anterior
56
57
58 316 chamber, hypotony, surgery-related iridodialysis, complicated cataract, retinal
59
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4 317 or choroidal detachment, bleb complications (leakage or infection) and
5
6 318 endophthalmitis, will be evaluated and recorded.
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10 319 **Safety consideration**

11
12
13 320 The safety evaluations of the study will include complications associated with
14
15 321 surgeries and drugs as well as adverse events. The procedures and drugs
16
17 322 used in the study are routinely administered in daily practice. Thus, the trial
18
19 323 has risks not exceeding usual clinical care that the patients would otherwise
20
21 324 receive. Throughout the study, all adverse events will be recorded and
22
23 325 managed.
24
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29 326 Drug-related complications include unanticipated events caused by
30
31 327 cycloplegia, anti-glaucoma drugs, and chloral hydrate. Dilation will be
32
33 328 established following a slit lamp examination. Doctors will closely monitor the
34
35 329 patients' pupil reflexes and vital signs after administering the medications.
36
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40 330 Vision-threatening complications, such as suprachoroidal hemorrhage, retinal
41
42 331 detachment, and endophthalmitis, will constitute major adverse events.
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46 332 **Data management and monitoring**

47
48
49 333 All data collected at the scheduled follow-up visits (Table 1), will be recorded in
50
51 334 the case report forms and entered into a digital database by trained
52
53 335 researchers. Softcopies of digital data in the devices will be stored in a server
54
55 336 at the end of each visit day. The completed case report forms and hardcopy
56
57 337 data forms will be kept in locked cabinets in the research center to protect the
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4 338 privacy of the participants. The implementation of the trial will be monitored by
5
6 339 the principal investigator. Access to the final dataset will be limited to the trial
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8
9 340 administrator and the statistician.
10

11 341 **Statistical analysis**

12
13
14
15 342 An intention-to-treat analysis will be performed. All statistical analyses will be
16
17
18 343 performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA). The continuous
19
20
21 344 data will be expressed as the mean (SD) and analysed using the
22
23
24 345 Mann-Whitney U test or independent *t* test. The categorical data will be
25
26 346 expressed as the number of patients (percentage) or median (IQR (IQR)) and
27
28
29 347 analysed using chi-square tests or Fisher's exact test.
30

31
32 348 The Kaplan-Meier method will be used to estimate a curve of the
33
34 349 probability that the IOP is under control versus the time after surgery. The
35
36
37 350 log-rank test will be employed to compare curves for the trabeculotomy and
38
39
40 351 CTT groups. Comparison of continuous variables such as the HCD, AL,
41
42 352 corneal thickness, C/D ratio, and the distribution of refractive errors between
43
44
45 353 the two groups will be performed using Student's *t*-test or the Wilcoxon
46
47 354 nonparametric test as appropriate, while within-group comparisons will be
48
49
50 355 performed using paired *t*-test or Wilcoxon's signed rank test. The Chi-square
51
52
53 356 test or Fisher's exact test will be used to compare the proportions of the visual
54
55
56 357 outcome, the number of anti-glaucoma drugs, and complications between the
57
58 358 two surgical groups. In addition, reasons for loss to follow-up will also be
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4 359 documented.

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7 360 **Participant timeline**

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10 361 Recruitment began in the first quarter of 2015. Currently, 75% of the sample
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12 362 size has been attained. It is anticipated that the study will reach the recruitment
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14 363 target of 248 participants by the fourth quarter of 2019. The interim analysis
15
16 364 will be conducted to evaluate one, two, and three years outcomes of
17
18 365 trabeculotomy versus CTT for PCG.

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24 366 **ETHICS AND DISSEMINATION**

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27 367 This study was approved by ethics committee of Zhongshan Ophthalmic
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29 368 Center (reference number 2014MEKY023). The study protocol was also
30
31 369 reviewed by the “5010 Plan” evaluation committee at Sun Yat-sen University,
32
33 370 Guangzhou, China. Every year the evaluation committee will examine the
34
35 371 study progress and adherence to the study protocol. The project leader will
36
37 372 ensure that this study is conducted in accordance with the principles of the
38
39 373 World Medical Association Declaration of Helsinki.

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46 374 The study results will be presented at national and international meetings
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48 375 on ophthalmology.

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52 376 **DISCUSSION**

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55 377 This trial is a prospective, randomized, controlled intervention trial intended to
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57 378 provide evidence for ophthalmologists to make better decisions regarding

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4 379 surgical options for patients with PCG. To the best of our knowledge, this trial
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6 380 is the largest clinical trial in the field of pediatric glaucoma. The findings are
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8
9 381 expected to provide evidence for whether trabeculotomy is not inferior to CTT
10
11
12 382 in treating PCG with an HCD of 12-14 mm.

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14
15 383 This trial enrolled subjects with PCG with an HCD of 12-14 mm to reduce
16
17 384 selection bias. For PCG with an HCD less than 12 mm, the anatomic
18
19 385 abnormality of Schlemm's canal is usually not significant, facilitating its
20
21
22 386 identification during the operation. As a result, angle surgery alone is sufficient
23
24
25 387 to lower IOP in these patients. Advanced PCG with an HCD greater than 14
26
27
28 388 mm is usually associated with a significant anatomic anomaly of the anterior
29
30
31 389 drainage angle. The abnormally stretched anatomy of the limbus in these
32
33
34 390 patients frequently makes it difficult to clearly identify the lumen of Schlemm's
35
36 391 canal that has to be cannulated for the trabeculotomy. Thus, the success rate
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38
39 392 of trabeculotomy in advanced PCG cases is lower. Quigley *et al*²⁵ reported the
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41
42 393 results of trabeculotomy in 28 eyes with congenital glaucoma. The success
43
44 394 rate in eyes with a corneal diameter greater than 14 mm was 67% compared
45
46 395 with 100% in eyes with a smaller corneal diameter. Both conditions described
47
48
49 396 above will lead to biases to the results. Moreover, most PCG cases in China
50
51
52 397 are diagnosed with an HCD ranging from 12 mm to 14 mm.^{7,26} These patients
53
54 398 have a good chance to preserve useful VA if treated correctly.

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56
57 399 No unified guideline is currently available to determine PCG severity
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60 400 based on corneal diameter. Kiskis *et al*²⁷ studied the HCD and AL in PCG

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4 401 patients and concluded that HCD measurement was a more reliable guide
5
6 402 than AL in the assessment of PCG. Currently, we are unaware of any studies
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8
9 403 comparing long-term outcomes between CTT and trabeculotomy in PCG
10
11 404 patients with homogeneity in terms of disease severity. After considering the
12
13
14 405 above information, we selected an HCD of 12-14 mm as an inclusion criterion.
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16
17 406 However, selection of surgical methods of the treatment of PCG and the
18
19 407 evaluation of PCG severity based only on HCD are issues requiring further
20
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22 408 investigations and improvement.

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24
25 409 In conclusion, this trial is a large clinical trial aiming to provide evidence for
26
27 410 the optimum first-line surgery for patients with PCG with an HCD of 12-14 mm.
28
29 411 If the trabeculotomy group is associated with comparable surgical success and
30
31 412 fewer postoperative complications compared with CTT group, trabeculotomy
32
33 413 should be recommended as a primary surgical treatment for PCG with an HCD
34
35 414 of 12-14 mm, saving trabeculectomy for future intervention. In addition,
36
37 415 complications associated with trabeculectomy will be reduced. The visual
38
39 416 outcome in this trial may help provide insight into the effects of surgical
40
41 417 methods on VA. The findings of our study are expected to provide guidance to
42
43 418 clinicians weighing the benefit and risk of trabeculotomy compared to CTT for
44
45 419 the treatment of PCG.

420 **Acknowledgments**

421 We would like to thank all research assistants and nursing staff involved in this
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4 422 trial, who contributed to the practical organization and execution of this study.
5

6
7 423 **Author affiliations**
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26
27 430 China.
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29
30 431 **Author Contributions** XL conceived the study and is the project leader for the
31
32 432 trial. XL, XXG, YFY, JJH, YMZ, XXC and LF participated in the study design
33
34 433 and recruited the patients. LF wrote the manuscript. XL, XXG, and XYX
35
36 434 critically revised the manuscript. JZ designed the database system and
37
38 435 performed the statistics-related design. All authors read and approved the final
39
40 436 manuscript.
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46
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48
49 438 Clinical Research 5010 Program (2014016) and the National Natural Science
50
51 439 Foundation of China (81800879). The sponsor had no role in the protocol
52
53 440 design or conduct of this study.
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58 441 **Competing interests** None.
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4 442 **Patient consent** Obtained.

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6
7 443 **Ethics approval** This study was approved by ethics committee of Zhongshan
8
9
10 444 Ophthalmic Center (reference number 2014MEKY023). The study protocol
11
12 445 was also reviewed by the “5010 Plan” evaluation committee at Sun Yat-sen
13
14
15 446 University, Guangzhou, China.

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17 447 **Provenance and peer review** Not commissioned; externally peer reviewed.

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20 448 **Data sharing statement** No additional data available.

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23 449 **REFERENCES**

- 24
25 450 1. Liu B, Huang W, He M, *et al.* An investigation on the causes of blindness
26
27 451 and low vision of students in blind school in Guangzhou [in Chinese]. *Yan*
28
29 452 *Ke Xue Bao* 2007;23:117-20.
- 30
31
32 453 2. Mandal AK, Chakrabarti D. Update on congenital glaucoma. *Indian J*
33
34 454 *Ophthalmol* 2011;59:S148–57.
- 35
36
37 455 3. Haddad MAO, Sei M, Sampaio MW, *et al.* Causes of visual impairment in
38
39 456 children: Study of 3210 cases. *J Pediatr Ophthalmol Strabismus* 2007;44:
40
41 457 232-40.
- 42
43
44 458 4. Levy J, Tessler Z, Tamir O, *et al.* Primary congenital glaucoma. *Harefuah*
45
46 459 2004;143:876–80.
- 47
48
49 460 5. Bowman RJ, Dickerson M, Mwende J, *et al.* Outcomes of goniotomy for
50
51 461 primary congenital glaucoma in East Africa. *Ophthalmology* 2011;118:
52
53 462 236–40.
- 54
55
56 463 6. Morales J, Al Shahwan S, Al Odhayb S, *et al.* Current surgical options for
57
58
59
60

- 1
2
3
4 464 the management of pediatric glaucoma. *J Ophthalmol* 2013;2013: 1-16.
5
6
7 465 7. Zhang X, Du S, Fan Q, *et al.* Long-term surgical outcomes of primary
8
9 466 congenital glaucoma in China. *Clinics (Sao Paulo)* 2009;64:543–51.
10
11
12 467 8. Huang JL, Huang JJ, Zhong YM, *et al.* Surgical Outcomes of
13
14 468 Trabeculotomy in Newborns with Primary Congenital Glaucoma. *Chin Med*
15
16
17 469 *J (Engl)* 2016; 129:2178–83.
18
19
20 470 9. Khalil DH, Abdelhakim MA. Primary trabeculotomy compared to combined
21
22 471 trabeculectomy-trabeculotomy in congenital glaucoma: 3-year study. *Acta*
23
24
25 472 *Ophthalmol* 2016;94:e550-4.
26
27
28 473 10. Al-Hazmi A, Awad A, Zwaan J, *et al.* Correlation between surgical success
29
30 474 rate and severity of congenital glaucoma. *Br J Ophthalmol* 2005;89:449-53.
31
32
33 475 11. Hsu CR, Chen YH, Tai MC, *et al.* Combined trabeculotomy-
34
35 476 trabeculectomy using the modified Safer Surgery System augmented with
36
37
38 477 MMC: its long-term outcomes of glaucoma treatment in Asian children.
39
40
41 478 *Graefe's Arch Clin Experiment Ophthalmol* 2018;256:1187-94.
42
43
44 479 12. Rodrigues A M, Paranhos JA, Montezano FT, *et al.* Comparison between
45
46 480 results of trabeculectomy in primary congenital glaucoma with and without
47
48 481 the use of Mitomycin C. *J Glaucoma* 2004;13:228–32.
49
50
51 482 13. Ozkiris A, Tamcelik N. Long-term results of trabeculectomy with different
52
53 483 concentrations of mitomycin C in refractory developmental glaucoma. *J*
54
55
56 484 *Pediatr Ophthalmol Strabismus* 2005;42:97–102.
57
58
59 485 14. Jalil A, Au L, Khan I, *et al.* Combined trabeculotomy-trabeculectomy
60

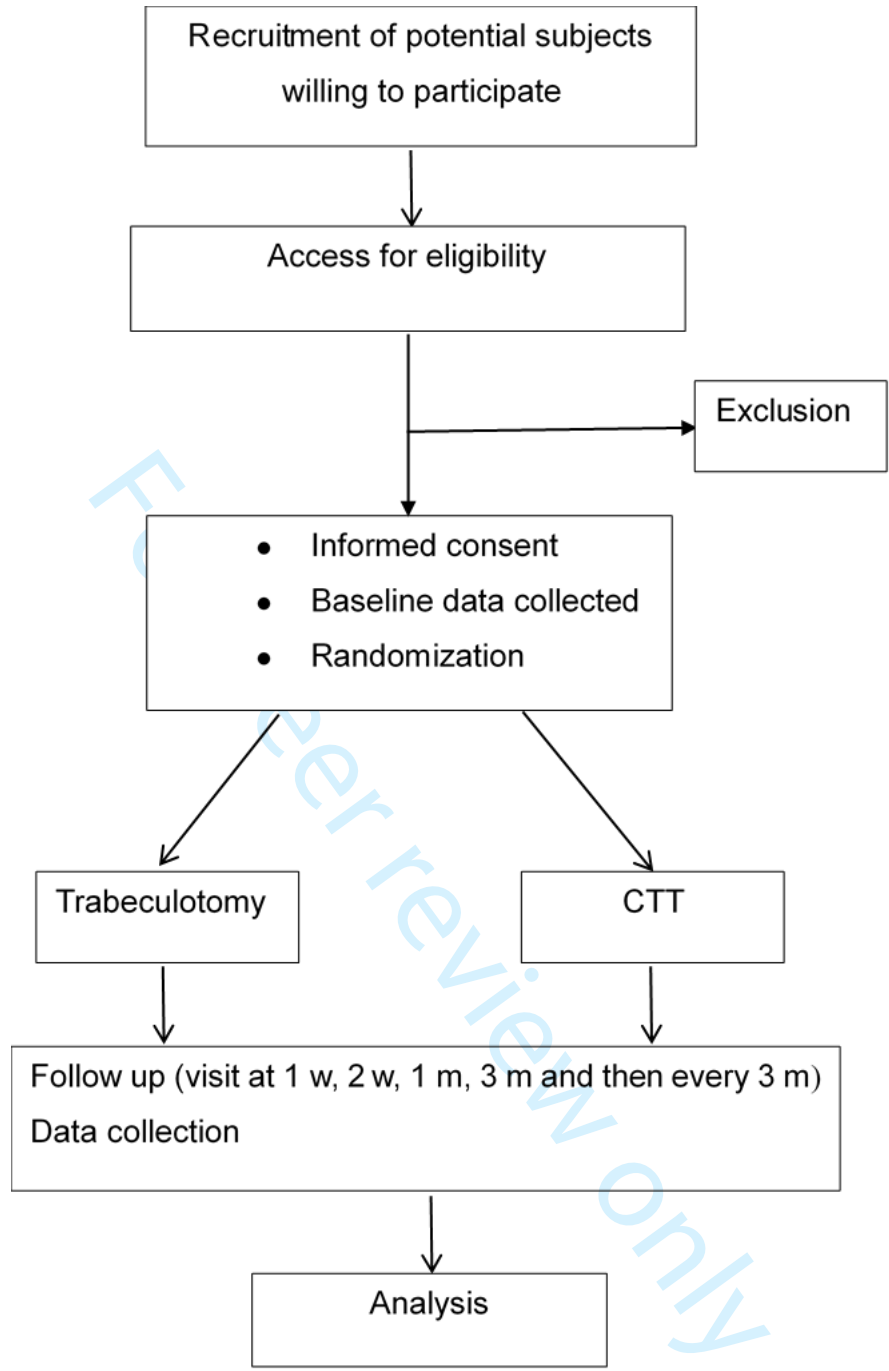
- 1
2
3
4 486 augmented with 5-fluorouracil in paediatric glaucoma. *Clin Experiment*
5
6 487 *Ophthalmol* 2011;39:207–14.
7
8
9 488 15. Biedner B.Z., Rothkoff L. Combined trabeculotomy-trabeculectomy
10
11 489 compared with primary trabeculotomy for congenital glaucoma. *J Pediatr*
12
13 490 *Ophthalmol Strabismus* 1998;35:49–50.
14
15
16
17 491 16. Chen TC, Chen PP, Francis BA, *et al.* Pediatric glaucoma surgery: a report
18
19 492 by the American Academy of Ophthalmology. *Ophthalmology* 2014;121:
20
21 493 2107–15.
22
23
24
25 494 17. Ghate D, Wang X. Surgical interventions for primary congenital glaucoma.
26
27 495 *Cochrane Database Syst Rev* 2015;1:CD008213.
28
29
30 496 18. Yu Chan JY, Choy BN, Ng AL, *et al.* Review on the management of
31
32 497 primary congenital glaucoma. *J Curr Glaucoma Pract* 2015;9:92-9.
33
34
35 498 19. Mandal AK, Matalia JR, Krishnaiah S. Combined trabeculotomy and
36
37 499 trabeculectomy in advanced primary developmental glaucoma with corneal
38
39 500 diameter of 14 mm or more. *Eye* 2005;20:135-43.
40
41
42
43 501 20. Thau A, Lloyd M, Freedman S, *et al.* New classification system for
44
45 502 pediatric glaucoma: implications for clinical care and a research registry.
46
47 503 *Curr Opin Ophthalmol* 2018;29:385-94.
48
49
50
51 504 21. Bach A, Villegas VM, Gold AS, *et al.* Axial length development in children.
52
53 505 *Int J Ophthalmol* 2019;12:815-9.
54
55
56 506 22. Mandal AK, Bhatia PG, Arumugam B, *et al.* Long-term surgical and visual
57
58 507 outcomes in Indian children with developmental glaucoma operated on
59
60

- 1
2
3
4 508 within 6 months of birth. *Ophthalmology* 2004;111:283-90.
- 5
6
7 509 23. Mandal AK, Gothwal VK, Nutheti R. Surgical outcome of primary
8
9 510 developmental glaucoma: a single surgeon's long-term experience from a
10
11 511 tertiary eye care centre in India. *Eye* 2007;17:764-74.
- 12
13
14 512 24. Negrel AD, Maul E, Pokharel GP, et al. Refractive error study in children:
15
16 513 sampling and measurement methods for a multi - country survey. *Am J*
17
18 514 *Ophthalmol* 2000;129:421-6.
- 19
20
21 515 25. HA Q. Childhood glaucoma: results with trabeculotomy and study of
22
23 516 reversible cupping. *Ophthalmology* 1982;89:219-26.
- 24
25
26 517 26. Cai Y, Li MY, Shen YY, et al. Long-term effect of trabeculotomy on
27
28 518 primary congenital glaucoma [in Chinese]. *Zhonghua Yan Ke Za Zhi*
29
30 519 2004;40:733-6.
- 31
32
33 520 27. Kiskis AA, Markowitz SN, Morin JD. Corneal diameter and axial length in
34
35 521 congenital glaucoma. *Can J Ophthalmol* 1985;20:93-7.
- 36
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524 **Figure Legend**

525 Figure 1 Flowchart of the study. CTT, combined
526 trabeculotomy-trabeculectomy.

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158(3):200-207

		Page
	Reporting Item	Number
Administrative information		
Title	#1 Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

1	Trial registration	#2a	Trial identifier and registry name. If not yet registered,	3
2			name of intended registry	
3				
4				
5				
6	Trial registration: data	#2b	All items from the World Health Organization Trial	N/A
7	set		Registration Data Set	
8				
9				
10				
11	Protocol version	#3	Date and version identifier	6
12				
13				
14				
15	Funding	#4	Sources and types of financial, material, and other support	24
16				
17				
18	Roles and	#5a	Names, affiliations, and roles of protocol contributors	1,23
19	responsibilities:			
20	contributorship			
21				
22				
23				
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25				
26	Roles and	#5b	Name and contact information for the trial sponsor	23
27	responsibilities:			
28	sponsor contact			
29	information			
30				
31				
32				
33				
34				
35				
36	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	23
37	responsibilities:		collection, management, analysis, and interpretation of	
38	sponsor and funder		data; writing of the report; and the decision to submit the	
39			report for publication, including whether they will have	
40			ultimate authority over any of these activities	
41				
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48	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	N/A
49	responsibilities:		centre, steering committee, endpoint adjudication	
50	committees		committee, data management team, and other individuals	
51			or groups overseeing the trial, if applicable (see Item 21a	
52			for data monitoring committee)	
53				
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1	Introduction			
2				
3				
4	Background and	#6a	Description of research question and justification for	4-6
5	rationale		undertaking the trial, including summary of relevant studies	
6			(published and unpublished) examining benefits and harms	
7			for each intervention	
8				
9				
10				
11	Background and	#6b	Explanation for choice of comparators	5-6
12	rationale: choice of			
13	comparators			
14				
15				
16	Objectives	#7	Specific objectives or hypotheses	6
17				
18				
19	Trial design	#8	Description of trial design including type of trial (eg, parallel	6.7
20			group, crossover, factorial, single group), allocation ratio,	
21			and framework (eg, superiority, equivalence, non-inferiority,	
22			exploratory)	
23				
24				
25	Methods:			
26				
27	Participants,			
28				
29	interventions, and			
30				
31	outcomes			
32				
33				
34				
35	Study setting	#9	Description of study settings (eg, community clinic,	7
36			academic hospital) and list of countries where data will be	
37			collected. Reference to where list of study sites can be	
38			obtained	
39				
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44	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If	7,8
45			applicable, eligibility criteria for study centres and	
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1		individuals who will perform the interventions (eg,	
2		surgeons, psychotherapists)	
3			
4			
5			
6	Interventions:	#11a Interventions for each group with sufficient detail to allow	13,14
7			
8	description	replication, including how and when they will be	
9			
10		administered	
11			
12			
13	Interventions:	#11b Criteria for discontinuing or modifying allocated	8
14			
15	modifications	interventions for a given trial participant (eg, drug dose	
16		change in response to harms, participant request, or	
17		improving / worsening disease)	
18			
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22			
23	Interventions:	#11c Strategies to improve adherence to intervention protocols,	N/A
24			
25	adherence	and any procedures for monitoring adherence (eg, drug	
26		tablet return; laboratory tests)	
27			
28			
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30			
31	Interventions:	#11d Relevant concomitant care and interventions that are	14
32			
33	concomitant care	permitted or prohibited during the trial	
34			
35			
36	Outcomes	#12 Primary, secondary, and other outcomes, including the	17,18
37			
38		specific measurement variable (eg, systolic blood	
39		pressure), analysis metric (eg, change from baseline, final	
40		value, time to event), method of aggregation (eg, median,	
41		proportion), and time point for each outcome. Explanation	
42		of the clinical relevance of chosen efficacy and harm	
43		outcomes is strongly recommended	
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53	Participant timeline	#13 Time schedule of enrolment, interventions (including any	20,
54			
55		run-ins and washouts), assessments, and visits for	Table1
56			
57		participants. A schematic diagram is highly recommended	
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		(see Figure)	
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3			
4	Sample size	#14 Estimated number of participants needed to achieve study	9
5			
6		objectives and how it was determined, including clinical and	
7			
8		statistical assumptions supporting any sample size	
9			
10		calculations	
11			
12			
13	Recruitment	#15 Strategies for achieving adequate participant enrolment to	N/A
14			
15		reach target sample size	
16			
17			
18			
19	Methods: Assignment		
20			
21	of interventions (for		
22			
23	controlled trials)		
24			
25			
26	Allocation: sequence	#16a Method of generating the allocation sequence (eg,	12
27			
28	generation	computer-generated random numbers), and list of any	
29			
30		factors for stratification. To reduce predictability of a	
31			
32		random sequence, details of any planned restriction (eg,	
33			
34		blocking) should be provided in a separate document that is	
35			
36		unavailable to those who enrol participants or assign	
37			
38		interventions	
39			
40			
41			
42			
43	Allocation	#16b Mechanism of implementing the allocation sequence (eg,	12
44			
45	concealment	central telephone; sequentially numbered, opaque, sealed	
46			
47	mechanism	envelopes), describing any steps to conceal the sequence	
48			
49		until interventions are assigned	
50			
51			
52			
53	Allocation:	#16c Who will generate the allocation sequence, who will enrol	12
54			
55	implementation	participants, and who will assign participants to	
56			
57		interventions	
58			
59			
60			

1	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg,	12,13
2			trial participants, care providers, outcome assessors, data	
3			analysts), and how	
4				
5				
6				
7				
8	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is	N/A
9	emergency		permissible, and procedure for revealing a participant's	
10	unblinding		allocated intervention during the trial	
11				
12				
13				
14				
15				
16	Methods: Data			
17	collection,			
18	management, and			
19	analysis			
20				
21				
22				
23				
24				
25				
26	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline,	9-11,
27			and other trial data, including any related processes to	Table1
28			promote data quality (eg, duplicate measurements, training	
29			of assessors) and a description of study instruments (eg,	
30			questionnaires, laboratory tests) along with their reliability	
31			and validity, if known. Reference to where data collection	
32			forms can be found, if not in the protocol	
33				
34				
35				
36				
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42				
43	Data collection plan:	#18b	Plans to promote participant retention and complete follow-	N/A
44	retention		up, including list of any outcome data to be collected for	
45			participants who discontinue or deviate from intervention	
46			protocols	
47				
48				
49				
50				
51				
52				
53	Data management	#19	Plans for data entry, coding, security, and storage,	18,19
54			including any related processes to promote data quality	
55			(eg, double data entry; range checks for data values).	
56				
57				
58				
59				
60				

1		Reference to where details of data management	
2		procedures can be found, if not in the protocol	
3			
4			
5			
6	Statistics: outcomes	#20a Statistical methods for analysing primary and secondary	19
7		outcomes. Reference to where other details of the	
8		statistical analysis plan can be found, if not in the protocol	
9			
10			
11			
12			
13	Statistics: additional	#20b Methods for any additional analyses (eg, subgroup and	19
14	analyses	adjusted analyses)	
15			
16			
17			
18			
19	Statistics: analysis	#20c Definition of analysis population relating to protocol non-	N/A
20	population and	adherence (eg, as randomised analysis), and any statistical	
21	missing data	methods to handle missing data (eg, multiple imputation)	
22			
23			
24			
25			
26	Methods: Monitoring		
27			
28			
29	Data monitoring:	#21a Composition of data monitoring committee (DMC);	N/A
30	formal committee	summary of its role and reporting structure; statement of	
31		whether it is independent from the sponsor and competing	
32		interests; and reference to where further details about its	
33		charter can be found, if not in the protocol. Alternatively, an	
34		explanation of why a DMC is not needed	
35			
36			
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43			
44	Data monitoring:	#21b Description of any interim analyses and stopping	20
45	interim analysis	guidelines, including who will have access to these interim	
46		results and make the final decision to terminate the trial	
47			
48			
49			
50			
51	Harms	#22 Plans for collecting, assessing, reporting, and managing	18
52		solicited and spontaneously reported adverse events and	
53		other unintended effects of trial interventions or trial	
54			
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1		conduct	
2			
3			
4	Auditing	#23 Frequency and procedures for auditing trial conduct, if any,	20
5			
6		and whether the process will be independent from	
7			
8		investigators and the sponsor	
9			
10			
11	Ethics and		
12			
13	dissemination		
14			
15			
16	Research ethics	#24 Plans for seeking research ethics committee / institutional	20
17			
18	approval	review board (REC / IRB) approval	
19			
20			
21	Protocol	#25 Plans for communicating important protocol modifications	N/A
22			
23	amendments	(eg, changes to eligibility criteria, outcomes, analyses) to	
24		relevant parties (eg, investigators, REC / IRBs, trial	
25		participants, trial registries, journals, regulators)	
26			
27			
28			
29			
30			
31	Consent or assent	#26a Who will obtain informed consent or assent from potential	11
32		trial participants or authorised surrogates, and how (see	
33		Item 32)	
34			
35			
36			
37			
38			
39	Consent or assent:	#26b Additional consent provisions for collection and use of	N/A
40			
41	ancillary studies	participant data and biological specimens in ancillary	
42		studies, if applicable	
43			
44			
45			
46			
47	Confidentiality	#27 How personal information about potential and enrolled	18,19
48			
49		participants will be collected, shared, and maintained in	
50		order to protect confidentiality before, during, and after the	
51		trial	
52			
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56			
57	Declaration of	#28 Financial and other competing interests for principal	23
58			
59			
60			

1	interests		investigators for the overall trial and each study site	
2				
3				
4	Data access	#29	Statement of who will have access to the final trial dataset,	19
5			and disclosure of contractual agreements that limit such	
6			access for investigators	
7				
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9				
10				
11	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and for	N/A
12			compensation to those who suffer harm from trial	
13	trial care		participation	
14				
15				
16				
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18				
19	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial	N/A
20			results to participants, healthcare professionals, the public,	
21	trial results		and other relevant groups (eg, via publication, reporting in	
22			results databases, or other data sharing arrangements),	
23			including any publication restrictions	
24				
25				
26				
27				
28				
29				
30				
31	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	20
32			professional writers	
33	authorship			
34				
35				
36	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,	N/A
37			participant-level dataset, and statistical code	
38	reproducible research			
39				
40				
41				
42	Appendices			
43				
44				
45	Informed consent	#32	Model consent form and other related documentation given	N/A
46			to participants and authorised surrogates	
47	materials			
48				
49				
50	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	N/A
51			biological specimens for genetic or molecular analysis in	
52			the current trial and for future use in ancillary studies, if	
53			applicable	
54				
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2 License CC-BY-ND 3.0. This checklist can be completed online using <https://www.goodreports.org/>, a
3 tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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Trabeculotomy Versus Combined Trabeculotomy-Trabeculectomy for Primary Congenital Glaucoma: Study Protocol of a Randomized Controlled Trial

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Secondary Subject Heading:	Ophthalmology, Paediatrics, Surgery
Keywords:	Primary congenital glaucoma, Trabeculotomy, PCG, Combined trabeculotomy-trabeculectomy, Randomized controlled trial

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4 1 **Trabeculotomy Versus Combined Trabeculotomy-Trabeculectomy for**
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6 2 **Primary Congenital Glaucoma: Study Protocol of a Randomized**
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8 3 **Controlled Trial**
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10

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14 5 Yingting Zhu,¹ Jielei Huang,^{1,4} Jingjing Huang,¹ Yimin Zhong,¹ Xiaoyu Xu,¹
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51 17 China.
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54 18 **Word count: 3820**
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1
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3
4 20 **Abstract**
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6

7 21 **Introduction:** Trabeculotomy and combined trabeculotomy-trabeculectomy
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9
10 22 (CTT) are major surgical options for primary congenital glaucoma (PCG).
11
12 23 However, it is unclear which of these two surgical procedures should be
13
14 24 recommended as the optimum first-line treatment for PCG. This trial aims to
15
16 25 determine whether the surgical outcomes of trabeculotomy are noninferior to
17
18 26 those of CTT in PCG with a horizontal corneal diameter (HCD) of 12-14 mm.
19
20
21
22

23 27 **Methods and analysis:** This is a 3-year, noninferiority, prospective,
24
25 28 randomized controlled trial. We plan to recruit 248 participants (aged ≤ 3
26
27 29 years) with PCG with an HCD of 12-14 mm from the Department of Glaucoma,
28
29 30 Zhongshan Ophthalmic Center, Guangzhou, China. One eye per participant
30
31 31 will be randomly (1:1) assigned to receive trabeculotomy or CTT. The primary
32
33 32 outcome is the 3-year postoperative success rate in lowering IOP, and the
34
35 33 secondary clinical outcomes will include IOP reduction, visual acuity (VA),
36
37 34 HCD, central corneal thickness, axial length, cup-disc ratio, refractive error,
38
39 35 and postoperative complications. Data will be analyzed by the intention-to-treat
40
41 36 principle.
42
43
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48
49

50 37 **Ethical approval and dissemination:** The study protocol has been approved
51
52 38 by the ethics committee of Zhongshan Ophthalmic Center (2014MEKY023)
53
54 39 and the "5010 Plan" evaluation committee at Sun Yat-Sen University,
55
56 40 Guangzhou, China. The results will be disseminated in international academic
57
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4 41 meetings and published in peer-reviewed journals.
5
6

7 42 **Trial registration:** Chinese Clinical Trial Registry, ChiCTR-IOR-14005588;
8

9 43 Date registered: 20 November 2014.
10

11 44 **Keywords:** PCG, Primary congenital glaucoma, Trabeculotomy, Combined
12
13
14
15 45 trabeculotomy-trabeculectomy, Randomized controlled trial
16
17

18 46 **Article Summary**

19 20 21 47 **Strengths and limitations of this study**

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24
25 48 ■ The trial design is prospective, randomized and controlled with a relatively
26
27 49 large sample size, and the follow-up is comparatively long (3 years).

30
31 50 ■ The study is the first randomized controlled trial to comprehensively
32
33 51 evaluate the surgical and visual outcomes of trabeculotomy and CTT in
34
35
36 52 PCG patients with an HCD of 12 to 14 mm.

37
38
39 53 ■ This study assesses important clinical measurements with significant
40
41 54 clinical implications, including HCD, axial length, central corneal
42
43
44 55 thickness, C/D ratio, refractive errors and VA. All data will be obtained
45
46
47 56 following standardized protocols and assessed longitudinally.

48
49
50 57 ■ The IOP criteria (≤ 21 mmHg) used to define glaucoma and surgical
51
52 58 success rate may be relatively high for children younger than 3 years old.

53
54
55
56 59 ■ Instead of the gold applanation tonometry, IOP is measured by Tono-Pen
57
58
59 60 tonometry.

61 INTRODUCTION

62 Primary congenital glaucoma (PCG) is one of main causes of blindness in
63 children. Liu *et al*¹ reported that congenital glaucoma accounted for 5.1% of all
64 congenital ocular diseases in a Chinese population. It is estimated to account
65 for 0.01–0.04% of blindness worldwide.² In India, this disease accounts for
66 4.2% of all childhood blindness.² Haddad *et al*³ evaluated 3210 visually
67 impaired children and found that PCG was responsible for 10.2% of visual
68 impairments. Since at least 50% of eyes with PCG presenting at birth will
69 become legally blind, patients with PCG require prompt treatment and
70 follow-up examinations throughout their lives.⁴

71 Surgical intervention is the main treatment for PCG. Goniotomy and
72 trabeculotomy are considered initial procedures because of their high success
73 rates.^{5,6} However, Clear corneal is a premise for goniotomy but not necessarily
74 for trabeculotomy. Trabeculotomy reduces intraocular pressure (IOP) by
75 tearing the trabecular meshwork into the anterior chamber. Regarding
76 complications, hyphema is more common in trabeculotomy but can resolve
77 spontaneously and cause no additional problems.⁷⁻⁹

78 Combined trabeculotomy-trabeculectomy (CTT) has been advocated for
79 treating moderate to severe congenital glaucoma.¹⁰ The rationale for CTT is to
80 gain access to the dual outflow through Schlemm's canal and the
81 trabeculectomy fistula. The application of Mitomycin-C (MMC) can improve the

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3
4 82 surgical success rates of CTT,¹¹ which is, however, disputed by some other
5
6 83 studies.^{12,13} Complications after CTT surgery, such as hyphema, bleb-related
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8
9 84 infections, and choroidal detachment, have been reported.¹⁴
10
11

12 85 Although some studies have indicated that trabeculotomy and CTT are
13
14
15 86 equally effective in lowering IOP,^{7,9,15} their results
16
17 87 were inconsistent with others.^{10,16} There is a paucity of randomized controlled
18
19 88 trials with large sample sizes that compare the results of trabeculotomy with
20
21
22
23 89 CTT for PCG. A randomized trial conducted by Khalil *et al*⁹ included a cohort of
24
25 90 28 eyes of 28 children younger than 2 years old with a mean follow-up time of
26
27
28 91 3 years. They concluded that both trabeculotomy and CTT with MMC had
29
30
31 92 similar outcomes. However, due to limitations of sample sizes, it remains
32
33 93 inconclusive as which procedure is preferable.¹⁷
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35

36 94 The horizontal corneal diameter (HCD) is typically increased in PCG patients,
37
38
39 95 which serves as an indication for disease severity and a key factor for surgery
40
41
42 96 selection.¹⁸ In general, angle surgeries are recommended for PCG with an
43
44 97 HCD <12 mm.⁸ Trabeculectomy or CTT with or without the use of MMC is
45
46
47 98 usually chosen for advanced cases with an HCD exceeding 14 mm.^{7,19} For
48
49 99 PCG with an HCD of 12-14 mm, trabeculotomy and CTT are the two major
50
51
52 100 surgical options. However, it remains unknown whether trabeculotomy, when
53
54
55 101 compared to CTT, yields comparable results and fewer postoperative
56
57 102 complications in PCG with an HCD of 12-14 mm. Therefore, we design a study
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59
60 103 to determine whether the clinical outcomes of trabeculotomy are noninferior to

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4 104 those of CTT for PCG with an HCD of 12-14 mm.
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6

7 105 **Study objectives**
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9

10 106 The primary outcome of our study is to compare the 3-year success rate in
11
12 107 lowering IOP between trabeculotomy and CTT in patients with PCG with an
13
14 108 HCD of 12-14 mm. The secondary outcome is to assess changes in IOP and
15
16 109 the morphometric parameters of the eyeball, visual outcomes and
17
18 110 postoperative complications in these two surgical procedures.
19
20
21
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23
24 111 **METHODS AND ANALYSIS**
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26

27 112 This protocol is developed in line with the Standard Protocol Items
28
29 113 Recommendations for Interventional Trails (SPIRIT). The SPIRIT checklist for
30
31 114 the protocol is available as 'supplement'. The trail was registered at the
32
33 115 Chinese Clinical Trail Registry (www.Chictr.org.cn) on 20, November 2014
34
35 116 with a trial identification of ChiCTR-IOR-14005588. Protocol of this trial was
36
37 117 approved on 25 August 2014.
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43 118 **Trial design and setting**
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46
47 119 This study is a 3-year, prospective, randomized, single-center, noninferiority
48
49 120 trial comparing clinical outcomes and postoperative complications between
50
51 121 trabeculotomy and CTT in treating PCG with an HCD of 12- 14 mm. Eligible
52
53 122 patients will be enrolled and randomly assigned to receive either
54
55 123 trabeculotomy or CTT (figure 1). The trial is being conducted at the Zhongshan
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57 124 Ophthalmic Center, Guangzhou, China.
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4 125 **Participant selection**

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7 126 Inclusion criteria

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10 127 Participants will be included if they meet all of the following criteria: (1)
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12 128 diagnosis of PCG in either eye, (2) equal to or under 3 years of age, (3) HCD
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14 129 between 12 and 14 mm, and (4) no previous intraocular surgery or laser
15
16 130 treatment.

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21 131 PCG is defined as follows:²⁰

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25 132 1. Age \leq 3 years old.

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28 133 2. IOP $>$ 21 mmHg.

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31 134 3. Absence of other ocular or systemic diseases.

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33
34 135 4. Combined with one or more of the following clinical signs: (1) corneal
35
36 136 findings: Haab's striae, corneal edema, corneal diameters $>$ 11 mm in the
37
38 137 newborns, $>$ 12mm in children younger than 1 year old, and $>$ 13mm in children
39
40 138 older than 1 year old; (2) increased ($>$ 0.3) or asymmetric ($>$ 0.2) C/D ratio;
41
42 139 and (3) abnormally increased axial length (AL).

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48 140 Normal AL is as follows: 3 mo-3yrs: 19-22 mm.²¹

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51 141 Only one eye per patient will be enrolled. If both eyes of a patient are eligible
52
53 142 for the study, the eye with the higher baseline IOP will be selected. The
54
55 143 treatment for the fellow eye will be determined at the physician's discretion.

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60 144 Exclusion criteria

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4 145 Patients will be excluded if they meet any of the following criteria:
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7 146 ■ Inability of the patients' legal guardian to give informed consent.
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9

10 147 ■ Inability of the patient to return to the clinic for the scheduled study visits.
11
12

13 148 ■ Contraindications to anesthesia or surgery for ocular disease.
14
15

16 149 ■ Severe corneal cloudiness precluding anterior chamber visualization.
17
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19 150 ■ Secondary congenital glaucoma.
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22 151 ■ Other coexisting ocular diseases such as an abnormal cornea, congenital
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24 152 iris abnormality, congenital cataract, or retinopathy of prematurity.
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29 153 **Withdrawal criteria**
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31

32 154 1. Failure to locate or dissect Schlemm's canal by 120°.
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35 155 2. The presence of any of the following issues during the operation: severe
36
37 156 anesthesia accident, suprachoroidal hemorrhage, or a change in the
38
39 157 operative procedure according to the patient's condition.
40
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44 158 3. A desire to quit the trial.
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48 159 The withdrawal criteria described above have been established to ensure that
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50 160 the outcomes of the two procedures (trabeculotomy and CTT) will be
51
52 161 effectively analyzed for the full 3-year duration of the study.
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56 162 **Interventions**
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59 163 All surgeries will be performed under general anesthesia by attending
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4 164 surgeons.

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6
7 165 Trabeculotomy

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9
10 166 This technique has been previously described.⁸ In brief, a superior quadrant
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13 167 fornix-based flap will be created. A 3-mm × 3-mm superficial (12 o'clock)
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15
16 168 scleral flap of three-quarters thickness will be made. A 2-mm radial incision will
17
18
19 169 be made starting from the gray zone up to the white zone, followed by entering
20
21
22 170 Schlemm's canal externally. An incision will be slowly deepened until the outer
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24
25 171 wall of Schlemm's canal is opened and seeping aqueous humor is observed.
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27
28 172 Schlemm's canal will be dissected by 120° in both directions using a
29
30
31 173 trabeculotome probe. The scleral flap will then be replaced with three
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33
34 174 interrupted 10-0 nylon sutures. The conjunctival flap will also be replaced with
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36
37 175 8-0 absorbable sutures.

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40 176 CTT

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42
43 177 In the superior quadrant, CTT with MMC will be performed. A fornix-based
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45
46 178 conjunctival flap will be dissected. After dissection of a superficial (12 o'clock)
47
48
49 179 scleral flap measuring 4 × 3 mm², MMC (0.3 mg/ ml) soaked pieces of
50
51
52 180 micro sponge will be applied under the scleral flap and the conjunctiva for 3
53
54
55 181 min, and the area will then be washed thoroughly with balanced salt solution.
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57
58 182 Then, trabeculotomy will be performed as described above. Trabeculectomy
59
60 183 will be performed by cutting a 1-mm × 2-mm deep scleral flap, followed by a
184 peripheral iridectomy. The scleral flap and conjunctiva will then be replaced.

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4 185 Finally, the anterior chamber will be reformed with balanced salt solution.
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7 186 Intraoperative data, including the duration of surgery, the doses and duration
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10 187 of MMC used during the operation, anesthesia accidents, intraoperative
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12 188 complications, such as hyphema, iris/vitreous damage, and
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15 189 trabeculotomy-related problems, such as failure to identify Schlemm's canal or
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18 190 an inability to dissect Schlemm's canal by 120 degrees, will be collected.
19

20 21 191 **Postoperative treatment and patient follow-up**

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23
24 192 Patients will be treated with prednisolone acetate 1% (Allergan,
25
26
27 193 Parsippany-Troy Hills, NJ, USA) 6 times daily in combination with topical
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29
30 194 antibiotics (tobramycin 0.3%, s.a. ALCON-COUVREUR n.v) and pilocarpine
31
32 195 1% (Bausch & Lomb, Rochester, NY) 4 times daily for the first 4 weeks after
33
34
35 196 the surgery.

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38 197 Postoperative follow-up visits will be performed in the pediatric glaucoma clinic
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41 198 at Week 1, Week 2, Week 4, Month 3 and then every 3 months (± 1 weeks) for
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43
44 199 3 years. The scheduled examinations of the follow-up visits are summarized in
45
46
47 200 Table 1. Chloral hydrate 10% (0.8 ml/kg, oral or rectal administration, the
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51 201 maximum dose is 10 ml per day) will be applied to patients not compliant for
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54 202 examinations.

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57 203 If IOP is found to be high at a scheduled visit, topical antiglaucoma medication
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60 204 will be prescribed and the scheduled follow-up interval (if longer than 2 weeks)
205
206 205 will be shortened to 2 weeks. Additional surgery will be performed if the IOP is

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4 206 > 21 mmHg on maximum anti-glaucoma medications (including pilocarpine
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6 207 1%, brinzolamide 1%, and latanoprost 0.005%) in two consecutive study visits.
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For peer review only

213 Table 1 Scheduled examinations of follow-up visits.

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Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Examination	Baseline	Procedure	1 w ± 2 d	2 w ± 2 d	1 m ± 7 d	3 m ± 7 d	6 m ± 7 d	9 m ± 7 d	12 m ± 7 d	15 m ± 7 d	18 m ± 7 d	21 m ± 7 d	24 m ± 7 d	27 m ± 7 d	30 m ± 7 d	33 m ± 7 d	36 m ± 7 d
Informed consent	x																
Demographic data	x																
Medical history	x																
Physical examination	x																
IOP	x		x	x	x	x	x	x	x	x	x		x	x	x	x	x
AL	x					x	x		x		x		x		x		x
HCD	x	x			x	x	x	x	x	x	x		x	x	x	x	x
Slit lamp examination	x		x	x	x	x	x	x	x	x	x		x	x	x	x	x
Fundus photography	x					x	x		x		x		x		x		x
B-scan ultrasound*	x					x	x		x		x		x		x		x
Refraction	x					x	x		x		x		x		x		x

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VA	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Corneal transparency	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
CCT	x																x
Medications	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Reoperation					x	x	x	x	x	x	x	x	x	x	x	x	x

215 * In the event of nonvisibility of the fundus, B-scan ultrasound will be used to measure cupping. IOP, intraocular pressure; AL, axial
 216 length; HCD, horizontal corneal diameter; VA, visual acuity; CCT, central corneal thickness.

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3 217 **Outcome assessment**

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7 219 Primary outcome

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10 220 The primary outcome is the success rate in lowering IOP at 3 years after
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12 221 surgery. Success is defined as:

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15 222 1. IOP \geq 5 mmHg and \leq 21 mmHg on two consecutive follow-up visits with or
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17 223 without anti-glaucoma medications.^{5, 22}

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21 224 2. The absence of severe vision-threatening postoperative complications, such
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23 225 as suprachoroidal hemorrhage, retinal detachment or endophthalmitis.

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26 226 3. No need for additional surgical intervention to control the IOP.

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30 227 Complete success is defined as meeting success criteria without the need for
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32 228 anti-glaucoma medications. Qualified success is defined as meeting success
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34 229 criteria with the use of anti-glaucoma medications.

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39 230 Secondary outcomes

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42 231 The secondary outcomes will be evaluated by IOP reduction and changes in
43
44 232 the morphometric and functional parameters of eyeball: HCD, corneal
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46 233 transparency, CCT, C/D ratio, AL, VA, and refraction. Postoperative
47
48 234 complications, including hyphema, shallow anterior chamber, hypotony,
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50 235 surgery-related iridodialysis, complicated cataract, retinal or choroidal
51
52 236 detachment, bleb complications (leakage or infection) and endophthalmitis, will
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54 237 be evaluated and recorded.

238 **Sample size calculation**

239 The sample calculation was based on the hypothesis that the 3-year success
240 rate of trabeculotomy will be noninferior to that of CTT. Published studies have
241 shown that the success rate at the 3rd year after CTT ranges from 72.6% to
242 87%.^{1,9,23,24} We assume that the 3-year success rate of CTT will be
243 approximately 80%. Therefore, 224 subjects (112 per group) will be needed
244 to provide the trial with a power of at least 80% to demonstrate the
245 noninferiority (-15% margin) of trabeculotomy to CTT (one-sided α value:
246 0.025). Assuming a 10% loss to follow-up, a sample size of 248 participants is
247 required for this study, with 124 participants in each group.

248 **Patient recruitment and baseline data collection**

249 All subjects will first be assessed for potential participation in the study by the
250 primary investigator. Patients who gave consent to the study will be invited to
251 undergo enrollment examinations to determine enrollment status.

252 **Examinations**

253 IOP. IOP will be measured with a Tono-Pen Avia (Reichert, Depew, New York,
254 USA) under sedation with chloral hydrate 10% and topical anesthesia.
255 Although the use of anesthetic agents during examination under anesthesia
256 (EUA) may influence IOP and affect the accuracy of IOP documentation,
257 chloral hydrate has been shown to have a minimal effect on IOP in pediatric
258 ophthalmic examinations.¹⁸

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4 259 Slit-lamp examination. The condition of the anterior segment, including corneal
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6 260 clarity, corneal edema, Haab's striae, anterior chamber depth, iris, pupil, and
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9 261 lens, will be evaluated using a hand-held slit lamp (Keeler, Bucks, England).

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12 262 Corneal clarity will be recorded as mild (iris texture clearly seen), moderate (iris
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15 263 seen but texture not clearly visible), and severe (iris not visible).

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18 264 HCD. A caliper will be used to measure the HCD (white to white) by
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21 265 ophthalmologists. Participants with an HCD less than 12 mm or greater than
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24 266 14 mm will be excluded.

25
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27 267 Central corneal thickness (CCT). CCT will be measured using ultrasound
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30 268 pachymetry (IOPac, Heidelberg Engineering, Heidelberg, Germany). Topical
31
32 269 anesthetic will be used prior to the application of the ultrasonic probe to the
33
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35 270 corneal surface. All measurements were taken with the child in the supine
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38 271 position. Ten measurements will be taken for each eye, and the lowest reading
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41 272 will be recorded.

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43 273 C/D ratio. The C/D ratio will be evaluated using direct ophthalmoscopy (66
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46 274 Vision, Suzhou, China) as permitted by the media clarity. Images showing the
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49 275 C/D ratio will be obtained using a hand-held retinal camera (Kowanonmyd a-D
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51 276 III; KowaOptimedInc, Aichi, Japan) through a dilated pupil. For children with
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53
54 277 hazy media, whose fundus cannot be visualized, a B-scan ultrasound (Quantel
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57 278 Medical, CF, France) will be used to rule out any intraocular pathology and to
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59 279 detect excavation of the optic nerve head.
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4 280 Ocular biometry. Ocular biometry, including AL, anterior chamber depth, lens
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6 281 thickness, and vitreous chamber depth, will be measured using A-scan
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9 282 ultrasound (Quantel Medical, CF, France). Ten repeated measurements will be
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11 283 taken and averaged for analysis.

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15 284 Visual acuity (VA). VA will be measured using suitable procedures. Teller
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17 285 acuity cards (Vistech Consultants, Inc. Dayton, OH, USA) will be utilized at a
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19 286 distance of 55 cm in nonverbal children. The Lea symbols (Precision Vision, La
20
21 287 Salle, IL) with a test distance of 3 meters and the Early Treatment of Diabetic
22
23 288 Retinopathy Study (ETDRS) LogMAR E chart (Precision Vision, Villa Park,
24
25 289 Illinois, USA) with a test distance of 4 meters will be employed for verbal
26
27 290 children. Monocular VA will be assessed in the right eye followed by the left
28
29 291 eye. For children who cannot complete the quantified VA examinations
30
31 292 mentioned above, the ability to fix and follow light will be evaluated.

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35 293 Refractive error. Refraction will be measured by retinoscopy after cycloplegia.
36
37 294 Cycloplegia will be induced with two drops of cyclopentolate 1% instilled 5 min
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39 295 apart, with a third drop administered after 20 min. Cycloplegia will be then
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41 296 evaluated after an additional 15 min. Cycloplegia is considered complete if the
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43 297 pupil dilates to ≥ 6 mm and a light reflex is absent.²⁵

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47 298 All ophthalmological examinations described above will be performed in both
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49 299 eyes. Chloral hydrate 10% will be applied to patients not compliant for
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51 300 examinations.

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4 301 Written informed consent will be collected from each eligible participant's legal
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6 302 guardian prior to inclusion in the study. For eligible participants, demographic
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9 303 data (sex, date of birth, and laterality), family history of PCG and medical
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11 304 history (age of onset, initial syndrome, age at diagnosis, and medical
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14 305 treatment) will be recorded. Pregnancy and delivery information (gestational
15
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17 306 weeks, delivery mode, maternal drug intake and infection during pregnancy)
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20 307 will also be ascertained and recorded.

21 22 23 308 **Randomization**

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25
26 309 A randomization list was generated with the SAS V 9.3 software package (SAS
27
28 310 Institute, Cary, NC, USA) by a biostatistician who will not participate in data
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31 311 management. The 1:1 randomization procedure will be performed using
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34 312 varying block sizes. To ensure concealment, the block size will not be
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37 313 disclosed. The allocation of patients will be concealed using sequentially
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40 314 numbered, opaque sealed envelopes. A total of 248 envelopes will be
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43 315 prepared by two researchers not involved in the study. For each recruited
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46 316 patient, his/her group assignment will be revealed in the operating room on the
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49 317 day of surgery. Surgical management and intraoperative data will be collected.
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52 318 Postoperative follow-up will be performed by investigators who will not
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55 319 participate in patient care and are trained to follow-up patients prior to the
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58 320 study. The surgeon(s) and investigator(s) will not communicate with each other
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60 321 while collecting data.

322 **Data management and monitoring**

323 All data collected at the scheduled follow-up visits (Table 1) will be recorded in
324 the case report forms and entered into a digital database by trained
325 researchers. The soft copies of digital data will be stored in these devices and
326 then in a server at the end of each visit day. The completed case report forms
327 and hardcopy data forms will be kept in locked cabinets in the research center.
328 The implementation of the trial will be monitored by the principal investigator.
329 Access to the final dataset will be limited to the trial administrator and the
330 statistician.

331 **Statistical analysis**

332 All statistical analyses will be performed using SPSS 22.0 (SPSS Inc.,
333 Chicago, IL, USA). Continuous variables conformed to the normal distribution
334 will be expressed as the mean (SD). Dichotomous and nominal variables will
335 be expressed as frequencies, ordinal and discrete variables as median and
336 IQR.

337 The primary analysis will be based on the principle of intention-to-treat
338 (ITT) and will include all subjects who underwent randomization, with data
339 censored at the last schedule visit. We will perform a sensitivity analysis of the
340 post hoc worst-case scenario, in which subjects who did not complete
341 follow-up were considered failed outcomes, and a sensitivity analysis of a post
342 hoc complete-case scenario, in which only subjects who had complete data all

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4 343 through the trial will be included. We calculated 95% confidence interval for the
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6 344 estimates of the absolute differences between the two treatment groups
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9 345 regarding the 3-year success rate using the Cochran-Mantel-Haenszel
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11 346 method. Noninferiority would be met if the lower limit of the 95% CI of the
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14 347 absolute difference did not cross the prespecified noninferiority margin (-15%).
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17 348 The survival data (time-to-IOP controlled) will be analyzed using the
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19 349 Kaplan-Meier method. The log-rank test will be employed to compare curves in
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21
22 350 the trabeculotomy and CTT groups.
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25 351 Secondary outcomes will be assessed with two-sided tests. Comparisons
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28 352 of continuous variables distributed normally, such as the IOP, HCD, AL, and
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31 353 CCT will be performed between the two groups using Student's t-test. For
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33 354 continuous variables not distributed normally and for discrete variables
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36 355 (including the C/D ratio, number of anti-glaucoma drugs, and distribution of
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38 356 refractive errors) between the two groups comparison will be performed using
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41 357 Mann-Whitney U test. The Chi-square test or Fisher's exact test will be used to
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44 358 compare the proportions of the visual outcomes, and complications between
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46 359 the two surgical groups.
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49 360 **Safety consideration**

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52 361 The safety evaluations of the study will include complications associated with
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55 362 surgeries as well as drugs adverse events. The procedures and drugs used in
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58 363 the study are routinely administered in daily practice. Thus, the trial has risks
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4 364 not exceeding usual clinical care that the patients would otherwise receive.

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7 365 Throughout the study, all adverse events will be recorded and managed.

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10 366 Drug-related complications include unanticipated events caused by
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12 367 cycloplegia, anti-glaucoma drugs, and chloral hydrate. Dilation will be
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15 368 established following a slit lamp examination. Doctors will closely monitor the
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17 369 patients' pupil reflexes and vital signs after administering the medications.

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21 370 Vision-threatening complications, such as suprachoroidal hemorrhage, retinal
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23 371 detachment, and endophthalmitis, will constitute major adverse events.

24 25 26 372 **Trial status**

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30 373 Recruitment began in the first quarter of 2015. Currently, 75% of the sample
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32 374 size has been attained. It is anticipated that the study will reach the recruitment
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35 375 target of 248 participants by the fourth quarter of 2019. There are no plans for
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37 376 interim analysis.

38 39 40 377 **PATIENT AND PUBLIC INVOLVEMENT**

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44 378 Patients and public were not involved in the design of the study.

45 46 47 379 **ETHICS AND DISSEMINATION**

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51 380 This study was approved by the ethics committee of Zhongshan Ophthalmic
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53 381 Center (reference number 2014MEKY023). The study protocol was also
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56 382 reviewed by the "5010 Plan" evaluation committee at Sun Yat-sen University,
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58 383 Guangzhou, China. Every year, the evaluation committee will examine the
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4 384 study progress and its adherence to the study protocol. Any important
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6 385 modifications to the protocol will be documented in the study protocol as formal
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9 386 amendments. Such amendments will be submitted to the ethics committee of
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11 387 Zhongshan Ophthalmic Center and the “5010 Plan” evaluation committee of
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14 388 the Sun Yat-sen University for a review. The project leader will ensure that this
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17 389 study is conducted in accordance with the principles of the World Medical
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20 390 Association Declaration of Helsinki.

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23 391 The study results will be presented at national and international meetings
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25 392 on ophthalmology.

26 27 28 393 **DISCUSSION**

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32 394 This is a prospective, randomized, controlled intervention trial aims to provide
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34 395 evidence for clinicians for to better judgement regarding surgical options for
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37 396 patients with PCG. To the best of our knowledge, this trial is the largest clinical
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40 397 trial in the field of pediatric glaucoma. The findings are expected to provide
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42 398 evidence indicating whether trabeculotomy is noninferior to CTT in treating
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45 399 PCG with an HCD of 12-14 mm.

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48 400 For PCG with an HCD less than 12 mm, the anatomic abnormality of
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51 401 Schlemm’s canal is usually not significant, facilitating its identification during
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54 402 the operation. As a result, angle surgery alone is sufficient to lower IOP in
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56 403 these patients. Sampaolesi et al²⁶ proposed that trabeculotomy is suitable for
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59 404 children with PCG in whom the corneal diameter is less than 13 mm and the AL
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4 405 is less than 23 mm. Advanced PCG with an HCD greater than 14 mm is
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6 406 usually associated with a significant anatomic anomaly of the anterior drainage
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9 407 angle. The abnormally stretched anatomy of the limbus in these patients
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12 408 frequently makes it difficult to clearly identify the lumen of Schlemm's canal
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15 409 that has to be cannulated for the trabeculotomy. Thus, the success rate of
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17 410 trabeculotomy is lower in advanced PCG cases. Quigley *et al*²⁷ reported the
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19 411 results of trabeculotomy in 28 eyes with congenital glaucoma. The success
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22 412 rate in eyes with an HCD greater than 14 mm was 67% compared with 100%
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24
25 413 in eyes with a smaller HCD. Both of the conditions described above will lead to
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27 414 biases in the results. Moreover, most PCG cases in China have an HCD
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30 415 ranging from 12 mm to 14 mm,^{7,28} and these patients have a good chance of
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33 416 preserving useful VA if treated correctly.

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36 417 No unified guideline is currently available to determine PCG severity
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38 418 based on corneal diameter. Cronemberger *et al*²⁹ confirmed that a higher HCD
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41 419 will trigger higher HCD and AL at final follow-up. Kiskis *et al*³⁰ studied the HCD
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43
44 420 and AL in PCG patients and concluded that HCD measurement was a more
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46 421 reliable guide than AL in the assessment of PCG. Currently, we are unaware of
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48
49 422 any studies that compared long-term outcomes between CTT and
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52 423 trabeculotomy in PCG patients who exhibited homogeneity in terms of disease
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54
55 424 severity. After considering the above information, we selected an HCD of
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57 425 12-14 mm as an inclusion criterion. However, selection of surgical methods for
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59 426 the treatment of PCG and the evaluation of PCG severity based on HCD alone
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4 427 are issues requiring further investigation and improvement.
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7 428 With regard to IOP, we selected an IOP value of ≤ 21 mmHg as a success
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9 429 criterion based on the previous reports.^{5, 23, 31} In this study, IOP will be
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11 430 measured with Tono-pen which has been widely used in clinic for many years.
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13 431 We chose Tono-pen as the measurement by referring to the previous
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15 432 studies.³²⁻³⁴ On the other hand, Tono-pen is particularly useful with corneal
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17 433 scars or edema,³⁵ which are often seen in PCG eyes. We used Tono-pen for
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19 434 all patients at each scheduled visit, which eliminated any possibility of bias due
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21 435 to the use of different tonometry techniques in different patients.
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28 436 In conclusion, this is a large clinical trial aiming to provide evidence for the
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30 437 optimum first-line surgery for patients with PCG with an HCD of 12-14 mm. If
31
32 438 the trabeculotomy group is associated with comparable surgical success and
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34 439 fewer postoperative complications compared with CTT group, trabeculotomy
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36 440 should be recommended as a primary surgical treatment for PCG with an HCD
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38 441 of 12-14 mm, saving trabeculectomy for future intervention. In addition,
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40 442 complications associated with trabeculectomy will be reduced. The visual
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42 443 outcome in this trial may help provide insight into the effects of surgical
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44 444 methods on VA. The findings of our study are expected to provide guidance to
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46 445 clinicians weighing the benefit and risk of trabeculotomy compared to CTT for
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48 446 the treatment of PCG.
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58 447 **Acknowledgments**
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8
9 450 study.

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32 458 China.

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36 459 **Author Contributions** XL conceived the study and is the project leader for the
37
38 460 trial. XL, XXG, YFY, JJH, YMZ, XXC, JIH and LF participated in the study
39
40
41 461 design and recruited the patients. LF wrote the manuscript. XL, XXG, YTZ, and
42
43 462 XYX critically revised the manuscript. JZ designed the database system and
44
45
46 463 performed the statistics-related design. All authors read and approved the final
47
48
49 464 manuscript.

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51
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53
54 466 Clinical Research 5010 Program (2014016) and the National Natural Science
55
56
57 467 Foundation of China (81800879). The sponsor had no role in the protocol
58
59
60 468 design or conduct of this study.

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4 469 **Competing interests** None.

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7 470 **Patient consent** Obtained.

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10 471 **Ethics approval** This study was approved by the ethics committee of
11
12 472 Zhongshan Ophthalmic Center (reference number 2014MEKY023). The study
13
14 473 protocol was also reviewed by the “5010 Plan” evaluation committee at Sun
15
16 474 Yat-sen University, Guangzhou, China.

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19 475 **Provenance and peer review** Not commissioned; externally peer reviewed.

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21 476 **Data sharing statement** No additional data available.

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26 477 **REFERENCES**

- 27
28 478 1. Liu B, Huang W, He M, *et al.* An investigation on the causes of blindness
29
30 479 and low vision of students in blind school in Guangzhou [in Chinese]. *Yan*
31
32 480 *Ke Xue Bao* 2007; 23:117-20.
- 33
34
35 481 2. Mandal AK, Chakrabarti D. Update on congenital glaucoma. *Indian J*
36
37 482 *Ophthalmol* 2011;59:S148–57.
- 38
39
40 483 3. Haddad MAO, Sei M, Sampaio MW, *et al.* Causes of visual impairment in
41
42 484 children: Study of 3210 cases. *J Pediatr Ophthalmol Strabismus* 2007;44:
43
44 485 232-40.
- 45
46
47 486 4. Levy J, Tessler Z, Tamir O, *et al.* Primary congenital glaucoma. *Harefuah*
48
49 487 2004;143:876–80.
- 50
51
52 488 5. Bowman RJ, Dickerson M, Mwende J, *et al.* Outcomes of goniotomy for
53
54 489 primary congenital glaucoma in East Africa. *Ophthalmology* 2011;118:
55
56 490 236–40.

- 1
2
3
4 491 6. Morales J, Al Shahwan S, Al Odhayb S, *et al.* Current surgical options for
5
6 492 the management of pediatric glaucoma. *J Ophthalmol* 2013;2013: 1-16.
7
8
9 493 7. Zhang X, Du S, Fan Q, *et al.* Long-term surgical outcomes of primary
10
11 494 congenital glaucoma in China. *Clinics (Sao Paulo)* 2009;64:543–51.
12
13
14 495 8. Huang JL, Huang JJ, Zhong YM, *et al.* Surgical Outcomes of
15
16 496 Trabeculotomy in Newborns with Primary Congenital Glaucoma. *Chin Med*
17
18 497 *J (Engl)* 2016; 129:2178–83.
19
20
21
22 498 9. Khalil DH, Abdelhakim MA. Primary trabeculotomy compared to combined
23
24 499 trabeculectomy-trabeculotomy in congenital glaucoma: 3-year study. *Acta*
25
26 500 *Ophthalmol* 2016;94:e550-4.
27
28
29
30 501 10. Al-Hazmi A, Awad A, Zwaan J, *et al.* Correlation between surgical success
31
32 502 rate and severity of congenital glaucoma. *Br J Ophthalmol* 2005;89:449-53.
33
34
35 503 11. Hsu CR, Chen YH, Tai MC, *et al.* Combined trabeculotomy-
36
37 504 trabeculectomy using the modified Safer Surgery System augmented with
38
39 505 MMC: its long-term outcomes of glaucoma treatment in Asian children.
40
41 506 *Graefe's Arch Clin Experiment Ophthalmol* 2018;256:1187-94.
42
43
44
45 507 12. Rodrigues A M, Paranhos JA, Montezano FT, *et al.* Comparison between
46
47 508 results of trabeculectomy in primary congenital glaucoma with and without
48
49 509 the use of Mitomycin C. *J Glaucoma* 2004;13:228–32.
50
51
52
53 510 13. Ozkiris A, Tamcelik N. Long-term results of trabeculectomy with different
54
55 511 concentrations of mitomycin C in refractory developmental glaucoma. *J*
56
57 512 *Pediatr Ophthalmol Strabismus* 2005;42:97–102.
58
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3
4 513 14. Jalil A, Au L, Khan I, *et al.* Combined trabeculotomy-trabeculectomy
5
6 514 augmented with 5-fluorouracil in paediatric glaucoma. *Clin Experiment*
7
8
9 515 *Ophthalmol* 2011;39:207–14.
10
11 516 15. Biedner B.Z., Rothkoff L. Combined trabeculotomy-trabeculectomy
12
13 compared with primary trabeculotomy for congenital glaucoma. *J Pediatr*
14 517
15
16 518 *Ophthalmol Strabismus* 1998;35:49–50.
17
18 519 16. Chen TC, Chen PP, Francis BA, *et al.* Pediatric glaucoma surgery: a report
19
20 520 by the American Academy of Ophthalmology. *Ophthalmology* 2014;121:
21
22 521 2107–15.
23
24 522 17. Ghate D, Wang X. Surgical interventions for primary congenital glaucoma.
25
26 523 *Cochrane Database Syst Rev* 2015;1:CD008213.
27
28 524 18. Yu Chan JY, Choy BN, Ng AL, *et al.* Review on the management of
29
30 525 primary congenital glaucoma. *J Curr Glaucoma Pract* 2015;9:92-9.
31
32 526 19. Mandal AK, Matalia JR, Krishnaiah S. Combined trabeculotomy and
33
34 527 trabeculectomy in advanced primary developmental glaucoma with corneal
35
36 528 diameter of 14 mm or more. *Eye* 2005;20:135-43.
37
38 529 20. Thau A, Lloyd M, Freedman S, *et al.* New classification system for
39
40 530 pediatric glaucoma: implications for clinical care and a research registry.
41
42 531 *Curr Opin Ophthalmol* 2018;29:385-94.
43
44 532 21. Bach A, Villegas VM, Gold AS, *et al.* Axial length development in children.
45
46 533 *Int J Ophthalmol* 2019;12:815-9.
47
48 534 22. Lawrence SD, Netland PA. Trabeculectomy versus combined
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4 535 trabeculotomy-trabeculectomy in pediatric glaucoma. *J Pediatr Ophthalmol*
5
6 536 *Strabismus* 2012; 49: 359-65.
7
8
9 537 23. Mandal AK, Bhatia PG, Arumugam B, *et al.* Long-term surgical and visual
10
11 538 outcomes in Indian children with developmental glaucoma operated on
12
13 539 within 6 months of birth. *Ophthalmology* 2004;111:283-90.
14
15
16
17 540 24. Mandal AK, Gothwal VK, Nutheti R. Surgical outcome of primary
18
19 541 developmental glaucoma: a single surgeon's long-term experience from a
20
21 542 tertiary eye care centre in India. *Eye* 2007;17:764-74.
22
23
24
25 543 25. Negrel AD, Maul E, Pokharel GP, *et al.* Refractive error study in children:
26
27 544 sampling and measurement methods for a multi - country survey. *Am J*
28
29 545 *Ophthalmol* 2000;129:421-6.
30
31
32
33 546 26. Sampaolesi R, Zarate J, Sampaolesi JR. *The Glaucomas. v. I. Pediatric*
34
35 547 *Glaucomas. Leipzig, Germany: Springer-Verlag Berlin Heidelberg; 2009.*
36
37
38 548 27. HA Q. Childhood glaucoma: results with trabeculotomy and study of
39
40 549 reversible cupping. *Ophthalmology* 1982;89:219-26.
41
42
43 550 28. Cai Y, Li MY, Shen YY, *et al.* Long-term effect of trabeculotomy on
44
45 551 primary congenital glaucoma [in Chinese]. *Zhonghua Yan Ke Za Zhi*
46
47 552 2004;40:733-6.
48
49
50
51 553 29. Cronemberger S, Calixto N, Milhomens TGA *et al.* Effect of intraocular
52
53 554 pressure control on central corneal thickness, horizontal corneal diameter,
54
55 555 and axial length in primary congenital glaucoma. *J Pediatr Ophthalmol*
56
57 556 *Strabismus* 2014;18:433-6.
58
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4 557 30. Kiskis AA, Markowitz SN, Morin JD. Corneal diameter and axial length in
5
6 558 congenital glaucoma. *Can J Ophthalmol* 1985;20:93–7.
7
8
9 559 31. Essuman VA, Braimah IZ, Ndanu TA et al. Combined trabeculotomy and
10
11 560 trabeculectomy: outcome for primary congenital glaucoma in a West
12
13
14 561 African population. *Eye (Lond)* 2011; 25: 77-83.
15
16
17 562 32. Ben ZI, Tomkins O, Moore DB, et al. Surgical results in the management of
18
19 563 advanced primary congenital glaucoma in a rural pediatric population.
20
21
22 564 *Ophthalmology* 2011; 118: 231-5.e1.
23
24
25 565 33. Yalvac IS, Satana B, Eksioglu U, et al. Success of trabeculotomy in
26
27 566 patients with congenital glaucoma operated on within 3 months of birth.
28
29 567 *Eye (Lond)* 2007; 21: 459-64.
30
31
32 568 34. Sahin A, Tüfek A, Cingü AK, et al. The effect of I-gel™ airway on intraocular
33
34 569 pressure in pediatric patients who received sevoflurane or desflurane
35
36
37 570 during strabismus surgery. *Paediatr Anaesth* 2012; 22: 772-5.
38
39
40 571 35. Yilmaz I, Altan C, Aygit ED, et al. Comparison of three methods of
41
42 572 tonometry in normal subjects: Goldmann applanation tonometer,
43
44
45 573 non-contact airpuff tonometer, and Tono-Pen XL. *Clin Ophthalmol*
46
47 574 2014;8:1069e74.
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9 **581 Figure Legend**

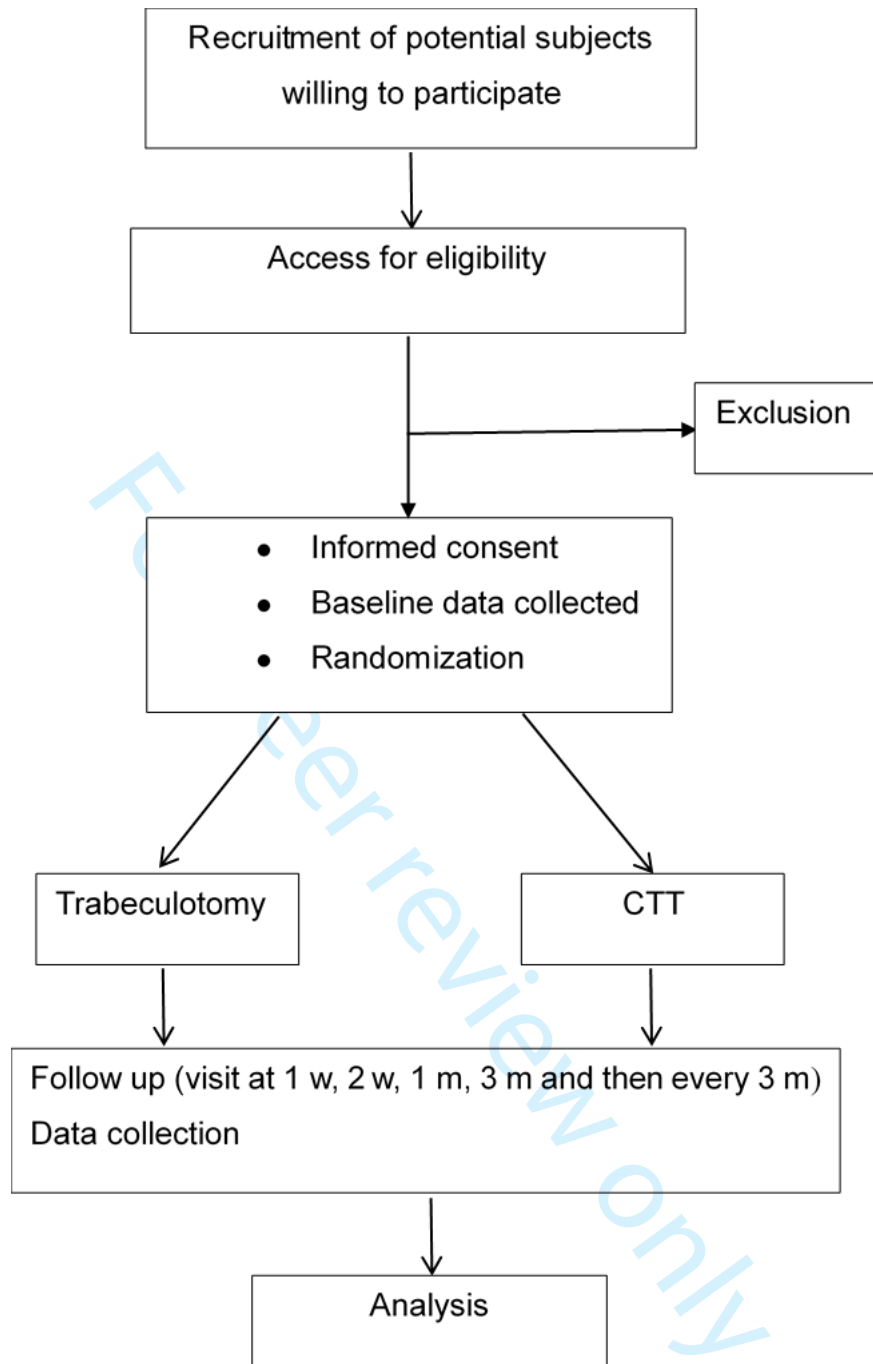
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11 582 Figure 1 Flowchart of the study. CTT, combined

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14 583 trabeculotomy-trabeculectomy.

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

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	Reporting Item	Page Number
Administrative information		
Title	#1 Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

1	Trial registration	#2a	Trial identifier and registry name. If not yet registered,	3
2			name of intended registry	
3				
4				
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6	Trial registration: data	#2b	All items from the World Health Organization Trial	N/A
7	set		Registration Data Set	
8				
9				
10				
11	Protocol version	#3	Date and version identifier	6
12				
13				
14				
15	Funding	#4	Sources and types of financial, material, and other support	24
16				
17				
18	Roles and	#5a	Names, affiliations, and roles of protocol contributors	1,24-25
19	responsibilities:			
20	contributorship			
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25	Roles and	#5b	Name and contact information for the trial sponsor	1,25
26	responsibilities:			
27	sponsor contact			
28	information			
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35	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	25
36	responsibilities:		collection, management, analysis, and interpretation of	
37	sponsor and funder		data; writing of the report; and the decision to submit the	
38			report for publication, including whether they will have	
39			ultimate authority over any of these activities	
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48	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	N/A
49	responsibilities:		centre, steering committee, endpoint adjudication	
50	committees		committee, data management team, and other individuals	
51			or groups overseeing the trial, if applicable (see Item 21a	
52			for data monitoring committee)	
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1	Introduction			
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4	Background and	#6a	Description of research question and justification for	4-6
5	rationale		undertaking the trial, including summary of relevant studies	
6			(published and unpublished) examining benefits and harms	
7			for each intervention	
8				
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11	Background and	#6b	Explanation for choice of comparators	5-6
12	rationale: choice of			
13	comparators			
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16	Objectives	#7	Specific objectives or hypotheses	6
17				
18				
19	Trial design	#8	Description of trial design including type of trial (eg, parallel	6
20			group, crossover, factorial, single group), allocation ratio,	
21			and framework (eg, superiority, equivalence, non-inferiority,	
22			exploratory)	
23				
24				
25	Methods:			
26				
27	Participants,			
28	interventions, and			
29	outcomes			
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35	Study setting	#9	Description of study settings (eg, community clinic,	6
36			academic hospital) and list of countries where data will be	
37			collected. Reference to where list of study sites can be	
38			obtained	
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44	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If	7,8
45			applicable, eligibility criteria for study centres and	
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1		individuals who will perform the interventions (eg,	
2		surgeons, psychotherapists)	
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6	Interventions:	#11a Interventions for each group with sufficient detail to allow	8-10
7			
8	description	replication, including how and when they will be	
9			
10		administered	
11			
12			
13	Interventions:	#11b Criteria for discontinuing or modifying allocated	10
14			
15	modifications	interventions for a given trial participant (eg, drug dose	
16		change in response to harms, participant request, or	
17		improving / worsening disease)	
18			
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22			
23	Interventions:	#11c Strategies to improve adherence to intervention protocols,	N/A
24			
25	adherence	and any procedures for monitoring adherence (eg, drug	
26		tablet return; laboratory tests)	
27			
28			
29			
30			
31	Interventions:	#11d Relevant concomitant care and interventions that are	10
32			
33	concomitant care	permitted or prohibited during the trial	
34			
35			
36	Outcomes	#12 Primary, secondary, and other outcomes, including the	14
37			
38		specific measurement variable (eg, systolic blood	
39		pressure), analysis metric (eg, change from baseline, final	
40		value, time to event), method of aggregation (eg, median,	
41		proportion), and time point for each outcome. Explanation	
42		of the clinical relevance of chosen efficacy and harm	
43		outcomes is strongly recommended	
44			
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53	Participant timeline	#13 Time schedule of enrolment, interventions (including any	10,
54			
55		run-ins and washouts), assessments, and visits for	Table1
56			
57		participants. A schematic diagram is highly recommended	
58			
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		(see Figure)	
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4	Sample size	#14 Estimated number of participants needed to achieve study	15
5			
6		objectives and how it was determined, including clinical and	
7			
8		statistical assumptions supporting any sample size	
9			
10		calculations	
11			
12			
13	Recruitment	#15 Strategies for achieving adequate participant enrolment to	N/A
14			
15		reach target sample size	
16			
17			
18			
19	Methods: Assignment		
20			
21	of interventions (for		
22			
23	controlled trials)		
24			
25			
26	Allocation: sequence	#16a Method of generating the allocation sequence (eg,	18
27			
28	generation	computer-generated random numbers), and list of any	
29			
30		factors for stratification. To reduce predictability of a	
31			
32		random sequence, details of any planned restriction (eg,	
33			
34		blocking) should be provided in a separate document that is	
35			
36		unavailable to those who enrol participants or assign	
37			
38		interventions	
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42			
43	Allocation	#16b Mechanism of implementing the allocation sequence (eg,	18
44			
45	concealment	central telephone; sequentially numbered, opaque, sealed	
46			
47	mechanism	envelopes), describing any steps to conceal the sequence	
48			
49		until interventions are assigned	
50			
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53	Allocation:	#16c Who will generate the allocation sequence, who will enrol	18
54			
55	implementation	participants, and who will assign participants to	
56			
57		interventions	
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1	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg,	18
2			trial participants, care providers, outcome assessors, data	
3			analysts), and how	
4				
5				
6				
7				
8	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is	N/A
9	emergency		permissible, and procedure for revealing a participant's	
10	unblinding		allocated intervention during the trial	
11				
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16	Methods: Data			
17	collection,			
18	management, and			
19	analysis			
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26	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline,	15-18,
27			and other trial data, including any related processes to	Table1
28			promote data quality (eg, duplicate measurements, training	
29			of assessors) and a description of study instruments (eg,	
30			questionnaires, laboratory tests) along with their reliability	
31			and validity, if known. Reference to where data collection	
32			forms can be found, if not in the protocol	
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43	Data collection plan:	#18b	Plans to promote participant retention and complete follow-	N/A
44	retention		up, including list of any outcome data to be collected for	
45			participants who discontinue or deviate from intervention	
46			protocols	
47				
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53	Data management	#19	Plans for data entry, coding, security, and storage,	19
54			including any related processes to promote data quality	
55			(eg, double data entry; range checks for data values).	
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1		Reference to where details of data management	
2		procedures can be found, if not in the protocol	
3			
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6	Statistics: outcomes	#20a Statistical methods for analysing primary and secondary	19-20
7			
8		outcomes. Reference to where other details of the	
9			
10		statistical analysis plan can be found, if not in the protocol	
11			
12			
13	Statistics: additional	#20b Methods for any additional analyses (eg, subgroup and	19-20
14			
15	analyses	adjusted analyses)	
16			
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18			
19	Statistics: analysis	#20c Definition of analysis population relating to protocol non-	19
20			
21	population and	adherence (eg, as randomised analysis), and any statistical	
22			
23	missing data	methods to handle missing data (eg, multiple imputation)	
24			
25			
26	Methods: Monitoring		
27			
28			
29	Data monitoring:	#21a Composition of data monitoring committee (DMC);	N/A
30			
31	formal committee	summary of its role and reporting structure; statement of	
32			
33		whether it is independent from the sponsor and competing	
34			
35		interests; and reference to where further details about its	
36			
37		charter can be found, if not in the protocol. Alternatively, an	
38			
39		explanation of why a DMC is not needed	
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44	Data monitoring:	#21b Description of any interim analyses and stopping	21
45			
46	interim analysis	guidelines, including who will have access to these interim	
47			
48		results and make the final decision to terminate the trial	
49			
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51	Harms	#22 Plans for collecting, assessing, reporting, and managing	22
52			
53		solicited and spontaneously reported adverse events and	
54			
55		other unintended effects of trial interventions or trial	
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1		conduct	
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4	Auditing	#23 Frequency and procedures for auditing trial conduct, if any,	21
5			
6		and whether the process will be independent from	
7			
8		investigators and the sponsor	
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11	Ethics and		
12			
13	dissemination		
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16	Research ethics	#24 Plans for seeking research ethics committee / institutional	21
17			
18	approval	review board (REC / IRB) approval	
19			
20			
21	Protocol	#25 Plans for communicating important protocol modifications	21-22
22			
23	amendments	(eg, changes to eligibility criteria, outcomes, analyses) to	
24		relevant parties (eg, investigators, REC / IRBs, trial	
25		participants, trial registries, journals, regulators)	
26			
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30			
31	Consent or assent	#26a Who will obtain informed consent or assent from potential	18
32		trial participants or authorised surrogates, and how (see	
33		Item 32)	
34			
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39	Consent or assent:	#26b Additional consent provisions for collection and use of	N/A
40			
41	ancillary studies	participant data and biological specimens in ancillary	
42		studies, if applicable	
43			
44			
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46			
47	Confidentiality	#27 How personal information about potential and enrolled	19
48			
49		participants will be collected, shared, and maintained in	
50		order to protect confidentiality before, during, and after the	
51		trial	
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57	Declaration of	#28 Financial and other competing interests for principal	25
58			
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1	interests		investigators for the overall trial and each study site	
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4	Data access	#29	Statement of who will have access to the final trial dataset,	19
5			and disclosure of contractual agreements that limit such	
6			access for investigators	
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11	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and for	N/A
12			compensation to those who suffer harm from trial	
13	trial care		participation	
14				
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19	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial	N/A
20			results to participants, healthcare professionals, the public,	
21	trial results		and other relevant groups (eg, via publication, reporting in	
22			results databases, or other data sharing arrangements),	
23			including any publication restrictions	
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31	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	25
32			professional writers	
33	authorship			
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36	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,	N/A
37			participant-level dataset, and statistical code	
38	reproducible research			
39				
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42	Appendices			
43				
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45	Informed consent	#32	Model consent form and other related documentation given	N/A
46			to participants and authorised surrogates	
47	materials			
48				
49				
50	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	N/A
51			biological specimens for genetic or molecular analysis in	
52			the current trial and for future use in ancillary studies, if	
53			applicable	
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BMJ Open

Trabeculotomy Versus Combined Trabeculotomy-Trabeculectomy for Primary Congenital Glaucoma: Study Protocol of a Randomized Controlled Trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-032957.R2
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Primary Subject Heading:	Research methods
Secondary Subject Heading:	Ophthalmology, Paediatrics, Surgery
Keywords:	Primary congenital glaucoma, Trabeculotomy, PCG, Combined trabeculotomy-trabeculectomy, Randomized controlled trial

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4 1 **Trabeculotomy Versus Combined Trabeculotomy-Trabeculectomy for**
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6 2 **Primary Congenital Glaucoma: Study Protocol of a Randomized**
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8 3 **Controlled Trial**
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12 4 Lei Fang,¹ Xinxing Guo,^{1,2} Yangfan Yang,¹Jian Zhang,¹ Xiangxi Chen,^{1,3}
13
14 5 Yingting Zhu,¹ Jielei Huang,^{1,4} Jingjing Huang,¹ Yimin Zhong,¹ Xiaoyu Xu,¹ Xing
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54 18 **Word count: 3896**
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4 20 **Abstract**
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7 21 **Introduction:** Trabeculotomy and combined trabeculotomy-trabeculectomy
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10 22 (CTT) are major surgical options for primary congenital glaucoma (PCG).
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12 23 However, it is unclear which of these two surgical procedures should be
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14 24 recommended as the optimum first-line treatment for PCG. This trial aims to
15
16 25 determine whether the outcomes of trabeculotomy are noninferior to those of
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18 26 CTT in moderate PCG with a horizontal corneal diameter (HCD) of 12-14 mm.
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23 27 **Methods and analysis:** This is a 3-year, noninferiority, prospective,
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25 28 randomized controlled trial. We plan to recruit 248 participants (aged ≤ 3 years)
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27 29 with PCG with an HCD of 12-14 mm from the Department of Glaucoma,
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29 30 Zhongshan Ophthalmic Center, Guangzhou, China. One eye per participant will
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31 31 be randomly (1:1) assigned to receive trabeculotomy or CTT. The primary
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33 32 outcome is the 3-year postoperative success rate in lowering IOP, and the
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35 33 secondary clinical outcomes will include IOP reduction, visual acuity (VA), HCD,
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37 34 central corneal thickness, axial length, cup-disc ratio, refractive error, and
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39 35 postoperative complications. Data will be analyzed by the intention-to-treat
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41 36 principle.
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50 37 **Ethical approval and dissemination:** The study protocol has been approved
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52 38 by the ethics committee of Zhongshan Ophthalmic Center (2014MEKY023) and
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54 39 the "5010 Plan" evaluation committee at Sun Yat-Sen University, Guangzhou,
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56 40 China. The results will be disseminated in international academic meetings and
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4 41 published in peer-reviewed journals.
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7 42 **Trial registration:** Chinese Clinical Trial Registry, ChiCTR-IOR-14005588;
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9 43 Date registered: 20 November 2014.
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11 44 **Keywords:** PCG, Primary congenital glaucoma, Trabeculotomy, Combined
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15 45 trabeculotomy-trabeculectomy, Randomized controlled trial
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18 46 **Article Summary**

19 20 21 47 **Strengths and limitations of this study**

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25 48 ■ The trial design is prospective, randomized and controlled with a relatively
26
27 49 large sample size, and the follow-up is comparatively long (3 years).
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31 50 ■ The study is the first randomized controlled trial to comprehensively
32
33 51 evaluate the surgical and visual outcomes of trabeculotomy and CTT in
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35 52 PCG patients with an HCD of 12 to 14 mm.
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39 53 ■ This study assesses important clinical measurements with significant
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41 54 clinical implications, including HCD, axial length, central corneal thickness,
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43 55 C/D ratio, refractive errors and VA. All data will be obtained following
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45 56 standardized protocols and assessed longitudinally.
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50 57 ■ The IOP criteria (≤ 21 mmHg) used to define glaucoma and surgical
51
52 58 success rate may be relatively high for children younger than 3 years old.
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55 56 ■ Instead of the gold applanation tonometry, IOP is measured by Tono-Pen
57
58 59 tonometry.
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61 INTRODUCTION

62 Primary congenital glaucoma (PCG) is one of main causes of blindness in
63 children. Liu *et al*¹ reported that congenital glaucoma accounted for 5.1% of all
64 congenital ocular diseases in a Chinese population. It is estimated to account
65 for 0.01–0.04% of blindness worldwide.² In India, this disease accounts for 4.2%
66 of all childhood blindness.² Haddad *et al*³ evaluated 3210 visually impaired
67 children and found that PCG was responsible for 10.2% of visual impairments.
68 Since at least 50% of eyes with PCG presenting at birth will become legally
69 blind, patients with PCG require prompt treatment and follow-up examinations
70 throughout their lives.⁴

71 Surgical intervention is the main treatment for PCG. Goniotomy and
72 trabeculotomy are considered initial procedures because of their high success
73 rates.^{5,6} However, Clear corneal is a premise for goniotomy but not necessarily
74 for trabeculotomy. Trabeculotomy reduces intraocular pressure (IOP) by tearing
75 the trabecular meshwork into the anterior chamber. Regarding complications,
76 hyphema is more common in trabeculotomy but can resolve spontaneously and
77 cause no additional problems.⁷⁻⁹

78 Combined trabeculotomy-trabeculectomy (CTT) has been advocated for
79 treating moderate to severe congenital glaucoma.¹⁰ The rationale for CTT is to
80 gain access to the dual outflow through Schlemm's canal and the
81 trabeculectomy fistula. The application of Mitomycin-C (MMC) can improve the

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4 82 surgical success rates of CTT,¹¹ which is, however, disputed by some other
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6 83 studies.^{12,13} Complications after CTT surgery, such as hyphema, bleb-related
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9 84 infections, and choroidal detachment, have been reported.¹⁴
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12 85 Although some studies have indicated that trabeculotomy and CTT are
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15 86 equally effective in lowering IOP,^{7,9,15} their results
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17 87 were inconsistent with others.^{10,16} There is a paucity of randomized controlled
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20 88 trials with large sample sizes that compare the results of trabeculotomy with
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23 89 CTT for PCG. A randomized trial conducted by Khalil *et al*⁹ included a cohort of
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25 90 28 eyes of 28 children younger than 2 years old with a mean follow-up time of
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27
28 91 3 years. They concluded that both trabeculotomy and CTT with MMC had
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31 92 similar outcomes. However, due to limitations of sample sizes, it remains
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33 93 inconclusive as which procedure is preferable.¹⁷
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36 94 The horizontal corneal diameter (HCD) is typically increased in PCG patients,
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39 95 which serves as an indication for disease severity and a key factor for surgery
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41
42 96 selection.¹⁸ In general, angle surgeries are recommended for PCG with an HCD
43
44 97 <12 mm.⁸ Trabeculectomy or CTT with or without the use of MMC is usually
45
46
47 98 chosen for advanced cases with an HCD exceeding 14 mm.^{7,19} For moderate
48
49
50 99 PCG with an HCD of 12-14 mm, trabeculotomy and CTT are the two major
51
52 100 surgical options. However, it remains unknown whether trabeculotomy, when
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55 101 compared to CTT, yields comparable results and fewer postoperative
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57 102 complications in PCG with an HCD of 12-14 mm. Therefore, we design a study
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60 103 to determine whether the clinical outcomes of trabeculotomy are noninferior to

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4 104 those of CTT for PCG with an HCD of 12-14 mm.
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7 105 **Study objectives**
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10 106 The primary outcome of our study is to compare the 3-year success rate in
11
12 107 lowering IOP between trabeculotomy and CTT in patients with PCG with an
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14 108 HCD of 12-14 mm. The secondary outcome is to assess changes in IOP and
15
16 109 the morphometric parameters of the eyeball, visual outcomes and
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18 110 postoperative complications in these two surgical procedures.
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24 111 **METHODS AND ANALYSIS**
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27 112 This protocol is developed in line with the Standard Protocol Items
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29 113 Recommendations for Interventional Trails (SPIRIT). The SPIRIT checklist for
30
31 114 the protocol is available as 'supplement'. The trial was registered at the Chinese
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33 115 Clinical Trial Registry (www.Chictr.org.cn) on 20, November 2014 with a trial
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35 116 identification of ChiCTR-IOR-14005588. Protocol of this trial was approved on
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37 117 25 August 2014.
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43 118 **Trial design and setting**
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46 119 This study is a 3-year, prospective, randomized, single-center, noninferiority
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48 120 trial comparing clinical outcomes and postoperative complications between
49
50 121 trabeculotomy and CTT in treating PCG with an HCD of 12- 14 mm. Eligible
51
52 122 patients will be enrolled and randomly assigned to receive either trabeculotomy
53
54 123 or CTT (figure 1). The trial is being conducted at the Zhongshan Ophthalmic
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56 124 Center, Guangzhou, China.
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4 125 **Participant selection**

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7 126 Inclusion criteria

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10 127 Participants will be included if they meet all of the following criteria: (1) diagnosis
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13 128 of PCG in either eye, (2) equal to or under 3 years of age, (3) HCD between 12
14
15
16 129 and 14 mm, and (4) no previous intraocular surgery or laser treatment.

17
18
19 130 PCG is defined as follows:²⁰

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21
22 131 1. Age \leq 3 years old.

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25 132 2. IOP $>$ 21 mmHg.

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27
28 133 3. Absence of other ocular or systemic diseases.

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32 134 4. Combined with one or more of the following clinical signs: (1) corneal findings:
33
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35 135 Haab's striae, corneal edema, corneal diameters $>$ 11 mm in the
36
37
38 136 newborns, $>$ 12mm in children younger than 1 year old, and $>$ 13mm in children
39
40
41 137 older than 1 year old; (2) increased ($>$ 0.3) or asymmetric ($>$ 0.2) C/D ratio; and
42
43
44 138 (3) abnormally increased axial length (AL).

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46 139 Normal AL is as follows: 3 mo-3yrs: 19-22 mm.²¹

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49 140 Only one eye per patient will be enrolled. If both eyes of a patient are eligible
50
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52 141 for the study, the eye with the higher baseline IOP will be selected. The
53
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55 142 treatment for the fellow eye will be determined at the physician's discretion.

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57 143 Exclusion criteria

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4 144 Patients will be excluded if they meet any of the following criteria:

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7 145 ■ Inability of the patients' legal guardian to give informed consent.

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10 146 ■ Inability of the patient to return to the clinic for the scheduled study visits.

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13 147 ■ Contraindications to anesthesia or surgery for ocular disease.

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16 148 ■ Severe corneal cloudiness precluding anterior chamber visualization.

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19 149 ■ Secondary congenital glaucoma.

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22 150 ■ Other coexisting ocular diseases such as an abnormal cornea, congenital
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26 151 iris abnormality, congenital cataract, or retinopathy of prematurity.

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29 152 **Withdrawal criteria**

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32 153 1. Failure to locate or dissect Schlemm's canal by 120°.

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35 154 2. The presence of any of the following issues during the operation: severe
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38 155 anesthesia accident, suprachoroidal hemorrhage, or a change in the
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41 156 operative procedure according to the patient's condition.

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44 157 3. A desire to quit the trial.

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47 158 The withdrawal criteria described above have been established to ensure that
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49
50 159 the outcomes of the two procedures (trabeculotomy and CTT) will be effectively
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53 160 analyzed for the full 3-year duration of the study.

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56 161 **Interventions**

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59 162 All surgeries will be performed under general anesthesia by 3 attending
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4 163 surgeons (XL, MBY, and MKL) who specialized in both types of surgery.
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7 164 Trabeculotomy
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10 165 This technique has been previously described.⁸ In brief, a superior quadrant
11
12 166 fornix-based flap will be created. A 3-mm × 3-mm superficial (12 o'clock) scleral
13
14 167 flap of three-quarters thickness will be made. A 2-mm radial incision will be
15
16 168 made starting from the gray zone up to the white zone, followed by entering
17
18 169 Schlemm's canal externally. An incision will be slowly deepened until the outer
19
20 170 wall of Schlemm's canal is opened and seeping aqueous humor is observed.
21
22 171 Schlemm's canal will be dissected by 120° in both directions using a
23
24 172 trabeculotome probe. The scleral flap will then be replaced with three
25
26 173 interrupted 10-0 nylon sutures. The conjunctival flap will also be replaced with
27
28 174 8-0 absorbable sutures.
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37 175 CTT
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40 176 In the superior quadrant, CTT with MMC will be performed. A fornix-based
41
42 177 conjunctival flap will be dissected. After dissection of a superficial (12 o'clock)
43
44 178 scleral flap measuring 4 × 3 mm², MMC (0.3 mg/ ml) soaked pieces of
45
46 179 micro sponge will be applied under the scleral flap and the conjunctiva for 3 min,
47
48 180 and the area will then be washed thoroughly with 30 ml of balanced salt solution.
49
50 181 Then, trabeculotomy will be performed as described above. Trabeculectomy
51
52 182 will be performed by cutting a 1-mm × 2-mm deep scleral flap, followed by a
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54 183 peripheral iridectomy. The scleral flap and conjunctiva will then be replaced.
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4 184 Finally, the anterior chamber will be reformed with balanced salt solution.
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7 185 Intraoperative data, including the duration of surgery, the same doses and
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10 186 duration of MMC used during the operation, anesthesia accidents,
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12 187 intraoperative complications, such as hyphema, iris/vitreous damage, and
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15 188 trabeculotomy-related problems, such as failure to identify Schlemm's canal or
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17
18 189 an inability to dissect Schlemm's canal by 120 degrees, will be collected.
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20 21 190 **Postoperative treatment and patient follow-up**

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24 191 Patients will be treated with prednisolone acetate 1% (Allergan, Parsippany-
25
26
27 192 Troy Hills, NJ, USA) 6 times daily in combination with topical antibiotics
28
29
30 193 (tobramycin 0.3%, s.a. ALCON-COUVREUR n.v) and pilocarpine 1% (Bausch
31
32 194 & Lomb, Rochester, NY) 4 times daily for the first 4 weeks after the surgery.
33

34
35 195 Postoperative follow-up visits will be performed in the pediatric glaucoma clinic
36
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38 196 at Week 1, Week 2, Week 4, Month 3 and then every 3 months (± 1 weeks) for
39
40
41 197 3 years. The scheduled examinations of the follow-up visits are summarized in
42
43 198 Table 1. Chloral hydrate 10% (0.8 ml/kg, oral or rectal administration, the
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45
46 199 maximum dose is 10 ml per day) will be applied to patients not compliant for
47
48 200 examinations.
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50
51 201 If IOP is found to be high at a scheduled visit, topical antiglaucoma medication
52
53
54 202 will be prescribed and the scheduled follow-up interval (if longer than 2 weeks)
55
56
57 203 will be shortened to 2 weeks. Additional surgery will be performed if the IOP is
58
59 204 > 21 mmHg on maximum anti-glaucoma medications (including pilocarpine 1%,
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4 205 brinzolamide 1%, and latanoprost 0.005%) in two consecutive study visits.
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211 Table 1 Scheduled examinations of follow-up visits.

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Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Examination	Baseline	Procedure	1 w ± 2 d	2 w ± 2 d	1 m ± 7 d	3 m ± 7 d	6 m ± 7 d	9 m ± 7 d	12 m ± 7 d	15 m ± 7 d	18 m ± 7 d	21 m ± 7 d	24 m ± 7 d	27 m ± 7 d	30 m ± 7 d	33 m ± 7 d	36 m ± 7 d
Informed consent	x																
Demographic data	x																
Medical history	x																
Physical examination	x																
IOP	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
AL	x					x	x		x		x		x				x
HCD	x	x			x	x	x	x	x	x	x	x	x	x	x	x	x
Slit lamp examination	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Fundus photography^{&}	x					x	x		x		x		x				x
B-scan ultrasound*	x					x	x		x		x		x		x		x
Refraction^{&}	x					x	x		x		x		x		x		x

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VA	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Corneal transparency	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
CCT	x																x
Medications	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Reoperation					x	x	x	x	x	x	x	x	x	x	x	x	x

213 In the event of nonvisibility of the fundus, & fundus photography and refraction will not be performed. *B-scan ultrasound will be
 214 used to measure cupping. IOP, intraocular pressure; AL, axial length; HCD, horizontal corneal diameter; VA, visual acuity; CCT,
 215 central corneal thickness.

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3 216 **Outcome assessment**

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7 218 Primary outcome

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10 219 The primary outcome is the success rate in lowering IOP at 3 years after
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12 220 surgery. Success is defined as:

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14
15 221 1. IOP \geq 5 mmHg and \leq 21 mmHg on two consecutive follow-up visits with or
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17
18 222 without anti-glaucoma medications.^{5, 22}

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20
21 223 2. The absence of severe vision-threatening postoperative complications, such
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23
24 224 as suprachoroidal hemorrhage, retinal detachment or endophthalmitis.

25
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27 225 3. No need for additional surgical intervention to control the IOP.

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30 226 Complete success is defined as meeting success criteria without the need for
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33 227 anti-glaucoma medications. Qualified success is defined as meeting success
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36 228 criteria with the use of anti-glaucoma medications.

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39 229 Secondary outcomes

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42 230 The secondary outcomes will be evaluated by IOP reduction and changes in
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44
45 231 the morphometric and functional parameters of eyeball: HCD, corneal
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47
48 232 transparency, CCT, C/D ratio, AL, VA, and refraction. Postoperative
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51 233 complications, including hyphema, shallow anterior chamber, hypotony,
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53
54 234 surgery-related iridodialysis, complicated cataract, retinal or choroidal
55
56
57 235 detachment, bleb complications (leakage or infection) and endophthalmitis, will
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59
60 236 be evaluated and recorded.

237 **Sample size calculation**

238 The sample calculation was based on the hypothesis that the 3-year success
239 rate of trabeculotomy will be noninferior to that of CTT. Published studies have
240 shown that the success rate at the 3rd year after CTT ranges from 72.6% to
241 87%.^{1,9,23,24} We assume that the 3-year success rate of CTT will be
242 approximately 80%. Therefore, 224 subjects (112 per group) will be needed
243 to provide the trial with a power of at least 80% to demonstrate the noninferiority
244 (-15% margin) of trabeculotomy to CTT (one-sided α value: 0.025). Assuming
245 a 10% loss to follow-up, a sample size of 248 participants is required for this
246 study, with 124 participants in each group.

247 **Patient recruitment and baseline data collection**

248 All subjects will first be assessed for potential participation in the study by the
249 primary investigator. Patients who gave consent to the study will be invited to
250 undergo enrollment examinations to determine enrollment status.

251 **Examinations**

252 IOP. IOP will be measured with a Tono-Pen Avia (Reichert, Depew, New York,
253 USA) under sedation with chloral hydrate 10% and topical anesthesia. Although
254 the use of anesthetic agents during examination under anesthesia (EUA) may
255 influence IOP and affect the accuracy of IOP documentation, chloral hydrate
256 has been shown to have a minimal effect on IOP in pediatric ophthalmic
257 examinations.¹⁸

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4 258 Slit-lamp examination. The condition of the anterior segment, including corneal
5
6 259 clarity, corneal edema, Haab's striae, anterior chamber depth, iris, pupil, and
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9 260 lens, will be evaluated using a hand-held slit lamp (Keeler, Bucks, England).

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11
12 261 Corneal clarity will be recorded as mild (iris texture clearly seen), moderate (iris
13
14
15 262 seen but texture not clearly visible), and severe (iris not visible).

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18 263 HCD. A caliper will be used to measure the HCD (white to white) by
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20 264 ophthalmologists. Participants with an HCD less than 12 mm or greater than 14
21
22
23 265 mm will be excluded.

24
25
26 266 Central corneal thickness (CCT). CCT will be measured using ultrasound
27
28
29 267 pachymetry (IOPac, Heidelberg Engineering, Heidelberg, Germany). Topical
30
31
32 268 anesthetic will be used prior to the application of the ultrasonic probe to the
33
34
35 269 corneal surface. All measurements were taken with the child in the supine
36
37
38 270 position. Ten measurements will be taken for each eye, and the lowest reading
39
40 271 will be recorded.

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42
43 272 C/D ratio. The C/D ratio will be evaluated using direct ophthalmoscopy (66
44
45 273 Vision, Suzhou, China) as permitted by the media clarity. Images showing the
46
47
48 274 C/D ratio will be obtained using a hand-held retinal camera (Kowanonmyd a-D
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51 275 III; KowaOptimedInc, Aichi, Japan) through a dilated pupil. For children with
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54 276 hazy media, whose fundus cannot be visualized, fundus photography will not
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56
57 277 be performed, and a B-scan ultrasound (Quantel Medical, CF, France) will be
58
59 278 used to rule out any intraocular pathology and to detect excavation of the optic
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4 279 nerve head.
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7 280 Ocular biometry. Ocular biometry, including AL, anterior chamber depth, lens
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10 281 thickness, and vitreous chamber depth, will be measured using A-scan
11
12 282 ultrasound (Quantel Medical, CF, France). Ten repeated measurements will be
13
14
15 283 taken and averaged for analysis.
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18 284 Visual acuity (VA). VA will be measured using suitable procedures. Teller acuity
19
20 285 cards (Vistech Consultants, Inc. Dayton, OH, USA) will be utilized at a distance
21
22
23 286 of 55 cm in nonverbal children. The Lea symbols (Precision Vision, La Salle, IL)
24
25
26 287 with a test distance of 3 meters and the Early Treatment of Diabetic Retinopathy
27
28 288 Study (ETDRS) LogMAR E chart (Precision Vision, Villa Park, Illinois, USA) with
29
30
31 289 a test distance of 4 meters will be employed for verbal children. Monocular VA
32
33
34 290 will be assessed in the right eye followed by the left eye. For children who
35
36 291 cannot complete the quantified VA examinations mentioned above, the ability
37
38
39 292 to fix and follow light will be evaluated.
40
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42 293 Refractive error. Refraction will be measured by retinoscopy after cycloplegia.
43
44
45 294 Cycloplegia will be induced with two drops of cyclopentolate 1% instilled 5 min
46
47
48 295 apart, with a third drop administered after 20 min. Cycloplegia will be then
49
50 296 evaluated after an additional 15 min. Cycloplegia is considered complete if the
51
52 297 pupil dilates to ≥ 6 mm and a light reflex is absent.²⁵ Refractive error will not be
53
54
55 298 evaluated when attempts to improve the view were not successful.
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58 299 All ophthalmological examinations described above will be performed in both
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4 300 eyes. Chloral hydrate 10% will be applied to patients not compliant for
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6 301 examinations.
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10 302 Written informed consent will be collected from each eligible participant's legal
11
12 303 guardian prior to inclusion in the study. For eligible participants, demographic
13
14 304 data (sex, date of birth, and laterality), family history of PCG and medical history
15
16 305 (age of onset, initial syndrome, age at diagnosis, and medical treatment) will be
17
18 306 recorded. Pregnancy and delivery information (gestational weeks, delivery
19
20 307 mode, maternal drug intake and infection during pregnancy) will also be
21
22 308 ascertained and recorded.
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28 309 **Randomization**

30 310 A randomization list was generated with the SAS V 9.3 software package (SAS
31
32 311 Institute, Cary, NC, USA) by a biostatistician who will not participate in data
33
34 312 management. The 1:1 randomization procedure will be performed using varying
35
36 313 block sizes. To ensure concealment, the block size will not be disclosed. The
37
38 314 allocation of patients will be concealed using sequentially numbered, opaque
39
40 315 sealed envelopes. A total of 248 envelopes will be prepared by two researchers
41
42 316 not involved in the study. For each recruited patient, his/her group assignment
43
44 317 will be revealed in the operating room on the day of surgery. Surgical
45
46 318 management and intraoperative data will be collected.
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50 319 Postoperative follow-up will be performed by investigators who will not
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52 320 participate in patient care and are trained to follow-up patients prior to the study.
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4 321 The surgeon(s) and investigator(s) will not communicate with each other while
5
6 322 collecting data.
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10 323 **Data management and monitoring**

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12
13 324 All data collected at the scheduled follow-up visits (Table 1) will be recorded in
14
15 325 the case report forms and entered into a digital database by trained researchers.

16
17
18 326 The soft copies of digital data will be stored in these devices and then in a server
19
20
21 327 at the end of each visit day. The completed case report forms and hardcopy
22
23 328 data forms will be kept in locked cabinets in the research center. The
24
25
26 329 implementation of the trial will be monitored by the principal investigator.

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28
29 330 Access to the final dataset will be limited to the trial administrator and the
30
31 331 statistician.
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34 332 **Statistical analysis**

35
36
37
38 333 All statistical analyses will be performed using SPSS 22.0 (SPSS Inc., Chicago,
39
40 334 IL, USA). Continuous variables conformed to the normal distribution will be
41
42
43 335 expressed as the mean (SD). Dichotomous and nominal variables will be
44
45
46 336 expressed as frequencies, ordinal and discrete variables as median and IQR.

47
48
49 337 The primary analysis will be based on the principle of intention-to-treat (ITT)
50
51 338 and will include all subjects who underwent randomization, with data censored
52
53
54 339 at the last schedule visit. We will perform a sensitivity analysis of the post hoc
55
56
57 340 worst-case scenario, in which subjects who did not complete follow-up were
58
59 341 considered failed outcomes, and a sensitivity analysis of a post hoc complete-
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4 342 case scenario, in which only subjects who had complete data all through the
5
6 343 trail will be included. We calculated 95% confidence interval for the estimates
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8
9 344 of the absolute differences between the two treatment groups regarding the 3-
10
11 345 year success rate using the Cochran-Mantel-Haenszel method. Noninferiority
12
13
14 346 would be met if the lower limit of the 95% CI of the absolute difference did not
15
16
17 347 cross the prespecified noninferiority margin (-15%). The survival data (time-to-
18
19 348 IOP controlled) will be analyzed using the Kaplan-Meier method. The log-rank
20
21
22 349 test will be employed to compare curves in the trabeculotomy and CTT groups.

23
24
25 350 Secondary outcomes will be assessed with two-sided tests. Comparisons
26
27
28 351 of continuous variables distributed normally, such as the IOP, HCD, AL, and
29
30
31 352 CCT will be performed between the two groups using Student's t-test.
32
33
34 353 Considering that the normal IOP in children is lower than that of adults, we will
35
36 354 use 18mmHg as a cut-off and compare the surgical outcomes between two
37
38 355 groups after 3 years of follow-up using Kaplan-Meier method. For continuous
39
40
41 356 variables not distributed normally and for discrete variables (including the C/D
42
43
44 357 ratio, number of anti-glaucoma drugs, and distribution of refractive errors)
45
46 358 between the two groups comparison will be performed using Mann-Whitney U
47
48
49 359 test. The Chi-square test or Fisher's exact test will be used to compare the
50
51
52 360 proportions of the visual outcomes, and complications between the two surgical
53
54 361 groups.

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57 362 **Safety consideration**
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4 363 The safety evaluations of the study will include complications associated with
5
6 364 surgeries as well as drugs adverse events. The procedures and drugs used in
7
8
9 365 the study are routinely administered in daily practice. Thus, the trial has risks
10
11 366 not exceeding usual clinical care that the patients would otherwise receive.
12
13
14 367 Throughout the study, all adverse events will be recorded and managed.
15
16

17 368 Drug-related complications include unanticipated events caused by cycloplegia,
18
19 369 anti-glaucoma drugs, and chloral hydrate. Dilation will be established following
20
21 370 a slit lamp examination. Doctors will closely monitor the patients' pupil reflexes
22
23 371 and vital signs after administering the medications.
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28 372 Vision-threatening complications, such as suprachoroidal hemorrhage, retinal
29
30 373 detachment, and endophthalmitis, will constitute major adverse events.
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33 34 374 **Trial status**

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37 375 Recruitment began in the first quarter of 2015. Currently, 75% of the sample
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39 376 size has been attained. it is anticipated that the study will reach the recruitment
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41 377 target of 248 participants by the fourth quarter of 2019. There are no plans for
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43 378 interim analysis.
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47 48 49 379 **PATIENT AND PUBLIC INVOLVEMENT**

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52 380 Patients and public were not involved in the design of the study.
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55 381 **ETHICS AND DISSEMINATION**

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58 382 This study was approved by the ethics committee of Zhongshan Ophthalmic
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4 383 Center (reference number 2014MEKY023). The study protocol was also
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6 384 reviewed by the “5010 Plan” evaluation committee at Sun Yat-sen University,
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8
9 385 Guangzhou, China. Every year, the evaluation committee will examine the
10
11 386 study progress and its adherence to the study protocol. Any important
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14 387 modifications to the protocol will be documented in the study protocol as formal
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17 388 amendments. These amendments will be submitted to the ethics committee of
18
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20 389 Zhongshan Ophthalmic Center and the “5010 Plan” evaluation committee of the
21
22 390 Sun Yat-sen University for a review. The project leader will ensure that this
23
24
25 391 study is conducted in accordance with the principles of the World Medical
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27 392 Association Declaration of Helsinki.

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30 393 The study results will be presented at national and international meetings
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33 394 on ophthalmology.

34 35 36 395 **DISCUSSION**

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39 396 This is a prospective, randomized, controlled intervention trial aims to provide
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42 397 evidence for clinicians for to better judgement regarding surgical options for
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45 398 patients with PCG. To the best of our knowledge, this trial is the largest clinical
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48 399 trial in the field of pediatric glaucoma. The findings are expected to provide
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51 400 evidence indicating whether trabeculotomy is noninferior to CTT in treating
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53 401 PCG with an HCD of 12-14 mm.

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56 402 For PCG with an HCD less than 12 mm, the anatomic abnormality of
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59 403 Schlemm’s canal is usually not significant, facilitating its identification during the
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4 404 operation. As a result, angle surgery alone is sufficient to lower IOP in these
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6 405 patients. Sampaolesi et al²⁶ proposed that trabeculotomy is suitable for children
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8 406 with PCG in whom the corneal diameter is less than 13 mm and the AL is less
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10
11 407 than 23 mm. Advanced PCG with an HCD greater than 14 mm is usually
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13
14 408 associated with a significant anatomic anomaly of the anterior drainage angle.
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16
17 409 The abnormally stretched anatomy of the limbus in these patients frequently
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19 410 makes it difficult to clearly identify the lumen of Schlemm's canal that has to be
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21
22 411 cannulated for the trabeculotomy. Thus, the success rate of trabeculotomy is
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24
25 412 lower in advanced PCG cases. Quigley et al²⁷ reported the results of
26
27 413 trabeculotomy in 28 eyes with congenital glaucoma. The success rate in eyes
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29 414 with an HCD greater than 14 mm was 67% compared with 100% in eyes with a
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31
32 415 smaller HCD. Both of the conditions described above will lead to biases in the
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34
35 416 results. Moreover, most PCG cases in China have an HCD ranging from 12 mm
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37 417 to 14 mm,^{7,28} and these patients have a good chance of preserving useful VA if
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40 418 treated correctly.

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42
43 419 No unified guideline is currently available to determine PCG severity
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45
46 420 based on corneal diameter. Cronemberger et al²⁹ confirmed that a higher HCD
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48 421 will trigger higher HCD and AL at final follow-up. Kiskis et al³⁰ studied the HCD
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50 422 and AL in PCG patients and concluded that HCD measurement was a more
51
52 423 reliable guide than AL in the assessment of PCG. Currently, we are unaware of
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54
55 424 any studies that compared long-term outcomes between CTT and
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57
58 425 trabeculotomy in PCG patients who exhibited homogeneity in terms of disease
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4 426 severity. After considering the above information, we selected an HCD of 12-
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6 427 14 mm as an inclusion criterion. However, selection of surgical methods for the
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9 428 treatment of PCG and the evaluation of PCG severity based on HCD alone are
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11 429 issues requiring further investigation and improvement.
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15 430 With regard to IOP, we selected an IOP value of ≤ 21 mmHg as a success
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17 431 criterion based on the previous reports.^{5, 23, 31} In this study, IOP will be
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19 432 measured with Tono-pen which has been widely used in clinic for many years.
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21 433 We chose Tono-pen as the measurement by referring to the previous studies.³²⁻
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23 434 ³⁴ On the other hand, Tono-pen is particularly useful with corneal scars or
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25 435 edema,³⁵ which are often seen in PCG eyes. We used Tono-pen for all patients
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27 436 at each scheduled visit, which eliminated any possibility of bias due to the use
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29 437 of different tonometry techniques in different patients.
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36 438 In conclusion, this is a large clinical trial aiming to provide evidence for the
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38 439 optimum first-line surgery for patients with PCG with an HCD of 12-14 mm. If
39
40 440 the trabeculotomy group is associated with comparable surgical success and
41
42 441 fewer postoperative complications compared with CTT group, trabeculotomy
43
44 442 should be recommended as a primary surgical treatment for PCG with an HCD
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46 443 of 12-14 mm, saving trabeculectomy for future intervention. In addition,
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48 444 complications associated with trabeculectomy will be reduced. The visual
49
50 445 outcome in this trial may help provide insight into the effects of surgical methods
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52 446 on VA. The findings of our study are expected to provide guidance to clinicians
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54 447 weighing the benefit and risk of trabeculotomy compared to CTT for the
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4 448 treatment of PCG.
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6

7 449 **Acknowledgments**
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9

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11
12
13 451 in this trial for contributing to the practical organization and execution of this
14
15
16 452 study.
17

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36 459 ⁴Department of ophthalmology, Zhongshan Aier Eye Hospital, Zhongshan,
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38
39 460 China.
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41
42 461 **Author Contributions** XL conceived the study and is the project leader for the
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44
45 462 trial. XL, XXG, YFY, JJH, YMZ, XXC, JIH and LF participated in the study design
46
47
48 463 and recruited the patients. LF wrote the manuscript. XL, XXG, YTZ, and XYX
49
50
51 464 critically revised the manuscript. JZ designed the database system and
52
53
54 465 performed the statistics-related design. All authors read and approved the final
55
56
57 466 manuscript.
58

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60

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5
6 469 Foundation of China (81800879). The sponsor had no role in the protocol
7
8
9 470 design or conduct of this study.
10

11
12 471 **Competing interests** None.
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14
15 472 **Patient consent** Obtained.
16

17
18 473 **Ethics approval** This study was approved by the ethics committee of
19
20 474 Zhongshan Ophthalmic Center (reference number 2014MEKY023). The study
21
22 475 protocol was also reviewed by the “5010 Plan” evaluation committee at Sun
23
24 476 Yat-sen University, Guangzhou, China.
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29 477 **Provenance and peer review** Not commissioned; externally peer reviewed.
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31 478 **Data sharing statement** No additional data available.
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34 479 REFERENCES

- 35
36
37 480 1. Liu B, Huang W, He M, *et al*. An investigation on the causes of blindness
38
39 481 and low vision of students in blind school in Guangzhou [in Chinese]. *Yan*
40
41 482 *Ke Xue Bao* 2007; 23:117-20.
42
43
44 483 2. Mandal AK, Chakrabarti D. Update on congenital glaucoma. *Indian J*
45
46 484 *Ophthalmol* 2011;59:S148–57.
47
48
49 485 3. Haddad MAO, Sei M, Sampaio MW, *et al*. Causes of visual impairment in
50
51 486 children: Study of 3210 cases. *J Pediatr Ophthalmol Strabismus* 2007;44:
52
53 487 232-40.
54
55
56 488 4. Levy J, Tessler Z, Tamir O, *et al*. Primary congenital glaucoma. *Harefuah*
57
58
59
60

- 1
2
3
4 489 2004;143:876–80.
5
6
7 490 5. Bowman RJ, Dickerson M, Mwende J, *et al.* Outcomes of goniotomy for
8
9 491 primary congenital glaucoma in East Africa. *Ophthalmology* 2011;118: 236–
10
11 492 40.
12
13
14 493 6. Morales J, Al Shahwan S, Al Odhayb S, *et al.* Current surgical options for
15
16 494 the management of pediatric glaucoma. *J Ophthalmol* 2013;2013: 1-16.
17
18
19 495 7. Zhang X, Du S, Fan Q, *et al.* Long-term surgical outcomes of primary
20
21 496 congenital glaucoma in China. *Clinics (Sao Paulo)* 2009;64:543–51.
22
23
24 497 8. Huang JL, Huang JJ, Zhong YM, *et al.* Surgical Outcomes of Trabeculotomy
25
26 498 in Newborns with Primary Congenital Glaucoma. *Chin Med J (Engl)* 2016;
27
28 499 129:2178–83.
29
30
31
32 500 9. Khalil DH, Abdelhakim MA. Primary trabeculotomy compared to combined
33
34 501 trabeculectomy-trabeculotomy in congenital glaucoma: 3-year study. *Acta*
35
36 502 *Ophthalmol* 2016;94:e550-4.
37
38
39
40 503 10. Al-Hazmi A, Awad A, Zwaan J, *et al.* Correlation between surgical success
41
42 504 rate and severity of congenital glaucoma. *Br J Ophthalmol* 2005;89:449-53.
43
44
45 505 11. Hsu CR, Chen YH, Tai MC, *et al.* Combined trabeculotomy-
46
47 506 trabeculectomy using the modified Safer Surgery System augmented with
48
49 507 MMC: its long-term outcomes of glaucoma treatment in Asian children.
50
51 508 *Graefe's Arch Clin Experiment Ophthalmol* 2018;256:1187-94.
52
53
54
55
56 509 12. Rodrigues A M, Paranhos JA, Montezano FT, *et al.* Comparison between
57
58 510 results of trabeculectomy in primary congenital glaucoma with and without
59
60

- 1
2
3
4 511 the use of Mitomycin C. *J Glaucoma* 2004;13:228–32.
5
6
7 512 13. Ozkiris A, Tamcelik N. Long-term results of trabeculectomy with different
8
9 513 concentrations of mitomycin C in refractory developmental glaucoma. *J*
10
11 514 *Pediatr Ophthalmol Strabismus* 2005;42:97–102.
12
13
14 515 14. Jalil A, Au L, Khan I, *et al.* Combined trabeculotomy-trabeculectomy
15
16 516 augmented with 5-fluorouracil in paediatric glaucoma. *Clin Experiment*
17
18 517 *Ophthalmol* 2011;39:207–14.
19
20
21
22 518 15. Biedner B.Z., Rothkoff L. Combined trabeculotomy-trabeculectomy
23
24 519 compared with primary trabeculotomy for congenital glaucoma. *J Pediatr*
25
26 520 *Ophthalmol Strabismus* 1998;35:49–50.
27
28
29
30 521 16. Chen TC, Chen PP, Francis BA, *et al.* Pediatric glaucoma surgery: a report
31
32 522 by the American Academy of Ophthalmology. *Ophthalmology* 2014;121:
33
34 523 2107–15.
35
36
37
38 524 17. Ghatge D, Wang X. Surgical interventions for primary congenital glaucoma.
39
40 525 *Cochrane Database Syst Rev* 2015;1:CD008213.
41
42
43 526 18. Yu Chan JY, Choy BN, Ng AL, *et al.* Review on the management of primary
44
45 527 congenital glaucoma. *J Curr Glaucoma Pract* 2015;9:92-9.
46
47
48 528 19. Mandal AK, Matalia JR, Krishnaiah S. Combined trabeculotomy and
49
50 529 trabeculectomy in advanced primary developmental glaucoma with corneal
51
52 530 diameter of 14 mm or more. *Eye* 2005;20:135-43.
53
54
55
56 531 20. Thau A, Lloyd M, Freedman S, *et al.* New classification system for pediatric
57
58 532 glaucoma: implications for clinical care and a research registry. *Curr Opin*
59
60

- 1
2
3
4 533 *Ophthalmol* 2018;29:385-94.
5
6
7 534 21. Bach A, Villegas VM, Gold AS, *et al.* Axial length development in children.
8
9 535 *Int J Ophthalmol* 2019;12:815-9.
10
11
12 536 22. Lawrence SD, Netland PA. Trabeculectomy versus combined
13
14 537 trabeculotomy-trabeculectomy in pediatric glaucoma. *J Pediatr Ophthalmol*
15
16
17 538 *Strabismus* 2012; 49: 359-65.
18
19
20 539 23. Mandal AK, Bhatia PG, Arumugam B, *et al.* Long-term surgical and visual
21
22 540 outcomes in Indian children with developmental glaucoma operated on
23
24
25 541 within 6 months of birth. *Ophthalmology* 2004;111:283-90.
26
27
28 542 24. Mandal AK, Gothwal VK, Nutheti R. Surgical outcome of primary
29
30 543 developmental glaucoma: a single surgeon's long-term experience from a
31
32
33 544 tertiary eye care centre in India. *Eye* 2007;17:764-74.
34
35
36 545 25. Negrel AD, Maul E, Pokharel GP, *et al.* Refractive error study in children:
37
38 546 sampling and measurement methods for a multi - country survey. *Am J*
39
40
41 547 *Ophthalmol* 2000;129:421-6.
42
43
44 548 26. Sampaolesi R, Zarate J, Sampaolesi JR. The Glaucomas. v. I. Pediatric
45
46 549 Glaucomas. Leipzig, Germany: Springer-Verlag Berlin Heidelberg; 2009.
47
48
49 550 27. HA Q. Childhood glaucoma: results with trabeculotomy and study of
50
51 551 reversible cupping. *Ophthalmology* 1982;89:219-26.
52
53
54 552 28. Cai Y, Li MY, Shen YY, *et al.* Long-term effect of trabeculotomy on
55
56 553 primary congenital glaucoma [in Chinese]. *Zhonghua Yan Ke Za Zhi*
57
58
59 554 2004;40:733-6.
60

- 1
2
3
4 555 29. Cronemberger S, Calixto N, Milhomens TGA et al. Effect of intraocular
5
6 556 pressure control on central corneal thickness, horizontal corneal diameter,
7
8
9 557 and axial length in primary congenital glaucoma. *J Pediatr Ophthalmol*
10
11
12 558 *Strabismus* 2014;18:433-6.
- 13
14 559 30. Kiskis AA, Markowitz SN, Morin JD. Corneal diameter and axial length in
15
16 560 congenital glaucoma. *Can J Ophthalmol* 1985;20:93–7.
- 17
18
19 561 31. Essuman VA, Braimah IZ, Ndanu TA et al. Combined trabeculotomy and
20
21 562 trabeculectomy: outcome for primary congenital glaucoma in a West African
22
23 563 population. *Eye (Lond)* 2011; 25: 77-83.
- 24
25
26
27
28 564 32. Ben ZI, Tomkins O, Moore DB, et al. Surgical results in the management of
29
30 565 advanced primary congenital glaucoma in a rural pediatric population.
31
32 566 *Ophthalmology* 2011; 118: 231-5.e1.
- 33
34
35 567 33. Yalvac IS, Satana B, Eksioğlu U, et al. Success of trabeculotomy in patients
36
37 568 with congenital glaucoma operated on within 3 months of birth. *Eye (Lond)*
38
39 569 2007; 21: 459-64.
- 40
41
42 570 34. Sahin A, Tüfek A, Cingü AK, et al. The effect of I-gel™ airway on intraocular
43
44 571 pressure in pediatric patients who received sevoflurane or desflurane during
45
46 572 strabismus surgery. *Paediatr Anaesth* 2012; 22: 772-5.
- 47
48
49 573 35. Yilmaz I, Altan C, Aygit ED, et al. Comparison of three methods of tonometry
50
51 574 in normal subjects: Goldmann applanation tonometer, non-contact airpuff
52
53 575 tonometer, and Tono-Pen XL. *Clin Ophthalmol* 2014;8:1069e74.
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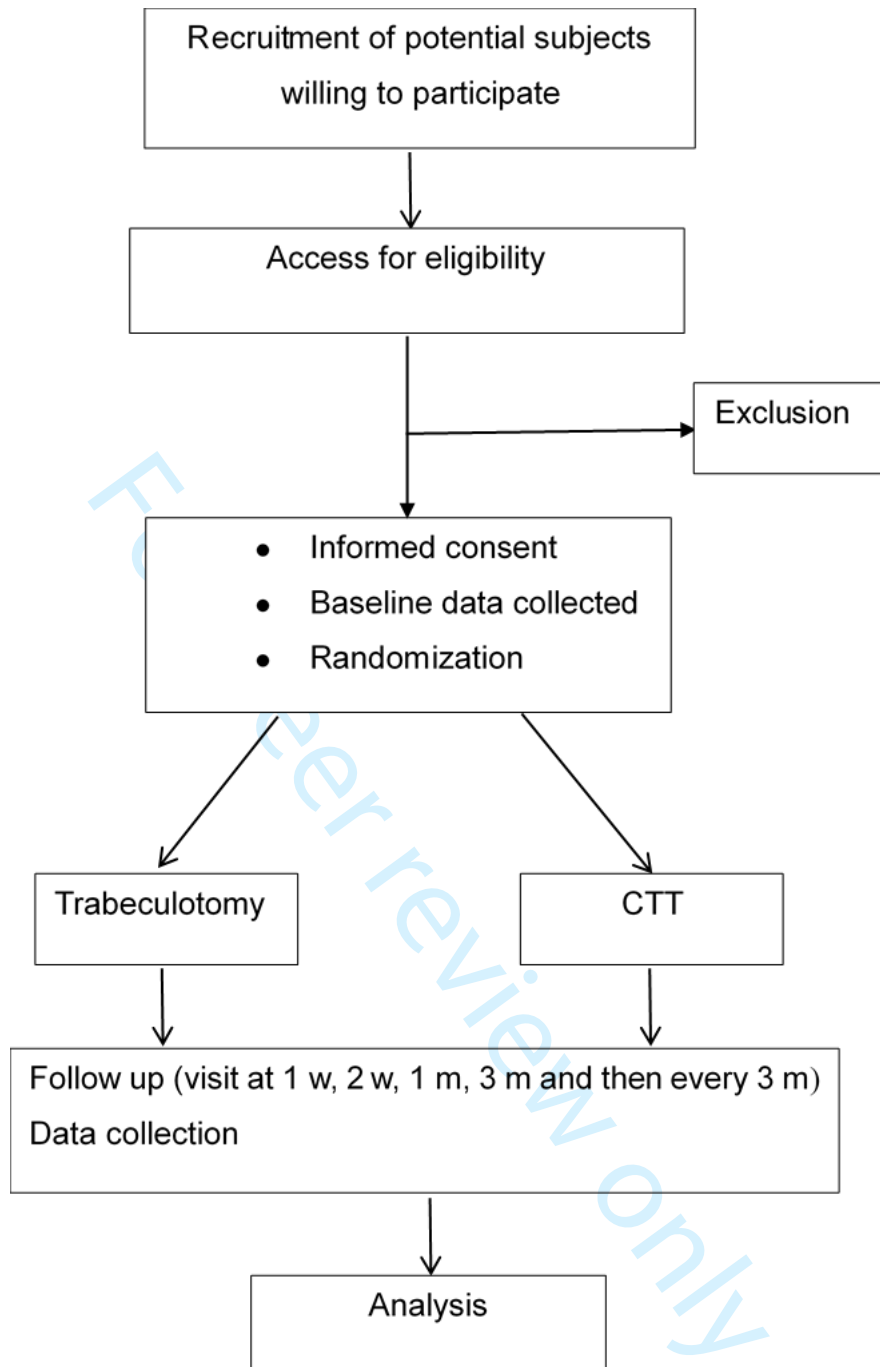
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17 582 **Figure Legend**

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19 583 Figure 1 Flowchart of the study. CTT, combined trabeculotomy-trabeculectomy.

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	6
Funding	#4	Sources and types of financial, material, and other support	24
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,24-25

1	Roles and	#5b	Name and contact information for the trial sponsor	1,25
2	responsibilities:			
3	sponsor contact			
4	information			
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6				
7	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	25
8	responsibilities:		collection, management, analysis, and interpretation of	
9	sponsor and funder		data; writing of the report; and the decision to submit the	
10			report for publication, including whether they will have	
11			ultimate authority over any of these activities	
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16	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	N/A
17	responsibilities:		centre, steering committee, endpoint adjudication	
18	committees		committee, data management team, and other individuals	
19			or groups overseeing the trial, if applicable (see Item 21a	
20			for data monitoring committee)	
21				
22				
23				
24	Introduction			
25				
26	Background and	#6a	Description of research question and justification for	4-6
27	rationale		undertaking the trial, including summary of relevant	
28			studies (published and unpublished) examining benefits	
29			and harms for each intervention	
30				
31				
32				
33	Background and	#6b	Explanation for choice of comparators	5-6
34	rationale: choice of			
35	comparators			
36				
37				
38	Objectives	#7	Specific objectives or hypotheses	6
39				
40				
41	Trial design	#8	Description of trial design including type of trial (eg,	6
42			parallel group, crossover, factorial, single group),	
43			allocation ratio, and framework (eg, superiority,	
44			equivalence, non-inferiority, exploratory)	
45				
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47				
48	Methods:			
49	Participants,			
50	interventions, and			
51	outcomes			
52				
53				
54				
55	Study setting	#9	Description of study settings (eg, community clinic,	6
56			academic hospital) and list of countries where data will be	
57			collected. Reference to where list of study sites can be	
58				
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60				

		obtained	
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2	Eligibility criteria	#10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7,8
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9	Interventions: description	#11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-10
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14	Interventions: modifications	#11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	10
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21	Interventions: adherence	#11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N/A
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27	Interventions: concomitant care	#11d Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
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31	Outcomes	#12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	14
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42	Participant timeline	#13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10, Table1
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49	Sample size	#14 Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
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55	Recruitment	#15 Strategies for achieving adequate participant enrolment to reach target sample size	N/A
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Methods:**Assignment of interventions (for controlled trials)**

Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	18
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	18
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	18
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	18
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the	15-18, Table1

		protocol	
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3	Data collection plan:	#18b Plans to promote participant retention and complete	N/A
4	retention	follow-up, including list of any outcome data to be	
5		collected for participants who discontinue or deviate from	
6		intervention protocols	
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9	Data management	#19 Plans for data entry, coding, security, and storage,	19
10		including any related processes to promote data quality	
11		(eg, double data entry; range checks for data values).	
12		Reference to where details of data management	
13		procedures can be found, if not in the protocol	
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17	Statistics: outcomes	#20a Statistical methods for analysing primary and secondary	19-20
18		outcomes. Reference to where other details of the	
19		statistical analysis plan can be found, if not in the protocol	
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21			
22	Statistics: additional	#20b Methods for any additional analyses (eg, subgroup and	19-20
23	analyses	adjusted analyses)	
24			
25			
26	Statistics: analysis	#20c Definition of analysis population relating to protocol non-	19
27	population and	adherence (eg, as randomised analysis), and any	
28	missing data	statistical methods to handle missing data (eg, multiple	
29		imputation)	
30			
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33	Methods: Monitoring		
34			
35	Data monitoring:	#21a Composition of data monitoring committee (DMC);	N/A
36	formal committee	summary of its role and reporting structure; statement of	
37		whether it is independent from the sponsor and competing	
38		interests; and reference to where further details about its	
39		charter can be found, if not in the protocol. Alternatively,	
40		an explanation of why a DMC is not needed	
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45	Data monitoring:	#21b Description of any interim analyses and stopping	21
46	interim analysis	guidelines, including who will have access to these interim	
47		results and make the final decision to terminate the trial	
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51	Harms	#22 Plans for collecting, assessing, reporting, and managing	22
52		solicited and spontaneously reported adverse events and	
53		other unintended effects of trial interventions or trial	
54		conduct	
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57	Auditing	#23 Frequency and procedures for auditing trial conduct, if	21
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any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	21
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	21-22
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	19
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	25
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	N/A
Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	25

1	authorship	professional writers	
2	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol, N/A
3	reproducible research		participant-level dataset, and statistical code
4			
5			

6 Appendices

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8	Informed consent	#32	Model consent form and other related documentation N/A
9	materials		given to participants and authorised surrogates
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12	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of N/A
13			biological specimens for genetic or molecular analysis in
14			the current trial and for future use in ancillary studies, if
15			applicable
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19 None The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution
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