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# Intraocular pressure and diurnal fluctuation of open-angle glaucoma and ocular hypertension: a baseline report from the LiGHT China trial cohort

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## ABSTRACT

**Aims** To report the baseline intraocular pressure (IOP) characteristics and its diurnal fluctuation in the Laser in Glaucoma and Ocular Hypertension China cohort.

**Methods** 622 primary open-angle glaucoma (POAG) patients and 149 ocular hypertension (OHT) patients were recruited at Zhongshan Ophthalmic Center from 2015 to 2019. Standardised ocular examinations were performed including IOP measurement using the Goldmann applanation tonometer. Daytime phasing IOP was recorded at 8:00, 10:00, 11:30, 14:30, 17:00 hour.

**Results** The mean baseline IOP was 20.2 mm Hg for POAG patients and 24.4 mm Hg for OHT. Multiple regression analysis revealed that thicker central corneal thickness (CCT) was correlated with higher IOP in both POAG and OHT. Male gender and younger age were correlated with higher IOP only for POAG. As for diurnal IOP fluctuation, mean IOP fluctuation was 3.4 mm Hg in POAG eyes and 4.4 mm Hg in OHT. The peak and trough IOP occurred at 8:00 and 14:30 hour in both POAG and OHT eyes.

**Conclusions** Younger age, male gender and thicker CCT are correlated to higher IOP in POAG patients while only thicker CCT is related to higher IOP in OHT patients. Peak IOP appears mostly at early morning or late afternoon and trough value occurs mostly at early afternoon.

## INTRODUCTION

Glaucoma, a group of disease characterised by optic nerve injury and progressive visual impairment, is regarded as one of the world's leading causes of irreversible blindness. Although it is a multifactorial disease, intraocular pressure (IOP) remains the only verified modifiable risk factor for the condition. Evidence suggests that high IOP<sup>1-3</sup> and IOP fluctuation<sup>4</sup> are both potential risk factors for the onset and progression of glaucomatous optic neuropathy. Thus, it is of great clinical interest to fully understand characteristics of IOP in ocular hypertension (OHT) and primary open angle glaucoma (POAG) patients for glaucoma prevention and prognosis.

Many factors, including age,<sup>5-8</sup> central cornea thickness (CCT)<sup>9-10</sup> and spherical equivalent<sup>11-12</sup> have been reported to be associated with IOP. However, all these results are inconsistent even in similar ethnicity and most of the studies are normal population based. Relatively little information on IOP and its related factors have been available in OHT or POAG patients.<sup>13-14</sup> Since the ocular

biometry can be different between normal and glaucoma eyes,<sup>15</sup> the risk factors for normal subjects may or may not influence the IOP of POAG or OHT patients.<sup>14</sup> On the other hand, it is acknowledged that IOP is not fixed, but varies during the 24-hour cycle.<sup>16</sup> Therefore, monitoring a patient's IOP during the daytime or over a 24-hour period known as phasing has obvious pragmatic benefits in the management of glaucoma.

The Laser in Glaucoma and Ocular Hypertension (LiGHT) China Trial is a single centre, prospective, randomised controlled trial, aiming to compare eye drops vs selective laser trabeculoplasty (SLT) as the first-line treatment for newly diagnosed patients with POAG or OHT. The purpose of this paper is to report the baseline IOP characteristics and its diurnal fluctuation in the LiGHT China cohort.

## METHODS

### Subjects

Eligible patients were recruited at the Zhongshan Ophthalmic Centre from March 2015 to January 2019. A total of 771 patients aged 18 years and above who met the eligibility criteria were enrolled in the LiGHT China. The details about the LiGHT China design have been published previously.<sup>17</sup> Briefly, patients with newly diagnosed, untreated POAG in one or both eyes (including normal tension glaucoma (NTG)) or OHT qualifying for treatment according to National Institute for Health and Care Excellence guidelines<sup>18</sup> were enrolled. Exclusion criteria included contraindications to SLT, unable to accept randomisation, having visually significant cataract or were having treatment for another ophthalmic condition, having any history of treatment for POAG or OHT or previous intraocular surgery. Written informed consent was also obtained from all study participants.

### Baseline IOP measurement

The key points of the protocol have been attached as an online supplemental appendix.<sup>17</sup> The series of examinations started with a standardised questionnaire that consisted of questions on the participants' personal information, general health condition, past history, family history, lifestyle and so forth. Complete ophthalmological examinations including Goldmann applanation tonometry (GAT), Schiottz tonometer, slit-lamp examination, gonioscopy, automated visual field test and Heidelberg Retinal Tomograph disc imaging were performed.

**Table 1** Baseline characteristics of 771 subjects in the LiGHT China

Parameters	OHT (n=149)	POAG (n=622)
Age, years, mean (SD)	38.81±14.69	49.76±17.19
Gender, male (%)	72 (48.3)	364 (58.5)
IOP, mm Hg, mean (SD)*	24.4±3.2	20.4±5.4
SE, dioptres, mean (SD)*	-3.10±3.52	-2.72±3.84
CCT, $\mu$ m, mean (SD)*	544.64±29.13	536.08±33.54

\*Data from 1376 eligible eye.

CCT, central cornea thickness; IOP, intraocular pressure; LiGHT, Laser in Glaucoma and Ocular Hypertension; OHT, ocular hypertension; POAG, primary open angle glaucoma; SE, spherical equivalent.

The refractive error was calculated as the spherical equivalent measured with an autorefractor (SE=spherical +1/2 cylindrical power). The CCT was measured with type A ultrasound. GAT was performed by technicians who had been trained followed the protocol and passed the consistency assessment before recruitment. The average of two readings was recorded and more readings were required if the difference between the first two readings is >1 mm Hg. Calibration of tonometry was checked on a weekly basis. IOP phasing was not included in the protocol of the Trial but was an alternative diagnostic item. Daytime phasing IOP was recorded using GAT at five time-intervals during the day (8:00, 10:00, 11:30, 14:30, 17:00 hour). All examinations were based on standard operating procedures and performed by examiners blinded to trial.

### Statistical analysis

Definitions of the terms used to describe fluctuation are shown below: (1) Peak IOP: highest IOP recorded in the stated time period; (2) Trough IOP: lowest IOP recorded in the stated time period; (3) IOP fluctuation: Peak IOP minus trough measured in the stated time period and (4) Mean amplitude of IOP excursions (MAPE): MAPE was calculated as the arithmetic mean value of the relevant IOP fluctuations meeting this criterion.<sup>19</sup> All categorical data were represented by frequency with percentage and it was analysed by  $\chi^2$ , Fisher's exact test. Continuous data were presented by mean with SD and tested by Student's t-test. Pearson correlation analysis and multivariate regression analysis were used to analyse the association with IOP. All p values were two sided and were considered statistically significant when  $p < 0.05$ . Statistical analysis was carried out using a commercially available statistical software package (SPSS for Windows, V.26.0).

**Table 2** Baseline eye characteristics of patients eligible for both eyes

	Mean±SD	Right eyes	Left eyes	P value
POAG (n=483)	IOP, mm Hg	20.1±5.3	20.5±5.4	0.003*
	SE, dioptres	-2.82±3.93	-2.67±3.82	0.019*
	CCT, $\mu$ m	536.13±32.49	536.87±33.43	0.063
OHT (n=122)	IOP, mm Hg	24.4±3.4	24.4±3.1	0.807
	SE, dioptres	-3.33±3.51	-3.10±3.47	0.018*
	CCT, $\mu$ m	545.33±29.46	545.89±29.76	0.330

\* $P < 0.05$  level.

CCT, central cornea thickness; IOP, intraocular pressure; OHT, ocular hypertension; POAG, primary open-angle glaucoma; SE, spherical equivalent.

### RESULTS

A total of 1105 POAG eyes and 271 OHT eyes of 771 participants (both eyes were eligible in 605 subjects, only the right eye was eligible in 73 subjects, and only the left eye in 93 subjects) were enrolled in the LiGHT China. Of the 1376 eyes identified, 945 POAG eyes and 264 OHT eyes accepted daytime phasing IOP measurements.

The mean age of the POAG patients was 49.76±17.19 years, and 364 (58.5%) were male. For OHT patients, the mean age was 38.81±14.69 years, and 72 (48.3%) were male. Mean IOP was 20.4±5.4 mm Hg for eyes diagnosed with POAG and 24.4±3.2 mm Hg for OHT eyes. OHT eyes had higher IOP and thicker CCT than POAG eyes with a statistical significance ( $p < 0.001$ ) (table 1). Notably, in patients with both eyes eligible, right eyes were more myopic than left eyes in both diagnostic group (both  $p < 0.05$ ). Also, in POAG group, IOP of left eyes was higher than that of right eyes with a statistical significance ( $p = 0.003$ ) (table 2).

Pearson correlation analysis demonstrated that higher IOP was significantly correlated to thicker CCT and younger age in OHT group (all  $p < 0.05$ ). For POAG patients, younger age, male gender, thicker CCT, lower SE were all correlated with increasing IOP with a statistical significance (all  $p < 0.01$ ) (table 3). With regard to the results of multiple regression analysis, in both groups, higher IOP was still significantly correlated to thicker CCT (all  $p < 0.05$ ), but not with spherical equivalence. Additionally, a statistic significant correlation was noted between increasing IOP and male gender, younger age in POAG group (all  $p < 0.01$ ) while this correlation was not significant in OHT group (table 3).

As for the diurnal variation in IOP, the highest IOP (POAG: 18.7±5.1 mm Hg, OHT: 23.3±3.3 mm Hg) occurred at 8:00

**Table 3** Correlation coefficients and multivariate regression analysis between IOP and other variables

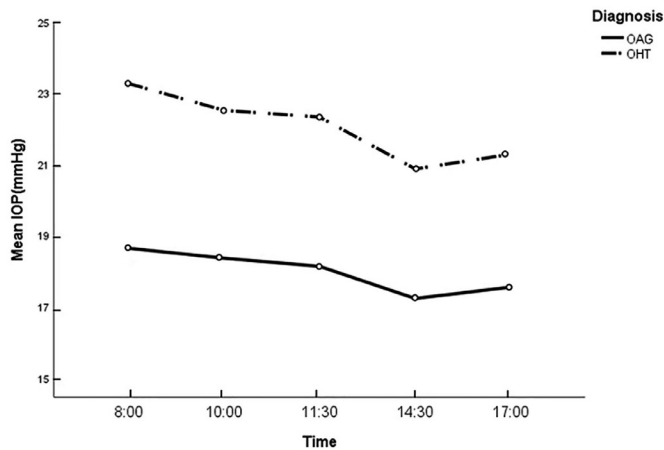
Variables	Correlation coefficients				Multivariate regression analysis			
	OHT		POAG		OHT		POAG	
	Pearson correlation	P value	Pearson correlation	P value	$\beta$	P value	$\beta$	P value
Age (years)	-0.16	0.045*	-0.23	<0.001*	-0.033	0.063	-0.066	<0.001*
Central cornea thickness ( $\mu$ m)	0.20	0.012*	0.16	<0.001*	0.019	0.022*	0.019	0.002*
Spherical equivalent (dioptres)	-0.013	0.873	-0.012	0.003*	0.049	0.501	0.047	0.472
Gender, female/male†‡	—	0.052	—	<0.001*	-0.707	0.137	-1.449	0.001*

\* $P < 0.05$  level.

†Student's t-test was used to compare the IOP of different gender.

‡Coding for dummy variables: male=0, female=1.

IOP, intraocular pressure; OHT, ocular hypertension; POAG, primary open-angle glaucoma.



**Figure 1** Diurnal variation in intraocular pressure in POAG and OHT eyes. IOP, intraocular pressure; OHT, ocular hypertension; POAG, primary open-angle glaucoma.

hour and gradually decreased during the day to reach its lowest value (POAG:  $17.3 \pm 4.5$  mm Hg, OHT:  $20.9 \pm 2.9$  mm Hg) at 14:30 hour (figure 1). The vast majority of eyes had their peak IOP recorded at 8:00 hour (POAG: 51.3%, OHT: 56.4%) and the lowest IOP values mostly occurred at 14:30 hour in both diagnostic groups (POAG: 31.7%, OHT: 42.8%). Additionally, on average, OHT eyes showed larger IOP fluctuation than POAG eyes in the daytime phasing curve ( $p < 0.001$ ). OHT eyes had higher level of MAPE than POAG eyes in the daytime phasing ( $p < 0.001$ ). In POAG group, there was no significant difference among different severities sub-groups with mean IOP ( $p = 0.631$ ), daytime peak IOP ( $p = 0.476$ ), daytime trough IOP ( $p = 0.769$ ), IOP fluctuation ( $p = 0.425$ ) or MAPE ( $p = 0.159$ ) (table 4).

A total of 1105 eyes of 622 OAG patients were enrolled in LiGHT China Trial, among which 620 eyes in 317 patients were recorded with baseline IOP lower than 21 mm Hg (51.0% in OAG). There is no detailed description or inclusion criteria of NTG in the protocol of the trial. We named them here NTG patients. The mean age of the enrolled NTG patients was  $52.69 \pm 17.16$  years old, including 155 males and 162 females. The mean baseline IOP of NTG eyes was  $16.7 \pm 2.5$  mm Hg (Mild OAG:  $16.8 \pm 2.4$  mm Hg, Mod OAG:  $16.8 \pm 2.7$  mm Hg, Severe OAG:  $16.2 \pm 2.7$  mm Hg). A total of 540 NTG eyes accepted daytime phasing IOP measurements. Similarly, the majority of eyes had their peak IOP recorded at 8:00 hour (52.6%) and the trough IOP values mostly occurred at 14:30 hour (29.6%) (table 4).

## DISCUSSION

IOP is an important indicator in the development and progression of glaucoma, thus fully understanding risk factors of elevated IOP and IOP fluctuation is of great significance. To our knowledge, this study is the first to report the baseline IOP, its associated factors and diurnal fluctuation of the POAG and OHT patients from the LiGHT China Trial.

The mean baseline IOP in OHT patients was  $24.4 \pm 3.2$  mm Hg, similar to  $24.9 \pm 2.7$  mm Hg reported in the Ocular Hypertension Treatment Study<sup>3</sup> and other studies that included OHT patients.<sup>12</sup> Average baseline IOP of POAG patients was  $20.2 \pm 5.4$  mm Hg, which was also similar to  $20.7 \pm 4.1$  mm Hg in the Early Manifest Glaucoma Trial<sup>20</sup> and other studies.<sup>21</sup> OHT eyes had significant higher baseline IOP and thicker CCT than POAG eyes in our cohort. As evidence, the results in our study have confirmed a positive relationship between IOP and CCT, which has been documented consistently in the literature.<sup>6,9,10</sup> Our data revealed that an increase of 10  $\mu\text{m}$  in CCT was associated with an increase of 0.21 mm Hg in OHT and 0.25 mm Hg in POAG, which close to a 0.23 mm Hg elevation reported in the Liwan Eye Study in China.<sup>10</sup>

The role of age and its relationship with IOP still remains controversial. Numerous studies have discovered a positive association between older age and higher IOP level.<sup>5,22</sup> However, in our study, multivariate analysis showed a significant negative correlation between age and IOP in POAG patients, consistent with the results of studies conducted in Asia populations.<sup>6,7,9</sup> Ageing is relevant to reduced production of aqueous humor,<sup>23</sup> which may be the reason for the reduction of IOP. But conversely, age-related structural changes in the trabecular meshwork can also increase the resistance to aqueous humour outflow and lead to elevated IOP.<sup>24</sup> Briefly, different changes in aqueous humour circulation may have caused those two opposite results. As for the observed gender difference in IOP of POAG patients, it was hard to explain, probably because of hormonal difference.<sup>25</sup>

Refractive error is postulated to influence IOP by altering the shape of the eye (axial elongation and scleral thinning) and subjecting it to greater stress as the spherical equivalent decreases.<sup>11,12,26</sup> Accordingly, some studies have found a negative association between IOP and SE,<sup>6,11</sup> however, this association was not significant after controlling for age.

As a physical phenomenon, IOP is known to be dynamic with short-term and long-term fluctuations. In our study, multiple IOP measurements during office time demonstrated that IOP reached a peak early in the morning and decreased steadily during the day, which was similar with other studies.<sup>27,28</sup> An average of 3.4 mm Hg IOP fluctuation in POAG eyes and 4.4 mm Hg in OHT eyes were reported in daytime phasing, and IOP fluctuation in OHT eyes was larger than that in OHT

**Table 4** Daytime phasing IOP measurements of included eyes

	Mean IOP, mm Hg (mean $\pm$ SD)	Peak IOP, mm Hg (mean $\pm$ SD)	Trough IOP, mm Hg (mean $\pm$ SD)	IOP fluctuation, mm Hg (mean $\pm$ SD)	MAPE, mm Hg (mean $\pm$ SD)
POAG (n=945 eyes)	18.0 $\pm$ 4.7	19.8 $\pm$ 5.3	16.4 $\pm$ 4.2	3.4 $\pm$ 2.2	2.4 $\pm$ 1.7
Mild POAG (n=598 eyes)	18.1 $\pm$ 4.6	20.0 $\pm$ 6.5	16.4 $\pm$ 4.1	3.6 $\pm$ 4.5	2.4 $\pm$ 1.7
Moderate POAG (n=251 eyes)	18.2 $\pm$ 5.0	20.0 $\pm$ 5.6	16.5 $\pm$ 4.5	3.5 $\pm$ 2.3	2.4 $\pm$ 1.7
Severe POAG (n=96 eyes)	17.7 $\pm$ 4.6	19.2 $\pm$ 5.0	16.1 $\pm$ 4.2	3.1 $\pm$ 1.9	2.1 $\pm$ 1.3
NTG (n=540 eyes)	15.1 $\pm$ 2.5	16.7 $\pm$ 4.9	13.8 $\pm$ 2.3	2.9 $\pm$ 4.4	1.9 $\pm$ 1.2
OHT (n=264 eyes)	22.1 $\pm$ 2.7	24.4 $\pm$ 3.2	20.0 $\pm$ 2.4	4.4 $\pm$ 2.4	2.8 $\pm$ 1.6

The severity of POAG is classified according to MD value of baseline visual field (mild POAG: MD value  $\geq 6$ ; moderate POAG:  $-6 > \text{MD value} \geq 12$ ; severe POAG: MD value  $\leq 12$ ). IOP, intraocular pressure; MAPE, mean amplitude of IOP excursion; NTG, normal tension glaucoma; OHT, ocular hypertension; POAG, primary open-angle glaucoma.



eyes, which were both within ‘normal’ range.<sup>16</sup> The MAPE of OHT eyes was also higher than that of POAG eyes. Besides, the mean MAPE of POAG eyes in our study was 4.18 mm Hg and similar to the mean MAPE reported in another study (4.16 mm Hg).<sup>19</sup> The daytime phasing demonstrated significant larger variation in IOP of OHT eyes than POAG eyes, possibly supporting the findings that IOP fluctuation might not be an independent risk factor for conversion from OHT to glaucoma.<sup>29,30</sup>

It is also interesting to mention that in both POAG and OHT patients the right eyes were more myopic than left eyes, which confirmed the findings that right eyes have longer axial length than left eyes.<sup>31</sup> However, the interocular IOP difference noted only in POAG patients was difficult for us to explain.

Potential limitations of our study should also be discussed. First, 24 hours IOP phasing with large sample size should be needed to get more accurate results, which will be shown in our other studies. Besides, risk factors in our study are still limited. Some parameters, such as ambulatory blood pressure<sup>9,11</sup> and axial length,<sup>32</sup> proved to be potential predictors of IOP were not included in our study.

In conclusion, for POAG patients, higher IOP is correlated to younger age, male gender, thicker CCT, whereas in patients with OHT, only thicker CCT seems to be risk factors of higher IOP. IOP of POAG or OHT eyes varies and reaches the peak value mostly at early morning or late afternoon and the trough value mostly at early afternoon.

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#### REFERENCES

- Leske MC, Heijl A, Hussein M, *et al*. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. *Arch Ophthalmol* 2003;121:48–56.
- Nouri-Mahdavi K, Hoffman D, Coleman AL, *et al*. Predictive factors for glaucomatous visual field progression in the Advanced Glaucoma Intervention Study. *Ophthalmology* 2004;111:1627–35.
- Kass MA, Heuer DK, Higginbotham EJ, *et al*. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol* 2002;120:701–13.
- Asrani S, Zeimer R, Wilensky J, *et al*. Large diurnal fluctuations in intraocular pressure are an independent risk factor in patients with glaucoma. *J Glaucoma* 2000;9:134–42.
- Bonomi L, Marchini G, Marraffa M, *et al*. Prevalence of glaucoma and intraocular pressure distribution in a defined population. The Egna-Neumarkt Study. *Ophthalmology* 1998;105:209–15.
- Kawase K, Tomidokoro A, Araie M, *et al*. Ocular and systemic factors related to intraocular pressure in Japanese adults: the Tajimi study. *Br J Ophthalmol* 2008;92:1175–9.
- Chua J, Chee ML, Chin CWL, *et al*. Inter-Relationship between ageing, body mass index, diabetes, systemic blood pressure and intraocular pressure in Asians: 6-year longitudinal study. *Br J Ophthalmol* 2019;103:196–202.
- Han X, Niu Y, Guo X, *et al*. Age-Related changes of intraocular pressure in elderly people in southern China: Lingtong eye cohort study. *PLoS One* 2016;11:e0151766.
- Tomoyose E, Higa A, Sakai H, *et al*. Intraocular pressure and related systemic and ocular biometric factors in a population-based study in Japan: the Kumejima study. *Am J Ophthalmol* 2010;150:279–86.
- Wang D, Huang W, Li Y, *et al*. Intraocular pressure, central corneal thickness, and glaucoma in chinese adults: the liwan eye study. *Am J Ophthalmol* 2011;152:454–62.
- Han X, Yang T, Zhang J, *et al*. Longitudinal changes in intraocular pressure and association with systemic factors and refractive error: Lingtong Eye Cohort Study. *BMJ Open* 2018;8:e019416.
- Ma D, Wei S, Sun Y, *et al*. Distribution of IOP and its relationship with refractive error and other factors: the Anyang University Students Eye Study. *Int J Ophthalmol* 2021;14:554–9.
- Ahn MW, Lee JW, Shin JH, *et al*. Relationship between intraocular pressure and parameters of obesity in ocular hypertension. *Int J Ophthalmol* 2020;13:794–800.
- Weih LM, Mukesh BN, McCarty CA, *et al*. Association of demographic, familial, medical, and ocular factors with intraocular pressure. *Arch Ophthalmol* 2001;119:875–80.
- Vasile P, Valeria C, Speranța S, *et al*. Sympathetic context of the disease - a new era in glaucoma management. *Rom J Ophthalmol* 2021;65:15–19.
- Quaranta L, Katsanos A, Russo A, *et al*. 24-hour intraocular pressure and ocular perfusion pressure in glaucoma. *Surv Ophthalmol* 2013;58:26–41.
- Yang Y, Jiang Y, Huang S, *et al*. Laser in Glaucoma and Ocular Hypertension Trial (LIGHT) in China A Randomized Controlled Trial: Design and Baseline Characteristics. *Am J Ophthalmol* 2021;S0002-9394:00219–1.
- National Institute for Health and Care Excellence. NICE L. NICE: Guidance on Glaucoma: Diagnosis and management of chronic open angle glaucoma and other ocular hypertension [Internet]. DoH, 2010. Available: [www.nice.org.uk/guidance/CG85/full/guideline](http://www.nice.org.uk/guidance/CG85/full/guideline)
- Zhai R, Cheng J, Xu H, *et al*. Mean amplitude of intraocular pressure excursions: a new assessment parameter for 24-h pressure fluctuations in glaucoma patients. *Eye* 2021;35:326–33.
- Leske MC, Heijl A, Hyman L, *et al*. Early Manifest Glaucoma Trial: design and baseline data. *Ophthalmology* 1999;106:2144–53.
- Lascaratos G, Garway-Heath DF, Burton R, *et al*. The United Kingdom Glaucoma Treatment Study: a multicenter, randomized, double-masked, placebo-controlled trial: baseline characteristics. *Ophthalmology* 2013;120:2540–5.
- Rochtchina E, Mitchell P, Wang JJ. Relationship between age and intraocular pressure: the Blue Mountains Eye Study. *Clin Exp Ophthalmol* 2002;30:173–5.
- Brubaker RF, Nagataki S, Townsend DJ, *et al*. The effect of age on aqueous humor formation in man. *Ophthalmology* 1981;88:283–8.
- Liu B, McNally S, Kilpatrick JJ, *et al*. Aging and ocular tissue stiffness in glaucoma. *Surv Ophthalmol* 2018;63:56–74.
- Feola AJ, Sherwood JM, Pardue MT, *et al*. Age and Menopause Effects on Ocular Compliance and Aqueous Outflow. *Invest Ophthalmol Vis Sci* 2020;61:16.
- Schmid KL, Li RWH, Edwards MH, *et al*. The expandability of the eye in childhood myopia. *Curr Eye Res* 2003;26:65–71.

- 27 David R, Zangwill L, Briscoe D, *et al.* Diurnal intraocular pressure variations: an analysis of 690 diurnal curves. *Br J Ophthalmol* 1992;76:280–3.
- 28 Gautam N, Kaur S, Kaushik S, *et al.* Postural and diurnal fluctuations in intraocular pressure across the spectrum of glaucoma. *Br J Ophthalmol* 2016;100:537–41.
- 29 Medeiros FA, Weinreb RN, Zangwill LM, *et al.* Long-term intraocular pressure fluctuations and risk of conversion from ocular hypertension to glaucoma. *Ophthalmology* 2008;115:934–40.
- 30 Hopf S, Schwantuschke D, Pfeiffer N, *et al.* The impact of intraocular pressure fluctuations and other factors on conversion of ocular hypertension to primary open-angle glaucoma. *Int Ophthalmol* 2020;40:1403–10.
- 31 Mahroo OA, Williams C, Hysi PG, *et al.* Interocular asymmetries in axial length and refractive error in 4 cohorts. *Ophthalmology* 2015;122:648–9.
- 32 Bikbov MM, Kazakbaeva GM, Zainullin RM, *et al.* Intraocular Pressure and Its Associations in a Russian Population: The Ural Eye and Medical Study. *Am J Ophthalmol* 2019;204:130–9.

## Appendix

### Key protocol of LiGHT China Trial

#### a. Eligibility criteria, operational definition of OAG & OHT:

We have used the NICE recommended thresholds for initiating treatment<sup>1</sup>, with stringent diagnostic definitions of disease (OAG or OHT) for entry into the study. Unioocular patients are eligible.

##### 1.1 Diagnosis of OAG

Open Angle Glaucoma is defined as an open drainage angle with no secondary causes (such as trauma):

(1) and reproducible glaucomatous visual field (VF) defects as tested by the SITA Standard white-on-white 24-2 algorithm on the Humphrey Visual Field Analyser (HVF) (i.e. reproducible defect, in at least, of two or more contiguous points with  $P < 0.01$  loss or greater, or three or more contiguous points with  $P < 0.05$  loss or greater, or abnormal Glaucoma Hemifield Test, GHT);

(2) or GON with localised absence of the neuro-retinal rim or, cup disc ratio of 0.7 or more, or asymmetry of cup disc ratio of 0.2 or more in similar sized eyes / optic discs.

And deemed to require treatment in the opinion of glaucoma specialist.

Subjects with pseudo-exfoliation are eligible, subjects who have undergone less than 4 weeks of medical treatment from their primary care ophthalmologists as a temporising control measure (with medications other than prostaglandins) will be permitted to enter the study, but will be required to undergo a 4-week washout period to establish their baseline IOP. Subjects with GON and IOP in the normal range are eligible. 'Phasing' (diurnal IOP pressure measurements) will be performed at the discretion of the treating clinician and if performed the maximum IOP recorded will be used as that day's measurement.

##### 1.2 Diagnosis of OHT

OHT with IOP above 21mmHg and requiring treatment as per NICE Guidelines. NICE OHT guidelines treat 4 categories of OHT on the basis of central corneal

thickness (CCT) and age (the rest are monitored for 3-5 years).

### **b. Criteria for treatment escalation decisions**

Treatment will be escalated under the following circumstances:

1. “Strong Evidence” of progression (as defined below) irrespective of IOP.
2. IOP above Target by more than a certain threshold at a single visit (irrespective of evidence for progression)
3. IOP above Target by less than threshold plus “Less Strong Evidence” for progression. If the IOP is above Target by less than threshold with no evidence for progression, then the 'Treatment Target IOP' will be re-evaluated. More detail of the indications for treatment escalation and 'Treatment Target IOP' re-evaluation, to deal with specific clinical scenarios, is given in the full version protocol of the trial.

### **c. Method and unit of randomization (eyes/patients)**

Randomization will be carried out according to a trial specific SOP. Online randomization (with blocking with random block sizes) will be used to randomize at the level of the patient and be stratified by diagnosis (OHT/OAG). The primary analysis will adjust for the stratification factor used in randomization. Participants will be randomized to medication or SLT group in equal proportion using a web-based randomization service provided by a specialist company to achieve full allocation concealment ([www.sealedenvelope.co.uk](http://www.sealedenvelope.co.uk)). ‘Sealed Envelope’ will also hold the randomization list. A backup telephone service will be available. The incremental escalation of treatment flow-chart displays the procedure of the trial (**Figure A**).

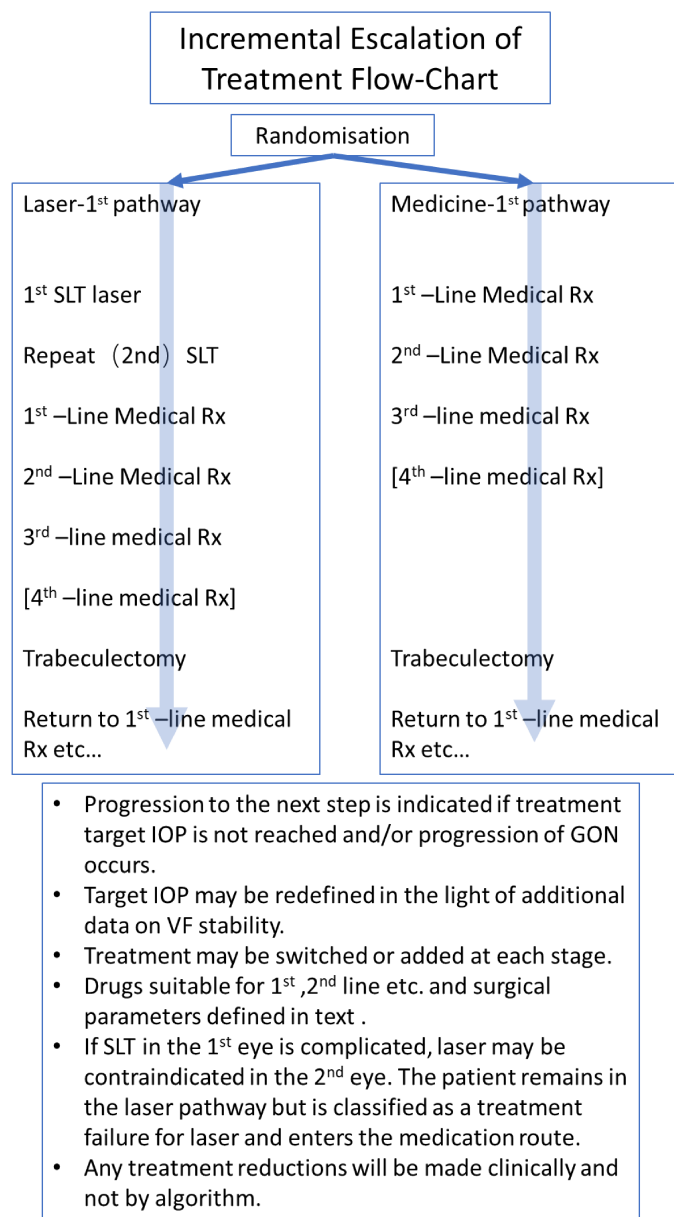


Figure A. Incremental escalation of treatment flow-chat.

#### d. Outcome measures

1. The primary outcome measure is Health Related Quality of Life(HRQL).
2. The secondary outcome measures including:
  - 2.1 Treatment Pathway Cost and Cost-Effectiveness



2.2 Glaucoma-specific treatment-related quality of life: Glaucoma Utility Index (GUI)

2.3 Patient Reported Visual Function: VF-14

2.4 Other secondary outcomes: Patient Reported Disease and Treatment Related Symptoms: Glaucoma Symptom Scale<sup>83</sup> (GSS), Patient Reported Visual Function: Glaucoma Quality of Life - 1510 (GQL-15), Objective measures of pathway effectiveness and visual function, Objective measures of the safety profiles of each pathway.

**e. Specific statement as to whether participants signed a consent document should be included.**

Informed consent was obtained from all individual participants included in the study. And all patients will be given a Patient Information Leaflet (PIL) and a copy of the Informed Consent. The original signed form will be retained at the study site. Vulnerable groups who would have difficulty in giving informed consent will not form part of this study. Patients who are unable to read Chinese but are able to retain and understand oral information about the study will be permitted to enter the study with an independent witness to counter-sign the consent form.

**f. Method for assessment of ocular and systemic conditions**

The baseline assessments will be done once the patient has been entered into the trial and before their first treatment. These will be the same as the screening assessment (slit-lamp examination, automated visual field test, HRT disc imaging, and KOWA simultaneous stereo digital disc photography) with the addition of self-completed baseline questionnaires (EQ5-D Glaucoma Utility Index (GUI), Glaucoma Symptom Scale (GSS), Glaucoma Quality of Life - 15 (GQL-15; a visual function measure) and Visual Function 14 (VF-14; a Chinese-validated function measure).

All patients will undergo a comprehensive medical history inquiry to find out if they had any history of other systemic diseases. The subjects will be tested for blood pressure and blood sugar to determine whether they had hypertension, diabetes,

asthma, angina, cardiac arrhythmia, ischaemic heart disease, migraines, cerebrovascular accident/stroke, peripheral vasospastic symptoms or blood loss/transfusion.

**Full version of protocol is available via the link as following:**

[https://www.moorfields.nhs.uk/sites/default/files/LiGHT%20Trial%20Protocol%203.0%20-%202020-5-2015\\_3.pdf](https://www.moorfields.nhs.uk/sites/default/files/LiGHT%20Trial%20Protocol%203.0%20-%202020-5-2015_3.pdf)