**Research Protocol**

**Project title:**

**Progressive retinal nerve fiber layer (RNFL) thinning as a biomarker to guide intraocular pressure (IOP)lowering treatment in ocular hypertensives (OHT)**

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**This study is complied with declaration of ICH-GCP.**

**Introduction**

Glaucoma is a leading cause of irreversible blindness, afflicting 21.8 million patients in China by 2020. While the Ocular Hypertension Treatment Study (OHTS) established the effectiveness of lowering the IOP in decreasing the risk of glaucoma development, <10% of the untreated patients worsened and developed glaucoma in 5 years. Treating non- progressing patients not only incurs unnecessary costs to patients and health-care providers, but also induces adverse effects that can compromise visual function and quality of life. Risk stratification using the OHTS-EGPS (European Glaucoma Prevention Study) prediction model has been proposed to identify high risk OHT (5-year risk >15%) for IOP-lowering treatment to prevent glaucoma development. Notably, the risk calculated by the OHTS-EGPS model relies on five biometric parameters measured cross sectionally, which can be highly variable during follow-up. The ability to distinguish high-risk from low-risk OHT remains imprecise and it is largely unclear when to initiate IOP-lowering treatment. Identifying biomarkers indicative of disease deterioration behavior to guide IOP-lowering

treatment for prevention of visual impairment is an unmet need in the management of

OHT. We hypothesize progressive RNFL thinning to be a biomarker predictive of subsequent visual field (VF) progression and that IOP-lowering treatment initiated upon detection of progressive RNFL thinning is an effective approach to direct OHT at risk of VF progression for treatment. We propose a 5-year prospective study, randomizing 310 OHT patients into two management paradigms with IOP-lowering treatment initiated upon detection of (I) progressive RNFL thinning, as determined by spectral-domain optical coherence tomography Trend-based Progression Analysis of serial RNFL thickness maps; or (II) a 5-year glaucoma conversion risk >15% calculated from the OHTS-EGPS model. All patients will undergo clinical examination, RNFL imaging and perimetry 4-monthly for 5 years. The objectives are to compare the proportion of patients requiring IOP-lowering treatment and the proportion of patients developing VF progression within the two management paradigms. We expect that the proportion of patients requiring treatment is smaller for patients randomized to management paradigm I with a comparable/smaller proportion of patients developing VF progression compared with those randomized to management paradigm II. The finding of the study will transform the management of OHT. Specifically, we would be able to target treatment to OHT at risk of VF progression based on a biomarker indicative of disease deterioration behavior. It also would minimize both costs and adverse effects, and enhance the rational re-allocation of resources within the healthcare system to those at most need.

**Study Objectives:**

1. To compare the proportions of OHT patients requiring IOP-lowering treatment and the total treatment costs between those randomized to IOP-lowering treatment upon detection of progressive RNFL thinning (management paradigm I) and those randomized to IOP-lowering treatment upon detection of a 5-year glaucoma conversion risk >15% calculated with reference to the OHTS-EPGS risk prediction model (management paradigm II) in 5 years.
2. To compare the proportions of patients with VF progression in 5 years between anagement paradigm I and management paradigm II.
3. To identify the risk factors for VF progression in Hong Kong Chinese with OHT.

**Study Impacts:**

(a) Long-term impact:

Through use of a novel approach to analyze a biomarker – progressive retinal nerve fiber layer (RNFL) thinning – that is predictive of subsequent development of visual impairment, this study will transform the management paradigm of ocular hypertension (OHT) by targeting treatment to patients at highest risk for worsening of disease. We hypothesize that the proportion of OHT patients requiring intraocular pressure (IOP)-lowering treatment is smaller for patients randomized to (I) IOP-lowering treatment upon detection of progressive RNFL thinning, than those randomized to (II) IOP-lowering treatment upon detection of a 5-year risk of glaucoma conversion >15% (calculated according to the Ocular Hypertensive Treatment Study (OHTS) and the European

Glaucoma Prevention Study (EGPS) risk prediction model) (1-3) and that the proportion of patients with visual field (VF) progression would be comparable/smaller for those randomized to the former than the latter. If the hypothesis is confirmed, the study will significantly impact and advance glaucoma care in affording a cost-effective approach for management of OHT patients. Specifically, (i) treatment will be targeted to patients with evidence of disease deterioration behavior predictive of VF progression; and consequently, (ii) treatment-related cost and side-effects consequential to treating non-progressing patients would be minimized. (iii) Further, the outcome of the study will be informative to regulatory authorities in considering the adoption of progressive RNFL thinning as an outcome measure in clinical trials for evaluation of glaucoma treatment.

(i) Targeting treatment to patients at risk of development of visual impairment

Currently, management of OHT is largely predicated on the OHTS-EGPS prediction model, which estimates the 5-year risk of glaucoma conversion based on age, IOP, vertical cup-to-disc ratio, central corneal thickness, and VF pattern standard deviation value measured from a single visit (1). While patients with a 5-year risk of glaucoma conversion >15% have been recommended for IOP-lowering treatment (4), the ability to distinguish high-risk from low-risk patients is imprecise (5). In a recent study, we demonstrated progressive RNFL thinning measured by Trend-based Progression Analysis (TPA) of serial RNFL thickness maps to be highly predictive of subsequent VF progression in glaucoma patients (6). Eyes with progressive RNFL thinning had more than 5-fold increase in risk of VF progression. Addressing whether IOP-lowering treatment initiated upon detection of progressive RNFL thinning is an effective approach to target OHT patients for treatment has the potential to bring forth a new paradigm to guide clinicians and patients to make an informed decision about the need of IOP-lowering treatment.

(ii) Minimizing the cost and side-effects consequential to treating non-progressing OHT Patients

In Hong Kong, the expenditure on ophthalmic medications, of which glaucoma medications constitute the largest portion, has increased substantially over the years. For example, between 2001 and 2006, the cost of ophthalmic medications incurred to the Hong Kong Government in the public health care system increased by 265%, from US$1.19 to US$4.36 million (7). With reference to our previous study investigating the safety and potential savings of decreasing medication use in OHT patients, we estimated that ~50.8% of OHT patients have a 5-year glaucoma conversion risk >15% in 5 years (7). In a pilot study following RNFL measurements in untreated OHT patients, we found that 30% developed progressive RNFL thinning determined by TPA in 5 years (unpublished data). In other words, we expect more patients can be safely observed without treatment if we adopt the management protocol with treatment initiated upon detection of progressive RNFL thinning. The new treatment paradigm can substantively decrease the cost and treatment related side-effects (e.g. ocular surface disease) for OHT patients.

(iii) Establishing the role of progressive RNFL thinning as an outcome measure in glaucoma treatment trials

The need for structural endpoints in glaucoma treatment trials has been discussed in the National Eye Institute/Food and Drug Administration (FDA) Glaucoma Clinical Trial Design and Endpoints Symposium (8), and the World Glaucoma Association Consensus meetings. Regulatory authorities, such as the FDA, consider structural parameters as outcome measures for glaucoma clinical trials only when there is evidence supporting that the new outcome measure is predictive of functional change (8). The study will provide an important reference demonstrating the feasibility of using a structural endpoint, progressive RNFL thinning, to guide treatment for prevention of functional impairment in OHT patients.

**Study Background:**

Ocular hypertension: When to initiate treatment? Ocular hypertension (OHT), defined as a mean

intraocular pressure (IOP) ≥24mmHg from 2 separate consecutive measurements in the Ocular

Hypertension Treatment Study (OHTS),9 is a major and the only modifiable risk factor for

glaucoma – a leading cause of irreversible blindness with an estimated 21.8 million patients in

China by 2020.10 Lowering the IOP has been consistently demonstrated to be effective to slow

down or prevent visual field (VF) progression in OHT patients.1-3 Five risk factors for development of glaucoma were recognized in OHTS: higher IOP, older age, thinner central corneal thickness, larger vertical cup-to-disc ratio (VCDR), and

greater VF pattern standard deviation (PSD).

A risk calculator based on the pooled OHT-

EFPS predictive model has been developed to estimate the 5-year risk of glaucoma conversion

based on age, IOP, CCT, VCDR, and VF PSD measured at baseline.1 While previous studies have established the importance of IOP in contributing to glaucoma progression, it remains largely

unclear when to initiate IOP-lowering treatment for patients diagnosed with OHT. Notably, treating all OHT patients is considered not to be cost-effective.11 Risk stratification with

reference to the OHTS-EGPS risk calculator has been proposed to identify patients at higher risk

of glaucoma progression for treatment. A review of population-based studies of patients with OHT

and glaucoma by a panel of glaucoma specialists suggests that patients with a lower than average

5-year glaucoma conversion risk (<5%) could be observed without treatment whereas patients with a higher than average 5-year risk (>15%) should be considered for treatment.4 Yet, the ability to distinguish high risk from low risk OHT patients is imprecise.5 In fact, the estimated 5-year risk of glaucoma development based on the OHTS-EPGS risk prediction model can vary up to 10-fold

within the same individual during follow-up because of the variability of IOP, CCT, VCDR and VF PSD measurements.5 In the latest edition of Terminology and Guidelines for Glaucoma published by the European Glaucoma Society (4th edition) in 2014, the editorial teams recognize that “there is uncertainty whether to treat none, some or all patients with OHT”.12 Identifying reliable biomarkers indicative of disease deterioration behavior to guide IOP-lowering treatment is an unmet need in the management of OHT. We hypothesize that progressive retinal nerve fiber layer (RNFL) thinning detected by spectral-domain optical coherence tomography (SDOCT) is an informative biomarker predictive of glaucomatous VF progression and that IOP-lowering treatment initiated upon detection of progressive RNFL thinning is an effective approach to target patients at risk of VF progression for treatment.

Progressive retinal nerve fiber layer (RNFL) thinning as a biomarker to predict VF progression:

What is the evidence? The RNFL is largely composed of the axons of retinal ganglion cells. As glaucoma exhibits progressive loss of retinal ganglion cells, measuring progressive RNFL thinning is useful to track disease progression. Using the time-domain optical coherence tomography (TDOCT) to measure the circumpapillary RNFL thickness, it has been shown that for each 10μm reduction in the average circumpapillary RNFL thicknesses (obtained from a circle scan with a diameter of ~3.45mm), the risk of VF progression increased by 18%, in 246 glaucoma suspects and glaucoma patients.13 Given the fact that RNFL abnormalities (i.e. RNFL measurements outside the normal reference ranges) can often be found before VF damages becomes detectable,15-18 it is conceivable that IOP-lowering treatment initiated upon detection of progressive RNFL thinning (i.e. before reaching the range of abnormalities) would be effective to prevent or delay VF progression.

Novelty and impact

The proposed study will transform the clinical practice of OHT management. Specifically, we would be able to target treatment to patients at risk of development of visual impairment with reference to a biomarker – progressive RNFL thinning – indicative of disease deterioration. The study will impact the clinical practice in alleviating the burden of glaucoma blindness, decreasing costs to patient and society, reducing potentially deleterious side effects and their influence on vision related and health quality of life, enabling more rational allocation of health care funds to those at highest need and obtaining a novel biomarker for diagnosing and following disease in clinical practice and research.

2(b) Research plan and Methodology

This is a 5-year prospective, multicenter, randomized trial to compare the treatment outcomes of

two management paradigms: (I) initiation of IOP-lowering treatment (≥20% IOP reduction from

baseline and a target IOP≤24mmHg) upon detection of progressive RNFL thinning; and (II) initiation of IOP-lowering treatment (≥20% IOP reduction and a target IOP≤24mmHg) to all OHT

patients with a 5-year glaucoma conversion risk >15% calculated according to the OHTS-EPGS risk prediction model.1 Primary outcome measure is (1) the proportion of patients requiring IOP-

lowering treatment in 5 years. Secondary outcome measures will include (2) the proportion of

patients with VF progression and (3) the total treatment costs in 5 years. Risk factors for development of glaucomatous VF defects including age, IOP levels (mean and standard deviation

during follow-up), glaucoma severity (baseline VF MD and average RNFL thickness), corneal biomechanical properties (cornea hysteresis and corneal deformation response), and other biometric variables (axial length, CCT) will be investigated. We expect that the proportion of patients requiring IOP-lowering treatment would be smaller with a comparable or smaller proportion of patients with VF progression in 5 years for those randomized to management paradigm I compared with those randomized to management paradigm II. Study end-points include: (1) development of VF progression (described in Detection of VF progression); (2) decrease in visual acuity (VA) ≥2 lines; and (3) IOP>32mmHg on 2 consecutive visits. Patients will exit the study and receive appropriate treatment if any of the study end-points is reached.

310 consecutive patients (see Sample size calculation) with OHT (≥23mmHg but <32mmHg in at least 1 eye and the fellow eye has an IOP ≥21mmHg but <32mmHg calculated from 3 separate baseline visits within 6 months) without prior history of glaucoma surgery/laser procedure and receiving no IOP lowering medication will be recruited from 5 study sites within 6 months. Eligible patients (described in Subjects) will be randomized to management paradigm I or II after the baseline visits. The randomization unit is the subject. All patients will be followed-up 4-monthly for clinical examination, perimetry and RNFL imaging for 60 months. For patients randomized to management paradigm I, IOP-lowering treatment (described in IOP-lowering treatment) will be initiated to an eye when progressive RNFL thinning is detected in the TPA RNFL thickness change map (described in Analysis of RNFL progression). At least 3 baseline and 1 follow-up visits are required for TPA to detect progressive RNFL thinning and the earliest follow-up time for initiation of IOP-lowering treatment is 4 months. For patients randomized to Treatment Paradigm II, the 5-year glaucoma conversion risk will be calculated according to the OHTS-EPGS risk prediction model.1 Eyes with a risk >15% confirmed in two consecutive visits separated by at least 4 months will receive IOP-lowering treatment (two consecutive visits are required for confirmation because of the variability in the risk calculation).5 In other words, the earliest follow-up time for initiation of IOP-lowering treatment is also 4 months. Analysis of progressive RNFL thinning and calculation of the 5-year risk will be performed in each follow-up visit and the decision to initiate treatment will be reviewed accordingly. Once an IOP-lowering treatment is initiated, it will continue to the end of the study as long as the treatment is acceptable to the patients. There is no risk involved between the two management paradigms. RNFL abnormalities can often be found before VF damages become detectable, in other words, it is conceivable that IOP-lowering treatment initiated upon detection of progressive RNFL thinning/management paradigm 1 (i.e. before reaching the range of abnormalities) would be effective to prevent or delay VF progression. It is a world-wide practice to initiate IOP-lowering treatment upon a risk >15% according to the OHTS-EPGS prediction model (management paradigm 2) confirmed in two consecutive visits.

Subjects

OHT patients will be consecutively recruited from Hong Kong Eye Hospital, Chinese

University of Hong Kong Eye Clinic, Prince of Wales Hospital, Alice Ho Miu Ling Nethersole Hospital and Tuen Mun Hospital with written informed consent obtained. They are invited to attend three separate baseline visits for IOP measurements, perimetry and RNFL imaging after a comprehensive clinical examination at the screening visit. Inclusion criteria include: age ≥18 years; best corrected VA ≥20/40; an average IOP ≥23mmHg but <32mmHg in at least 1 eye and ≥21mmHg but <32mmHg in the fellow eye measured from 3 separate baseline visits within 6 months; gonioscopically open anterior chamber angles; 3 reliable VF results without VF defects, normal optic disc and RNFL configuration in clinical examination; and no RNFL abnormalities (i.e. within the 95% normal ranges) in the OCT RNFL thickness deviation map ; no prior history of surgical/laser procedure for IOP lowering and receiving no topical IOP-lowering medication. IOP measurements for eligibility assessment are obtained after washout of prestudy topical IOP lowering medications for 4 weeks. Exclusion criteria are: secondary causes of elevated IOP; ocular or systemic diseases that may cause VF loss or optic disc abnormalities; high myopia (spherical error<-6.0D); inability to perform reliable VF; suboptimal quality of SDOCT images (see RNFL imaging); previous intraocular surgery other than uncomplicated cataract extraction; and diabetic retinopathy/maculopathy.

Clinical examination including VA measurement, slit-lamp biomicroscopy for anterior and posterior segments, VCDR measurement and Goldmann applanation tonometry are performed at all follow-up visits. At each visit, 2 IOP readings are obtained to calculate the mean. A third reading is measured when the difference between the first two is >2mmHg and the median is recorded. The mean of the 3 IOP measurements recorded at the 3 baseline visits represents the baseline IOP. Dark room indentation gonioscopy with Posner lens, axial length measurement with A-scan biometry, subjective and objective refraction are performed at the screening and the last follow-up visits. CCT with ultrasound pachymetry is performed yearly (assuming any change in CCT within one year is insignificant to impact the risk calculation). Dilated fundus examination for color optic disc stereophotography is performed at the baseline and then yearly.

Measurement of corneal biomechanical properties Two surrogate measures of corneal biomechanical properties will be measured at baseline. (1) Corneal hysteresis is measured with the ocular response analyzer (Reichert, Inc., Depew, NY) at the three baseline visits. A waveform score of ≥7 is considered to be reliable for inclusion.24 (2) Corneal deformation amplitude is measured with an ultra-high-speed Scheimpflug camera (Corvis ST; Oculus, Arlington, WA) at the three baseline visits. Please refer to our previous studies25,26 for the details of the procedures of ORA and Corvis ST measurements.

RNFL imaging is performed with the Cirrus HD-OCT (Carl Zeiss Meditec) [Cirrus OCT 4000 (SN) 4000-1012, Cirrus AngioPlex OCT (SN) 5000-50xx] using the optic disc cube scan (200x200 pixels), generating the RNFL thickness map (6x6mm2) around the optic disc. Only images with a signal strength ≥7 are included. Images with motion artifact, poor centration, or missing data (e.g. blinking) are checked by the operator and discarded with re-scanning performed in the same visit. Three sets of OCT scans will be obtained for each eye at the 3 baseline examinations. Perimetry is performed with the Humphrey Field Analyzer II 24-2 SITA standard strategy (Carl Zeiss Meditec) Cirrus OCT 4000 (SN) 4000-1012, Cirrus AngioPlex OCT (SN) 5000-50xx]. A reliable VF test has fixation losses, false positive and false negative errors <20%. Unreliable tests are repeated on the same day. A VF defect is defined as having ≥3 significant (p<0.05) non-edge contiguous points (except for the 6 nasal locations) with ≥1 at the p<0.01 level on the same side of horizontal meridian in the pattern deviation plot and classified outside normal limits in the Glaucoma Hemifield test and confirmed in three consecutive tests. OHT patients recruited in the study have no VF defects at baseline. Three reliable VFs will be obtained for each eye at baseline.

Analysis of RNFL progression Trend-based Progression Analysis (TPA) of the RNFL thickness maps will be performed to determine progressive RNFL thinning (Fig.1). Please refer to Reference 27 for the technical details of TPA. In brief, RNFL thickness data from serial RNFL thickness maps are exported to a computer to measure the rate of change of RNFL thickness (i.e. linear regression analysis between RNFL thickness and follow-up time) in individual superpixels of the RNFL thickness map (50x50 superpixels) after aligning and registering the longitudinal image series using a program custom-designed in MATLAB (The MathWorks Inc.). A TPA derived RNFL thickness change map is then generated (Fig.1A). To reduce the probability of Type I error (incorrect rejection of a true null hypothesis) (null hypothesis: the rate of change of RNFL thickness at an individual superpixel location was 0μm/year) consequential to multiple tests performed in the RNFL thickness maps, the significance level of hypothesis testing at individual superpixels is determined after controlling the false discovery rate (FDR) at ≤5%. We adopt the FDR controlling procedures to estimate the number of false positives without sacrificing the potential loss in sensitivity to detect change which would otherwise be inevitable with familywise error rate controlling procedures such as the Bonferroni adjustment. A FDR of 5% indicates that 5% of the superpixels detected with a significant change in the RNFL thickness change map would be considered as false positives. Progressive RNFL thinning in a superpixel location would be encoded in yellow in the TPA RNFL thickness change map if a significant negative trend is identified with a p≤5% in an individual regression analysis of a superpixel; and in red if the significant negative slope is detected after controlling the FDR at 5%. Progressive RNFL thinning is defined when ≥20 contiguous superpixels are encoded in red in the TPA RNFL thickness change map during follow-up. Analysis of VF progression: VF progression is analyzed according to the Early Manifest Glaucoma Trial criteria,28 which is available in in the Humphrey Field Analyzer Guided Progression Analysis (Carl Zeiss Meditec) [Cirrus OCT 4000 (SN) 4000-1012, Cirrus AngioPlex OCT (SN) 5000-50xx]. VF Progression is defined when there are ≥3 points that showed significant change (greater than the test-retest variability) compared with two baseline examinations for at least 3 consecutive tests (i.e. “likely progression”). Specificity of RNFL and VF progression analyses We examined the specificities of the above definitions of RNFL and VF progression analyses in 25 normal eyes followed weekly for 8 consecutive weeks for RNFL imaging and perimetry. No eyes demonstrated significant RNFL and VF changes. The estimated specificities were 100% (95% CI: 81.7%-99.9%)

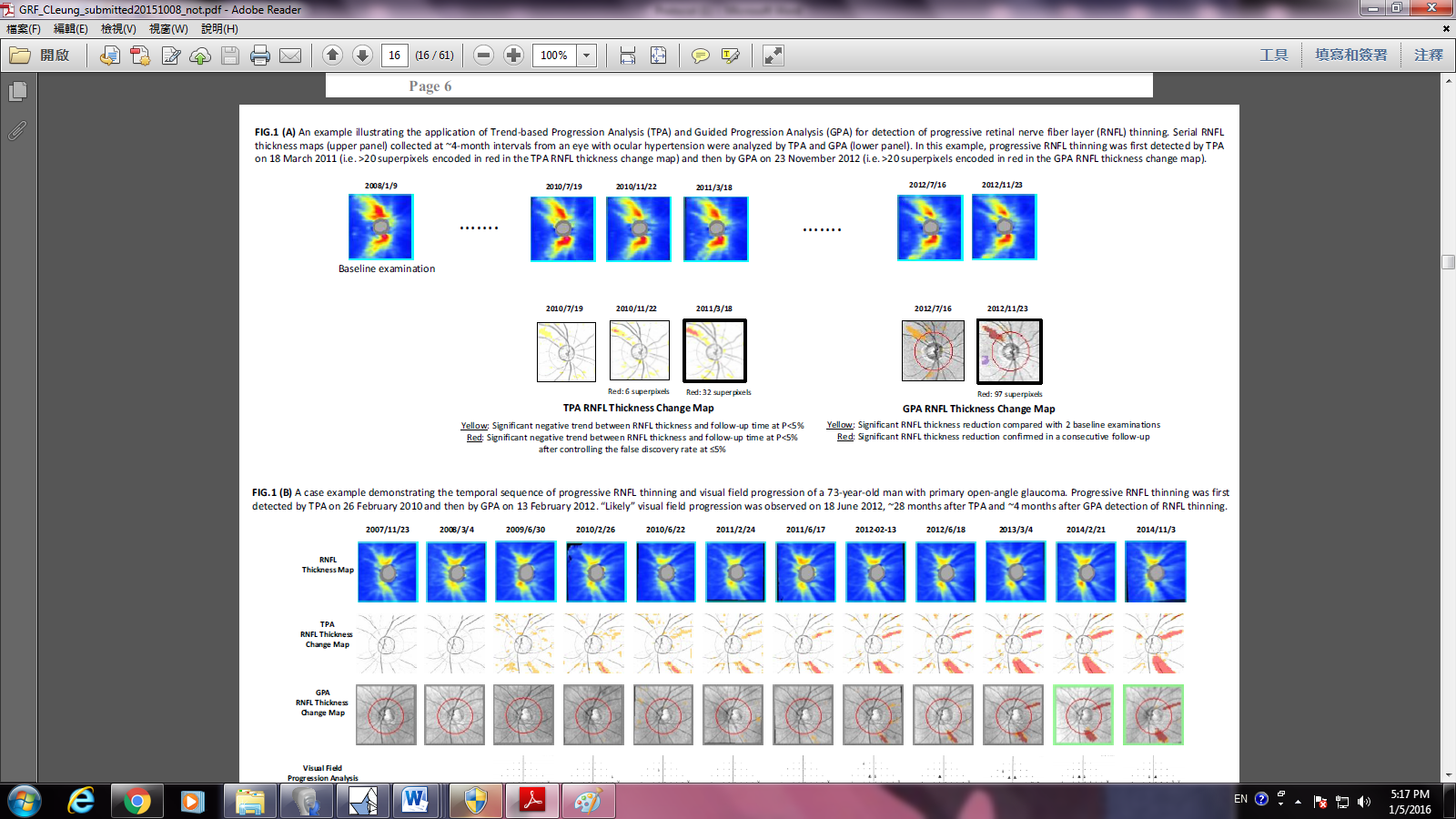
.IOP-lowering treatment will be given to eyes with progressive RNFL thinning (management paradigm I) or eyes with a 5-year glaucoma conversion risk >15% (management paradigm II) detected during the follow-up. Treatment will be provided in the following order: prostaglandin analogue, brimonidine, carbonic anhydrase inhibitor to achieve a target IOP≤24mmHg and 20% IOP reduction from baseline. If the target IOP cannot be attained with maximally tolerated medications, selective laser trabeculoplasty (SLT) will be performed with treatment protocol as described by Katz et al. (360° for ~100 applications).29

Statistical analysis (1) The primary analysis is to compare the proportions of patients requiring

IOP-lowering treatment (in one or both eyes) between management paradigms I and II at 5 years with a two-tailed z-test. The difference in time from baseline to treatment initiation between the 2

treatment paradigms will be compared with Kaplan-Meier survival analysis and log-rank test. (2) The secondary outcome measure, the proportions of patients with VF progression, are compared using similar statistical methods. The total medication costs and the average treatment cost per subject required throughout the 5-year study period will be calculated and compared with independent t-test between the two management paradigms. (3) Risk factors for development of VF progression (as described in lines 99-103) are analyzed with Cox proportional hazard models with correlation between fellow eyes in the same individual adjusted with shared frailty models. Sample size calculation In a previous study investigating the safety and potential savings of decreasing IOP-lowering medication in OHT patients recruited from Hong Kong Eye Hospital, we observed 26% of OHT patients had a 5-year risk of glaucoma conversion >15% (after medication washout) at baseline and an additional 6.2% of the untreated patients developed a 5-year risk >15% at 1 year of follow-up.7 Assuming the same proportion of patients (i.e. 6.2%) develop a 5-year risk >15% in each year of follow-up, 50.8% (26%+6.2%\*4) of OHT patients would have a 5-year risk >15% and require IOP-lowering treatment throughout the 5-year study period. In a pilot study following 38 OHT eyes for at least 5 years, we observed 30.0% of eyes having progressive RNFL thinning detected by TPA in 5 years. We therefore estimated that at least 248 subjects (124 subjects per randomization arm) are needed to detect a difference of 20% in the proportions of patients requiring IOP-lowering treatment in 5 years with a power of 90% and an alpha of 5%. Taking 20% attrition over the study period, 310 patients will be recruited and each study site will enroll approximately 62 patients.

Potential concerns and solutions: (1) Recruitment of 310 subjects within 6 months Five study sites serving a population of over 2 million with daily outpatient attendance of >3000 will contribute to the recruitment. It is likely that the recruitment can be completed within a short time. Supporting letters for commitment of patient recruitment from the study sites are attached. (2)Initiation of treatment upon detection of progressive RNFL thinning Although patients randomized to management paradigm I will only receive IOP-lowering treatment upon detection of progressive RNFL thinning, the study will ensure the safety of the patients by limiting the study inclusion to patients with IOP<32mmHg and providing frequent clinical examination and VF testing at 4-month intervals. Patients developing VF defects or reaching any end-points of the study (described in Study end-points) will exit the study and receive appropriate treatment. (3) TPA for analysis of progressive RNFL thinning We adopt TPA instead of GPA, a built-in event based algorithm in the Cirrus HD-OCT (Carl Zeiss Meditec) [Cirrus OCT 4000 (SN) 4000-1012, Cirrus AngioPlex OCT (SN) 5000-50xx], for RNFL progression analysis because TPA can detect progressive RNFL thinning earlier than GPA and more important, TPA detected RNFL thinning confers a higher risk of subsequent VF progression compared with GPA detected RNFL thinning.6 We believe the application of TPA will not limit the translation of the study into clinical practice as Carl Zeiss Meditec has agreed to license TPA. TPA will become available in the Cirrus HD-OCT in the near future. (4) Differentiation between disease-related from age-related RNFL thinning In the previous studies, we detected age-related RNFL thinning in normal healthy subjects30 and investigated the impact of age-related RNFL thinning on detection of disease-related RNFL thinning in glaucoma patients.31 Although we can control for age-related RNFL thinning in the TPA RNFL thickness change map to discriminate disease-related from age related RNFL thinning, we decided to adopt a more conservative approach – i.e. treating patients with progressive RNFL thinning regardless of age-related or disease-related to augment the safety of the study. (5) 20% IOP reduction might not be attainable in some eyes despite maximally tolerated mediations and SLT. As it is unknown to what degree of IOP-lowering would prevent VF progression, ≥20% IOP reduction from baseline and ≤24mmHg target IOP is only an arbitrary target taking reference form the OHTS.2 The proportion of subjects attaining the target IOP is expected to be similar between the treatment groups and therefore would not affect the comparisons even though some eyes may not attain the target IOP. (6) Detection of VF progression There is no consensus regarding what type or degree of VF change constitutes glaucomatous progression in OHT patients. We are aware of the fact that there are different criteria to define VF progression and they may not agree with each other.32 We decided to use the EMGT criteria because the criteria are widely adopted in clinical studies and daily practice and have been shown to be relatively specific.33 We believe having 3 VF locations showing significant changes from baseline is a reliable indicator signifying glaucomatous VF progression and yet inconsequential to have an impact on subjective vision and quality of life of patients. (7) Progressive changes of the optic disc/RNFL parameters are not included as outcome measures because progressive RNFL thinning is already adopted as an indicator variable to guide treatment. The lack of consensus and validated algorithms to quantify SDOCT optic disc changes (neuroretinal rim vs. optic nerve head surface deformation vs. lamina cribrosa deformation) would also complicate the analysis of outcomes. Nevertheless, data collected from the study can be analyzed anytime once consensus/software for optic disc progression analysis becomes available. (8) Additional cost consequential to a more frequent follow-up schedule While IOP-lowering treatment initiated upon detection of progressive RNFL thinning may decrease the proportion of patients requiring treatment and hence reduce the health care cost and treatment-related adverse effects, additional RNFL imaging and perimetry will incur additional expenses. However, it is likely that the benefits of potential savings of reducing the proportion of patients requiring treatment and the improvement in the quality of life would outweigh the additional expenses required for the investigations. (9) Quality of life and cost-effectiveness analyses are not included in the proposal because of the potential budget limit. While we are already applying for the GRF “Longer-term Research Grant”, additional funding support from the Department/University will be solicited for these studies once the GRF is secured. (10) Study duration is constrained for 5 years because of the limit set by the GRF. We are cognizant of the fact that a longer follow-up (6-10 years) would be needed to evaluate the long-term implications of the two management paradigms. It is our plan to conduct follow-up studies once the proposed 5-year study is completed. Although the project will need 66 months to complete taking consideration of the time required for recruitment (6 months), no extra funding is needed from the GRF as the recruitment will be completed by the investigators (all are glaucoma specialists). (11) Failure to show benefits of management paradigm I Even if the study fails to show significant differences in the outcome measures between the two management paradigms, the finding of the study will still be informative to address if treatment initiated with reference to the OHTS-EPGS risk prediction model is a viable option to prevent or delay VF progression in OHT patients. In addition, we will derive a better risk prediction model incorporating parameters (e.g. RNFL thickness/corneal hysteresis/corneal deformation response) that were not investigated in the OHTS/EPGS.



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**Ethical Concern**

Patient confidentiality is the only major ethical issue