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## Randomised Controlled Trial of Screening and Prophylactic Treatment to Prevent Primary Angle Closure Glaucoma.

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1 **Randomised Controlled Trial of Screening and Prophylactic Treatment to Prevent Primary**  
2 **Angle Closure Glaucoma.**

3

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9

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26

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39

40 **ABSTRACT**

41

42 **Purpose:** To determine if screening with ultrasound A-scan and prophylactic treatment of primary  
43 angle closure (PAC) with laser peripheral iridotomy (LPI) can reduce the incidence of primary angle  
44 closure glaucoma (PACG) in Mongolia.

45 **Methods:** A single-masked randomised controlled trial was initiated in 1999. 4725 volunteer  
46 Mongolian participants aged  $\geq 50$  years old from the capital Ulaanbaator or rural province of  
47 Bayanhongor were recruited, of which 128 were excluded with glaucoma. 4597 were randomly  
48 allocated to the control, no-screening arm or screening with ultrasound central anterior chamber  
49 depth (cACD), with cut off set at  $< 2.53$ mm. 685 screen positive participants were examined and  
50 angle-closure was identified by gonioscopy in 160, of which 156 were treated with prophylactic LPI.  
51 Primary outcome of incident PACG was determined using both structural and functional evidence  
52 from objective grading of paired disc photographs from baseline and follow up, objective grading of  
53 follow up visual fields and clinical examination.

54 **Results:** Six years later, 801 (17.42%) participants were known to have died, and 2047 (53.92%)  
55 were traced and underwent full ophthalmic examination. In an intention to treat analysis using  
56 available data, PACG was diagnosed in 33 participants (1.61%, 95% confidence interval (CI) =1.11-  
57 2.25%), of which 19 were in the screened group and 14 in the non-screened group (Odds Ratio (OR)  
58 =1.29, 95%CI=0.65-2.60,  $p=0.47$ ) indicating no difference between groups.

59 **Conclusions:** We were not able to identify a reduction in the 6 year incidence of PACG after  
60 screening with  $cACD < 2.53$ mm and prophylactic treatment of PAC.

61

62 **INTRODUCTION**

63 Primary angle closure glaucoma (PACG) is a major cause of blindness. By 2020, an estimated 5.9  
64 million will be blind from PACG worldwide, of which 60% will be in East Asia.<sup>1</sup> Chronic PACG is the  
65 more prevalent form of disease; with only a third having a history of an acute episode.<sup>2</sup> Historical  
66 studies have shown that prophylactic peripheral iridotomy can prevent acute angle closure in fellow  
67 eyes.<sup>3, 4</sup> More recent studies have also demonstrated that laser iridotomy can stabilise elevated  
68 intraocular pressure in non-glaucomatous eyes with occludable angles and primary angle closure  
69 (PAC).<sup>5</sup> Therefore, early detection and treatment can potentially reduce the incidence of PACG.  
70 A shallow central anterior chamber depth (cACD) is a strong risk factor for primary angle closure  
71 (PAC) in populations with a high prevalence of PACG.<sup>6, 7</sup> Measurement of cACD is effective in  
72 detecting occludable angles and PAC when compared with gonioscopy. Occludable angles and PAC  
73 therefore fulfil many of the Wilson-Jungner criteria for screening.<sup>8</sup>

74

75

76 We report the primary outcome of a randomised controlled trial of screening and prophylactic  
77 treatment of PAC to prevent PACG in Mongolia.

78

79 **METHODS**

80 Details of methods at baseline have been published.<sup>9</sup> The International Society for Geographical  
81 and Epidemiological Ophthalmology (ISGEO) criteria<sup>10</sup> were used for diagnosis of glaucoma and  
82 angle closure throughout the study This trial is reported in line with the CONSORT statement.

83

84 **Baseline (1999):**

85 Prior to field-work a computer generated allocation sequence was produced in London and stored in  
86 sealed envelopes. Mongolian volunteers aged ≥50 years old living in the capital UlaanBaator or the  
87 rural province of Bayankhongor for >3 months were recruited. After obtaining consent and  
88 randomisation, all underwent optic disc assessment to exclude those with glaucomatous optic  
89 neuropathy (GON). Optic discs of both eyes in all participants were photographed using a non-  
90 mydratic fundus camera (Canon CR4-45NM, Japan).

91

92 Participants randomised to intervention were screened with cACD measurement using a slitlamp  
93 mounted ultrasound biometer (Allergan-Humphrey model 820, Allergan, London, UK). Intraocular  
94 pressure (IOP) was measured with a Tonopen (Mentor Ophthalmics, MA, USA). A positive screening  
95 test was defined as cACD <2.53mm or IOP  $\geq$ 24mmHg. A cut off of <2.53mm produced sensitivity of  
96 77% and a specificity of 83% with a positive predictive value of 32%. This method performed better  
97 than handheld A-scan and is a relatively cheap and convenient instrument for screening.<sup>11</sup> A  
98 Tonopen IOP of 24mmHg was selected as the mean plus two standard deviations based on a  
99 random sample of 769 Mongolians. Participants who screened positive underwent a detailed  
100 ophthalmic examination including visual acuity, slitlamp biomicroscopy, Goldmann applanation  
101 tonometry (GAT) and dilated fundus examination. Visual fields were tested using a 56 point threshold  
102 strategy (Henson 3000, Topcon Medical Instruments, Newbury, UK) on patients with evidence of  
103 optic disc characteristics indicating possible GON. The drainage angle was assessed with a two  
104 mirror Goldmann lens and graded as open or occludable<sup>10</sup>. Participants with occludable or closed  
105 angles were offered bilateral laser iridotomies using a portable Yag laser (Visualas II, Carl Zeiss Ltd,  
106 Germany) prior to dilated examination. Participants randomised to the control, non-screening group  
107 received no further examination or treatment. Neither participants nor baseline staff were masked to  
108 group allocation. The flow of participants is shown in **Figure 1**. Between baseline and follow up,  
109 participants had access to the usual care provided by local services.

110

#### 111 **Follow up (2005):**

112 Participants were traced using available records from the baseline study. The names of untraceable  
113 participants were submitted to the central registration office in Ulaanbaatar to check for deaths and  
114 new addresses.

115 All traced participants received a detailed examination, similar to that performed at baseline. One  
116 ophthalmologist assessed the presence and patency of a LPI at follow up, whilst gonioscopy and  
117 dilated examination of the lens and optic disc was undertaken by a second ophthalmologist, masked  
118 to the allocation status of the participant throughout the field work. .

119

120 The same instrument and observer measured the cACD on all patients. A dilated examination was  
121 also performed on all who consented, to determine the presence of posterior synechiae, lens opacity,  
122 and assessment of the optic disc using an eyepiece mounted graticule to record cup disc ratio  
123 (CDR). All participants underwent dilated disc photography. Patients with evidence of structural  
124 glaucomatous damage or glaucoma suspects<sup>10</sup> had a visual field assessment. (**Table 1**) If the visual  
125 field was considered abnormal, the participant was advised to return for a repeat assessment.  
126 Because of the high numbers of subjects in the trial and the fact that many people travelled long  
127 distances to attend the clinic and could not stay for a long time, we were unable to perform visual  
128 fields on all participants due to the limited time available. People diagnosed with occludable angles  
129 were provided with one dose of acetazolamide 500mg and offered laser treatment the following day.  
130 All patients diagnosed with glaucoma were treated appropriately with topical medication and  
131 referred to the local ophthalmologist.  
132 Previous acute angle closure was diagnosed at follow up based on a history of sudden onset of  
133 severe pain and blurred vision with evidence of glaucomflecken, iris whorling or the presence of a PI  
134 which had not been performed at the baseline study.

135

### 136 **Study Outcomes**

137 The primary outcome was incident PACG. This was diagnosed either clinically in the field, or based  
138 on optic disc progression with visual field evidence of glaucomatous defect using objective criteria.  
139 PACG was diagnosed where there was evidence of both an occludable angle and GON with no  
140 evidence of secondary causes of glaucoma.

141

142 Optic disc progression was determined by side by side comparison of baseline and follow up  
143 monoscopic photographs at the Moorfields Image Reading Centre. The disc grading protocol was  
144 based on the Ocular Hypertension Treatment Study disc grading protocol, and used the same criteria  
145 to determine optic disc progression.<sup>12</sup> A standardised set of photographs was developed by  
146 glaucoma specialists and used to illustrate each aspect of disc progression.

147

148 Evidence of glaucomatous visual field defect was determined by two independent masked glaucoma  
149 specialists (PJF and WN), masked to the intervention allocation of the participant using standardised  
150 criteria. Agreement on visual field status was required for overall grading for each participant by both  
151 graders. When disagreement occurred, the visual fields for that participant were reassessed by both  
152 graders together and a consensus reached.

153

154 Incident PACG was identified by any or a combination of methods above, based on structural and  
155 functional changes or structural changes only. Structural changes were identified from clinical  
156 examination and/or photographic evidence of optic disc progression.

157

158 The study was conducted according to the Declaration of Helsinki, and ethical approval was obtained  
159 from the Ministry of Health, Ulaanbaator, Mongolia (baseline and follow up) and the London School of  
160 Hygiene and Tropical Medicine (follow-up). All participants gave informed consent in the local  
161 language.

162

### 163 **Statistical Methods**

164 The sample size calculations were based on a 5 year incidence of PACG of 1.4% (95% confidence  
165 interval 0.68% -2.1%). An estimated sample size of 5000 participants would have 85% power to  
166 detect a 70% reduction in risk of incident PACG and allow for 33% loss to follow up. We followed an  
167 intention to treat analysis strategy, where all patients were analysed according to randomisation  
168 group. Comparison of PACG incidence was patient based using the  $\chi^2$  test.

169

### 170 **Missing data**

171 Analyses for primary outcome were performed on observed data only. Due to the limitations of  
172 missing data from loss to follow up, we used a multiple imputation procedure<sup>13</sup> in a sensitivity  
173 analysis. The purpose of this part of the analysis was to determine whether the main results were  
174 within limits of estimates obtained from imputed data. The multiple imputation procedure substitutes  
175 missing values with several versions of imputed values. 50 sets of imputed data were generated.

176 Logistic regression models were fitted to the imputed data.



177 All statistical analyses were carried out using Stata 10 (Statcorp, Texas). The multiple imputation  
178 procedure and analysis were implemented with multiple imputation using chained equations  
179 commands "ice" and "mim".<sup>14,15</sup> This procedure is described further in the appendix.

180

## 181 **RESULTS**

182 The baseline study has previously been described in detail. Of 4,725 volunteers randomised and  
183 assessed for eligibility in 1999, 128 were excluded at baseline with glaucoma. Due to the logistical  
184 limitations and participant flow in the clinic during the baseline study, glaucoma was excluded after  
185 randomisation.

186

187 In 2005, a total 33 of 2,047 examined participants (1.61%, 95% confidence interval (CI)=1.11-2.25%)  
188 were diagnosed with incident PACG, of which 19 (1.81%, 95%CI=1.09-2.81%) were in the screened  
189 arm and 14 (1.40%, 95%CI=0.77-2.34%) were in the no screening arm, with no evidence of a  
190 statistically significant difference between groups (Odds Ratio (OR)=1.29, 95%CI=0.65-2.60,  
191  $p=0.47$ )(**Table 2**). Nineteen patients had both structural and functional evidence of PACG, of which  
192 seventeen patients had reproducible field defects. Fourteen patients were diagnosed using structural  
193 evidence only. For all types of evidence, there were greater or equal numbers of patients diagnosed  
194 with PACG in the screening arm, but there was no evidence of a statistical difference between  
195 groups from any diagnostic category. Ten of nineteen participants from the screening arm diagnosed  
196 with PACG were screen positive and examined in 1999. Of these, four had been diagnosed with  
197 occludable angles (PAC) and treated with laser PI, and six did not have occludable angles. A further  
198 nine participants in the screening arm were screen negative.

199 Forty two participants had been treated between the baseline and follow up studies: Nineteen (1.81%)  
200 were in the screened arm and 23 (2.31%) in the non-screened arm (**Table 3**). Of the 33 patients  
201 diagnosed with incident PACG, seventeen had evidence of a patent iridotomy, of which only four (of  
202 17) had been performed at baseline.

203

204 Six cases of acute angle closure (AAC) were elicited based on clinical examination and history at  
205 follow up, two of which were in the intervention group, and four in the control group. All were seen to

206 have patent peripheral iridotomies that had been performed between 1999 and 2005. The two  
207 patients with previous AAC in the screened group both had baseline cACD >2.53mm and did not  
208 undergo a slitlamp examination in 1999; both were diagnosed with PACG at follow up. Of the four  
209 patients in the control group with previous AAC, two were diagnosed with PACG and two with PAC.

210

211 Death was verified in similar proportions of participants from both arms (17.58% vs 17.27%,  $p>0.79$ ).

212 There was no evidence of localised lens opacity in any participants treated with LPI at baseline. Out

213 of 80 participants with follow up who had LPI at baseline, dilated examination was available for 75

214 right eyes and 73 left eyes. New posterior synechiae were identified in 4 right eyes and 3 left eyes.

215 Compared to participants who were examined but did not receive LPI, there was no evidence of

216 increased risk of posterior synechiae associated with LPI at baseline (4/75=5.33% vs 4/229=1.75%,

217  $p=0.09$  right eye; 3/73=4.11% vs 5/229=2.18%,  $p=0.37$  left eye).

218

219 A sensitivity analysis with imputed data to include all 4795 participants randomised supported the

220 findings from the complete case analysis. The observed odds ratios fell within the range of 95%

221 confidence intervals generated from analyses from imputed data (overall 95%CI from 0.57-2.20, all

222  $p>0.7$ )

223

224

## 225 **DISCUSSION**

226 We found that screening with cACD cut off value <2.53mm and prophylactic treatment with LPI did

227 not reduce the 6 year incidence of PACG. The overall incidence of PACG was 1.61%, 95%

228 confidence interval (CI)=1.1-2.25% which was within the range of estimates predicted at baseline

229 (0.68%-2.10%). There were more cases of AAC in the control arm compared to screening arm (4 vs.

230 2, OR=2.12, 95%CI=0.39-11.61), which could suggest that a protective effect from prophylactic LPI

231 for incident AAC although the association was also not statistically significant in this small group of

232 cases. Overall there was a low incidence of AAC (0.29%, 95% CI=0.11-0.64%).

233 No localised lens opacities or increased risk of posterior synechiae was observed in those treated

234 with LPI at baseline, which suggests that LPI is a safe prophylactic treatment.

235

236 This was a pragmatic and unique trial in a high risk population. The sample calculations allowed for  
237 33% loss to follow up, due to mortality in this older population. The observed death rate in the study  
238 population was 17.42% (95%CI=16.33-18.55%), which was lower than expected, as unrecorded  
239 deaths may have occurred.

240 Glaucoma was excluded after randomisation in line with trial protocol. Post randomisation exclusion  
241 in trials can introduce selection bias where participants are excluded in a systematic way to favour  
242 the intervention. In this trial, fewer participants were excluded with glaucoma in the control group at  
243 baseline, and greater numbers of missed glaucoma in the control group would have increased the  
244 likelihood of producing a positive result. However, objective criteria for diagnosis of glaucoma were  
245 clearly defined before the study and did not involve value judgements. Also, photographs were taken  
246 of all optic discs at baseline to determine the effect of missed glaucoma. Grading of baseline  
247 photographs suggest that out of 33 PACG cases detected at follow up, 6 may have been missed at  
248 baseline, of which 3 were in the screened group and 3 in control. These factors suggest that  
249 exclusion bias did not affect the study; furthermore, this trial did not demonstrate an effect, and this  
250 type of bias is less pertinent.

251 We were unable to trace 46% of participants thought to be still alive. This was partly due to  
252 unexpected social changes including renumbering dwellings in the outskirts of Ulaanbaatar. We  
253 examined differences in baseline characteristics between participants with and without follow up.  
254 Traced participants were older and more likely to be male, but there were no differences in screening  
255 IOP or CDR at baseline between groups (right CDR: 0.31 without follow up and 0.30 with follow up).  
256 As baseline IOP and CDR were associated with incident PACG, these results would suggest that  
257 there were no observable clinical differences between groups in ocular parameters. Assuming that  
258 there were no differences between groups with and without follow up with respect to primary  
259 outcome; then the effect on the trial would be loss of power. With the observed follow up, the  
260 effective power for this trial would have been 56%. In order to address the loss to follow up, we used  
261 multiple imputation as part of a sensitivity analysis with different imputation models, and the results  
262 supported the observations from the complete case analysis. This suggests that a plausible estimate

263 was obtained despite the loss to follow up, however, in this instance, it cannot compensate for the  
264 missing data.

265 Sixty nine more participants in the control arm were not followed up. People in the control group who  
266 were not screened may be less likely to remember their participation in the study and therefore less  
267 likely to return. If there were many cases of PACG in this group, then an effect may have occurred  
268 but not detected. However, assuming a high incidence of 2.1% ,(based on estimated incidence of  
269 1.4%, 95%CI= 0.68-2.1%), there would only have been an additional 1-2 cases of glaucoma. A  
270 further 17 cases would be required in the control group to detect a statistically significant difference. It  
271 is very unlikely that the incidence of PACG in these 69 participants was nearly 25%, and for a true  
272 effect to have been missed due to unequal loss to follow up.

273 The higher incidence of PACG in the intervention group may have occurred by chance. More  
274 participants who were not screened received treatment between baseline and follow up; this may  
275 have also reduced the incidence of PACG in the control arm. However, excluding all participants with  
276 interim LPI, there remains higher incidence of PACG in the screening arm (12 screening arm, 8 in  
277 control arm). The intervention under question was both screening with cACD and prevention of  
278 PACG with prophylactic LPI treatment. Therefore, we may not have been able to identify an effect  
279 because of poor performance of cACD in detection of appropriate cases to treat, or failure of LPI to  
280 prevent PACG, or both.

281

282 Only 9 of 19 participants in the intervention group with incident PACG were screen positive at  
283 baseline, of which 4 had LPI. Shallow cACD is a risk factor for PAC and PACG. Important risk factors  
284 that are important causal factors can perform poorly as screening tests. <sup>16</sup>

285 **Figure 2** shows that there is a large overlap between the distribution of both cACD and screening  
286 IOP between participants with incident PACG and those without, which suggests that cACD may not  
287 be a good discriminatory test to detect cases that develop incident PACG in this population.

288 Previous studies which have explored screening with ACD include an observational study from  
289 Greenland.<sup>17</sup> Alsbirk identified occludable angles in 20/69 participants based on a cumulative Shaffer  
290 grade<8, which is less stringent than the present ISGEO criteria. Ten years later, 7 of the 20 (35%)  
291 with occludable angles, and 4 of the 49(8%) without occludable angles were diagnosed with ISGEO

292 equivalent of PAC (relative risk=4.3). More stringent criteria would have classified more progressive  
293 cases as non-occludable at baseline. The ISGEO criteria were used in this study, therefore, some  
294 participants who may have been at risk of progression did not receive prophylactic treatment.

295

296 Natural history studies have shown that approximately a quarter of PAC progress to PACG over five  
297 years.<sup>18</sup> **Table 4** shows the clinical progression of disease in participants referred for examination. No  
298 participants with treated occludable angles progressed to PACG and 6.7% progressed to PAC over 6  
299 years. This compares favourably to an untreated Indian population of occludable angles where 22%  
300 progressed to PAC over 5 years.<sup>19</sup> Similarly, 11.8% of participants with PAC progressed to PACG  
301 over six years in this study compared to 28.5% over 5 years in the Indian population.<sup>18</sup> Although  
302 there are differences in population and diagnostic procedures, this comparison suggest that there  
303 was a lower rate of disease progression in those treated with LPI,

#### 304 **Conclusions**

305 This trial did not demonstrate a reduction in PACG incidence by screening with ultrasound  
306 cACD<2.53mm and prophylactic treatment of PAC with LPI. The trial was marred by high loss to  
307 follow up. However, this was a pragmatic trial on screening, undertaken in a challenging  
308 environment. Screening for angle closure remains a feasible strategy, although newer technologies  
309 have been investigated as potential screening tools in this area<sup>20</sup>, and may be more effective than  
310 ultrasound cACD. There is some evidence to suggest that LPI is effective in preventing PAC  
311 progression. Further work to determine the efficacy of LPI in the prevention of PACG in those with  
312 occludable angles and PAC would remove uncertainty about this prophylactic treatment. Such trials  
313 are currently underway in East Asia.

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**Table 1: Criteria for visual field tests at follow up**

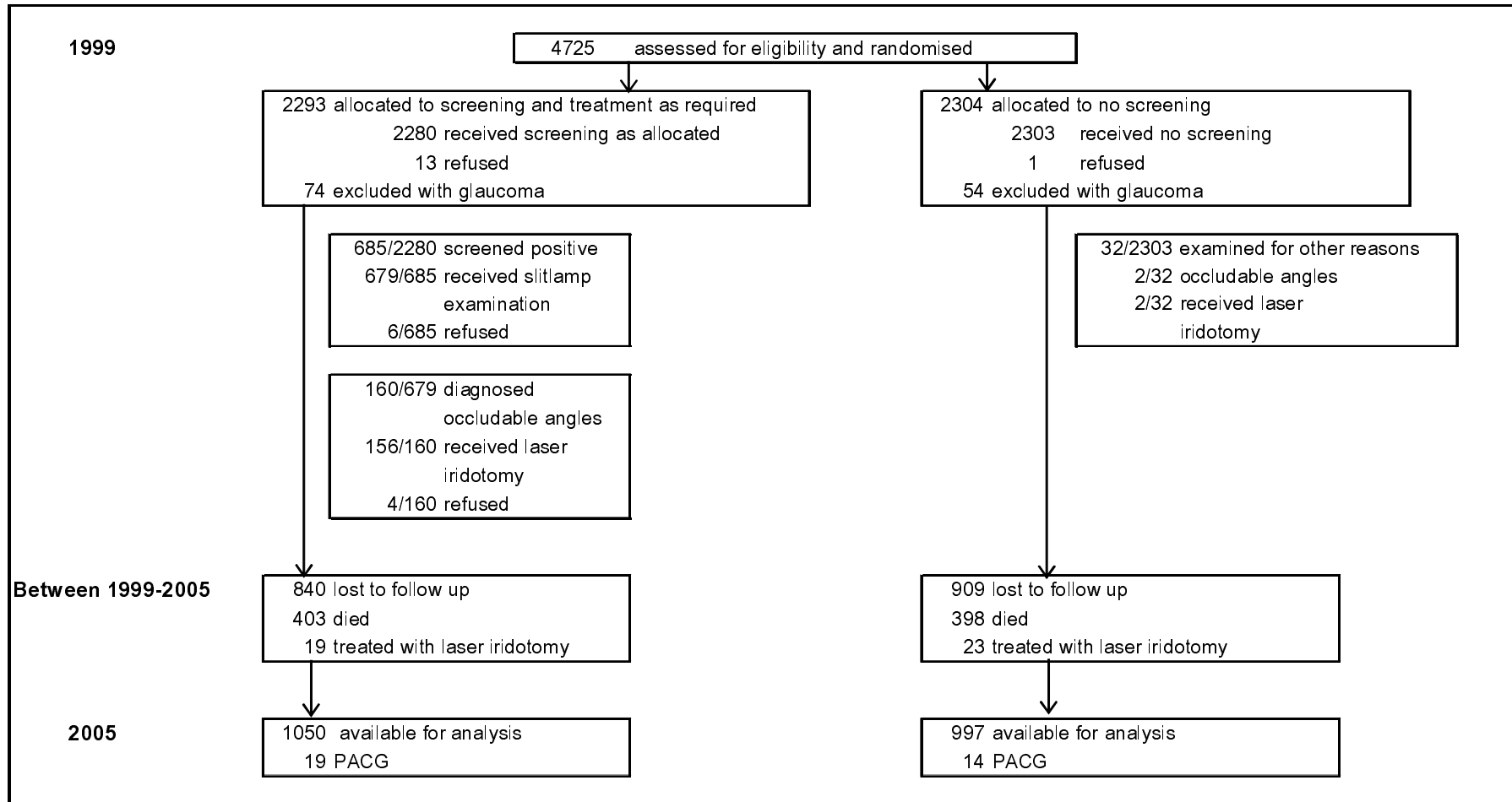
---

Disc suspects: Eyes with a CDR or CDR asymmetry $\geq 97.5^{\text{th}}$ percentile for the normal population (0.7 CDR and 0.2 asymmetry for Mongolians)
Those with optic disc margin haemorrhages
Those with an IOP $\geq 97.5^{\text{th}}$ percentile (19mmHg for Mongolians)
Those with an occludable drainage angle, but normal optic disc, IOP and no PAS

---

CDR=cup disc ratio IOP=intraocular pressure PAS=peripheral anterior synechiae

**Figure 1.** Flow chart of participants in the trial. All participants were Mongolian volunteers. Glaucoma was excluded in all randomised participants prior to receiving screening or no screening using direct ophthalmoscopy and slitlamp examination +/- visual field assessment where indicated. 32 participants from the control arm were examined due to observations on direct ophthalmoscopy. All clinical diagnoses of primary angle closure were based on ISGEO definitions.





**Table 2.** Incident cases of Primary angle closure glaucoma as identified by different methods.

Type of Evidence	Method of Identification	Right Eye	Left Eye	Either Eye	Either Eye		Risk Ratio N (95%CI)	p-value <sup>†</sup>
		N (%)	N (%)	N (%)	Group A (intervention)	Group B (control)		
		n (%)	n (%)	n (%)	n (%)	n (%)		
<b>Structural and Functional Evidence</b>	Both Clinical examination and photographic grading with Visual field grading	1 (0.05)	0 (0)	1 (0.05)	0 (0)	1 (0.10)		
	Clinical Examination with Visual field grading	14 (0.68)	9 (0.44)	18 (0.88)	11 (1.05)	7 (0.70)		
	Photographic grading with Visual Field Grading	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)		
	<b>All Structural and Functional evidence</b>	<b>15 (0.73)</b>	<b>9 (0.44)</b>	<b>19* (0.93)</b>	<b>11 (1.05)</b>	<b>8 (0.80)</b>	<b>1.31 (0.52-3.23)</b>	<b>0.56</b>
<b>Structural Evidence only</b>	Both Clinical examination and photographic grading	2 (0.10)	4 (0.20)	5 (0.24)	2 (0.19)	3 (0.30)		
	Clinical examination	7 (0.34)	6 (0.29)	8 (0.39)	5 (0.48)	3 (0.30)		
	Photographic Grading	1 (0.05)	2 (0.10)	1 (0.05)	1 (0.10)	0 (0)		
	<b>All Structural Evidence</b>	<b>10 (0.49)</b>	<b>12 (0.59)</b>	<b>14 (0.68)</b>	<b>8 (0.76)</b>	<b>6 (0.60)</b>	<b>1.27 (0.44-3.64)</b>	<b>0.66</b>
<b>Overall</b>	All types of evidence (observed data)	<b>25 (1.22)</b>	<b>21 (1.03)</b>	<b>33 (1.61)</b>	<b>19 (1.81)</b>	<b>14 (1.40)</b>	<b>1.29 (0.65-2.60)</b>	<b>0.47</b>
<b>N</b>	Total examined during follow up	<b>2047</b>	<b>2047</b>	<b>2047</b>	<b>1050</b>	<b>997</b>		

\*Of 19 cases with both structural and functional evidence, 17 cases had 2 or more visual fields and 2 cases only had 1 visual field.

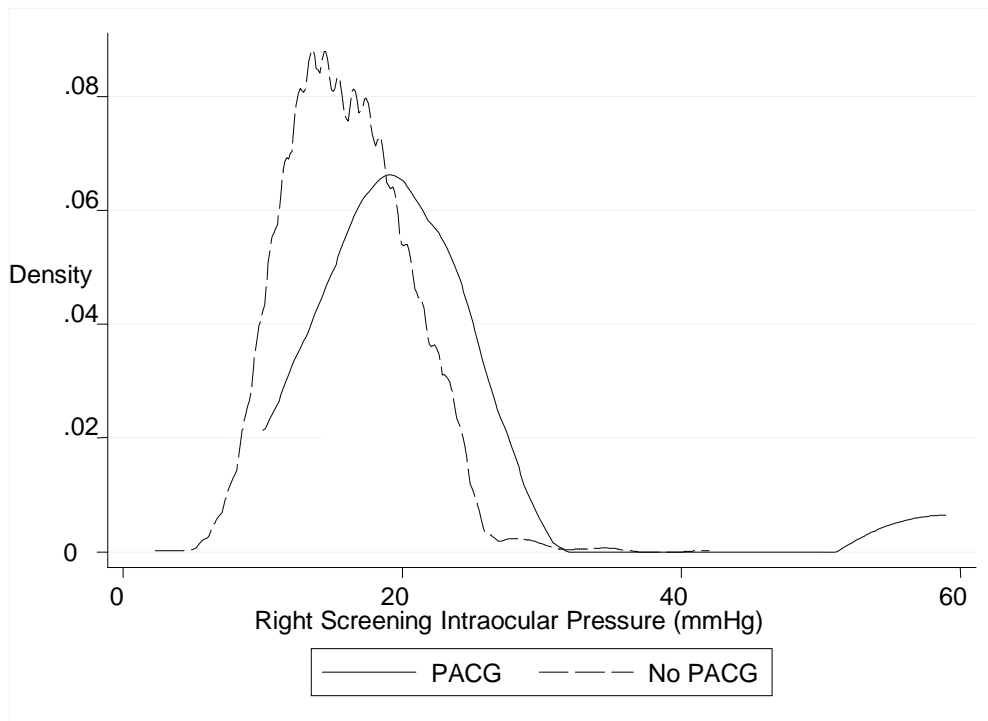
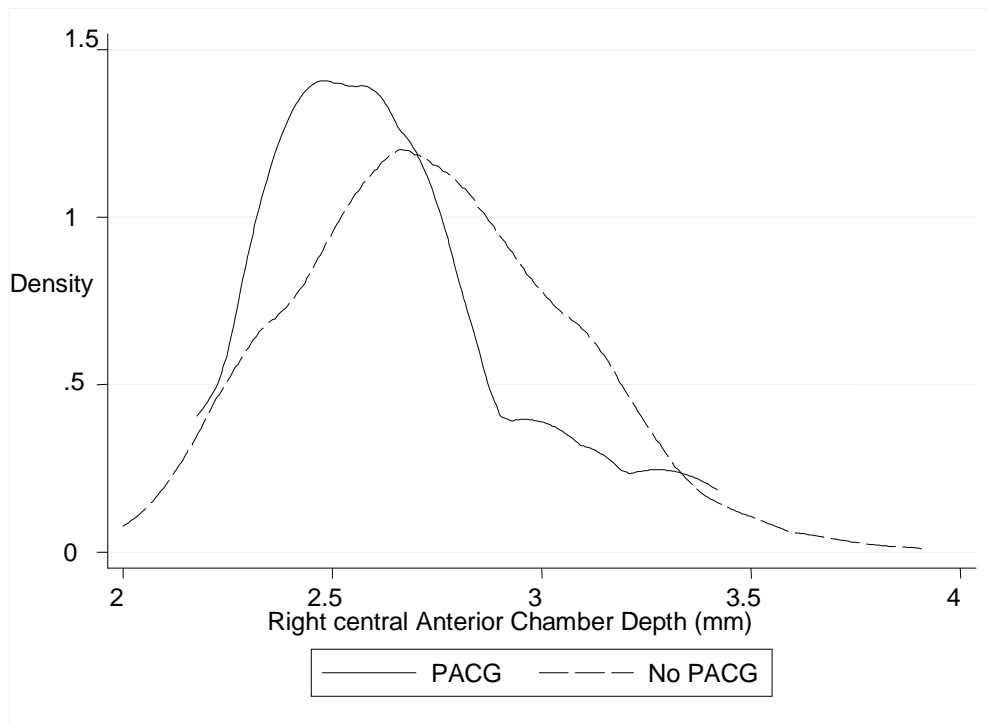
<sup>†</sup>Pearson's  $\chi^2$  test

Only participants with no evidence of secondary causes of glaucoma in the affected eye and evidence of primary angle closure using ISGEO definitions were categorised as case.

**Table 3.** Diagnoses of participants treated with peripheral iridotomy between baseline and follow up studies

	<b>Screened Group</b>	<b>Control Group</b>
	<b>n (%)</b>	<b>n (%)</b>
Primary angle closure glaucoma (PACG)	7 (36.8)	6 (26.1)
Primary angle closure (PAC)	1 (5.3)	4 (17.4)
Angle closure with pseudoexfoliation	4 (21.1)	4 (17.4)
Presumed previous occludable angles (open angles on follow up)	7 (36.8)	9 (39.2)
<b>Total</b>	<b>19</b>	<b>23</b>
Acute angle closure	2 (final diagnosis=PACG)	4 (final diagnosis, 2=PACG, 2=PAC)

**Figure 2.** Distribution of cACD and IOP in participants with incident PACG and those with no PACG at follow up. The cACD readings were calculated from the mean of three slitlamp-mounted ultrasound measurements of cACD. The IOP readings were obtained from Tonopen IOP readings. All measurements were from the right eye only.



cACD= central anterior chamber depth IOP=intraocular pressure PACG=primary angle closure glaucoma

**Table 4.** Clinical Progression of Disease from baseline diagnosis.

		Baseline Diagnosis		
		Normal	Occludable angles	PAC
<b>Follow up Diagnosis</b>	<b>Normal</b>	157 (66.5)	32 (71.1)	13* (38.2)
	<b>Occludable angles</b>	38 (16.1)	5 (11.1)	2* (5.9)
	<b>PAC</b>	9 (3.8)	3 (6.7)	10 (29.4)
	<b>PACG</b>	6 (2.7)	0 (0)	4 (11.8)
	<b>Other<sup>§</sup></b>	26 (10.6)	5 (11.0)	5 (14.6)
	<b>Total</b>	236	45	34

PAC=primary angle closure PACG=primary angle closure glaucoma PAS=peripheral anterior synechia

All participants in this group with occludable angles and PAC at baseline were treated with LPI at baseline.

\*12 participants had PAS at baseline, 7/12 were also diagnosed with PAS at followup, but with open angles.

\*None of these participants had PAS at baseline

§Other diagnoses included secondary glaucoma, open angle glaucoma, ocular hypertension and glaucoma suspects with open angles.

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## Appendix

### Multiple Imputation (MI) Procedure

Analyses for primary outcome were performed on observed data only. We used multiple imputation to estimate the potential effect of the missing data and effective loss of power in a sensitivity analysis. The multiple imputation procedure substitutes missing values with several versions of imputed values. There is an underlying assumption that missing data is missing at random, where the absence is not dependent on unobserved variables.

Logistic regression models were fitted to the imputed data.

#### Imputation

A logistic regression model was fitted using available baseline predictors of primary outcome, including age, sex, allocation group, right and left cup disc ratio(CDR), right and left central anterior chamber depth and diagnosis at baseline. The follow up variables, primary outcome, presence of an occludable angle, right and left CDR and death were also included in different models. Separate models were also generated to incorporate interactions between diagnosis and age. As not all subjects had diagnosis at baseline, this was also imputed using logistic regression using age, sex, right CDR and left CDR as predictors after conversion to a binary variable (occludable or open angle). Variables were chosen based on association with “missingness”, relevance to final analysis, and known association with outcome.

Assumptions of normality were dealt with by using the “match” option, or by bootstrap sampling. Fifty sets of imputed values for primary outcome were drawn from their distributions, conditional upon the observed data, and subsequently merged with the observed values to create fifty imputed data sets. Fifty sets were selected due to the relatively high proportion of missing values.

#### Analysis

Logistic regression analyses were performed on the imputed datasets. The resulting estimates and confidence intervals were noted. The parameter estimate from the complete case analysis (risk ratio = 1.29) was compared to the range of estimates from the imputed dataset analyses.