Qualitative Protocol Development Tool

The research protocol forms an essential part of a research project. It is a full description of the research study and will act as a 'manual' for members of the research team to ensure adherence to the methods outlined. As the study gets underway, it can then be used to monitor the study's progress and evaluate its outcomes.

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FULL/LONG TITLE OF THE STUDY

A Feasibility study: The efficacy and safety of heat applied to the eyelids in enhancing the delivery of ocular hypotensive eye drops in the treatment of Primary Open Angle Glaucoma

SHORT STUDY TITLE / ACRONYM

Heat **A**pplication to the eye **L**ids to enhance **O**cular drug delivery (**HALO)**

RESEARCH REFERENCE NUMBERS

IRAS Number:	**271825**
SPONSORS Number:	HP/271825/2023
FUNDERS Number:	SEE011

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:

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Name (please print):

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Position:

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Chief Investigator:

Signature: Date:

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Name: (please print):

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LIST of CONTENTS

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Committees	TBC

STUDY SUMMARY

Study Title	A Feasibility study: The efficacy and safety of heat applied to the eyelids in enhancing the delivery of ocular hypotensive eye drops in the treatment of Primary Open Angle Glaucoma
Internal ref. no. (or short title)	**H**eat **A**pplication to the eye **L**ids to enhance **O**cular drug delivery
Study Design	Interventional
Study Participants	Primary Open Angle Glaucoma/Ocular Hypertensive patients
Planned Size of Sample (if applicable)	24
Follow up duration (if applicable)	N/A

Planned Study Period	12 months
Research Question/Aim(s)	To investigate whether applying heat to the eye lids of patients with POAG or OHT in combination with ocular hypotensive eye drops results in further lowering of IOP. ***Primary objective*** The primary objective of the study is to demonstrate that heat applied to the eyelids in combination with the instillation of anti-Glaucoma eye drops induces a further lowering of IOPs when compared to the use of anti-Glaucoma eye drops alone. ***Secondary objective*** The secondary objective of the study is to determine whether there is a timepoint during the course of the day (phasing) that demonstrates the largest difference in IOP following heat and hypotensive eye drop combination.

FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
North West Anglia NHS Foundation Trust	Sight Research UK

PROTOCOL CONTRIBUTORS

Mr S.Alam (Ophthalmologist), Dr C.Willshire (Optometrist), Miss J. Williams (CTA/Ophthalmic technician) will be responsible for identifying suitable patients for the study. Mr S.Alam or Dr C.Willshire will receive informed consent from the patients. Dr C.Willshire will be responsible for collecting data, writing the manuscripts and associated patient documents. Data analysis will be conducted by ARU or Imperial College statisticians (TBC). Dissemination of the results from the study will be completed by Mr A.Nithy, Mr S.Alam and Dr C.Willshire.

The funder will not control the final decision regarding aspects of the study.

The protocol has been designed around similar previous studies and has involved the input of patients, members of the public or service users.

KEY WORDS: Heat, Hypotensive, Drug, Delivery, POAG, OHT, Ocular

STUDY FLOW CHART

Suitable patients identified and consented from Glaucoma clinics at HH and PCH-visual fields test completed

One week prior to the first phasing visit the patient will be asked to start completing their drop compliance diary, continued for the duration of the study

IOP phasing for POAG/OHT patients on topical therapy WITHOUT heat (no mask) – first visit

IOP phasing for POAG/OHT patients on topical therapy WITH heat - second visit

IOP phasing for POAG/OHT patients on topical therapy WITHOUT heat (wearing mask) - third visit

One to two weeks after completing the study a further visual fields test will be completed – safety visit including a visual fields test and visual acuity measure

Patient continues with their normal Glaucoma care

Abbreviations

BCVA	Best corrected visual acuity
CI	Chief Investigator
CRF	Case report form
GCP	Good clinical practice
HH	Hinchingbrooke Hospital
IOP	intraocular pressures
MGD	Meibomian Gland Dysfunction
mmHg	millimeters of mercury
NWAFT	North West Anglia NHS Foundation Trust
OHT	Ocular Hypertension
ORA	Ocular Response Analyser
OSDI	Ocular surface disease index
P value	Probability value
PCH	Peterborough City Hospital
PIS	Patient information sheet
PGA	Prostaglandin analogue
PI	Principle investigator
PPI	Patient and public involvement
POAG	Primary Open Angle Glaucoma
QoL	Quality of life
SD	Standard deviation
VF	Visual fields test

STUDY PROTOCOL

Title: A Feasibility study: The efficacy and safety of heat applied to the eyelids in enhancing the delivery of ocular hypotensive eye drops in the treatment of Primary Open Angle Glaucoma

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1 BACKGROUND

1.1 Primary Open Angle Glaucoma and Ocular Hypertension

Glaucoma is a disease characterised by damage to the optic nerve (Weinreb and Khaw, 2004) and is the leading cause of reversible blindness (Blomdahl et al., 1997). Primary Open Angle Glaucoma (POAG) is the most common sub-type of the condition (Quigley and Broman, 2006) in which people typically present with open drainage pathways and intra ocular pressures (IOPs) that increase gradually. In Ocular Hypertension excessively high IOPs can occur in the absence of any other optic nerve involvement in the early stages (Gordon et al., 2002; Kass et al., 2002). Both these conditions require long term management via a variety of therapies currently available. The most common approach to treatment in Glaucoma care is still the use of topical hypotensive eye drops to reduce the IOPs-the only modifiable risk factor for the disease (Bateman et al., 2002). If effective treatment is not delivered for an individual, raised IOPs present a risk of optic nerve damage resulting in a progressive and permanent loss of field of vision (Quigley, 1999; Weber and Harman, 2005). In the UK it was estimated that in 2000 the prevalence of Glaucoma was 3.3% of the population over the age of 40 years and 5% of the population over the age of 80 years (Gray, et al., 2000). It has recently been reported that 20% of the eye clinic workload consists of Glaucoma patients (Fu, et al., 2023).

1.2 Route of administration for anti-hypotensive ocular drugs

Currently there are a number of hypotensive eye drops that are considered the first line of treatment in the medical management of POAG and OHT (Alexander et al., 2002; McKee et al., 2005). The topical application of these drugs is advised for use directly to the ocular surface followed by eye closure and punctal occlusion for up to two minutes (Huang and Lee, 1989). By following this procedure, it is hoped that the active ingredients in these eye drops stay in contact with the ocular surface (cornea) for the maximum amount of time before being expelled from the eye by lacrimation, tear dilution and tear turnover (Patton and Francoeur, 1978). It is estimated that <10% of the applied dose actually reaches the intra-ocular tissue that it is intended to act upon (Burstein and Anderson, 1985), since some of the drops will be flushed from the eye after stimulating reflex tearing (Gaudana et al., 2010) and the tightness of the corneal barrier at a cellular level prevents absorption (Bachman and Wilson, 1985). It has been recognised that there may be an alternative drug delivery route for certain molecules that is non-corneal. This route may be able to deliver adequate levels of the active

ingredient from the instilled drop to the iris-ciliary body complex rather than the traditional aqueous humour levels pathway (Ahmed and Patton, 1985).

1.3 Previous strategies to enhance drug delivery

Several strategies have been employed in an attempt to enhance the penetrative properties of topical eye drops including combining the Glaucoma drug with a preservative (Sasaki et al., 1995) or EDTA (Grass et al., 1985; Sasaki et al., 1995). These additives were thought to weaken the tight junctions of the corneal epithelium to aid in the drop reaching its designated target. Unfortunately, these agents have had limited success and an often-detrimental effect to the ocular surface (Grass et al., 1985; Noecker, 2001) and as such resulted in reduced adherence to the eye drop regime by the patients (Friedman 2009; Sleath 2006).

1.4 Applied heat to enhance drug delivery

There has been some anecdotal evidence that the application of heat to the eyelids after instillation of topical mydriatic drops promoted drug permeation and aided in the breakdown of posterior synechiae in acute uveitis cases (Hobbs, 2013). It is on this theory that this proposed feasibility study is based: to find out whether application of heat to the eyelids in combination with the instillation of ocular hypotensive eye drops could lower the intraocular pressure further. This theory has not been studied in any detail and is a new approach for hypotensive therapy in POAG and OHT. The mechanisms in which the application of heat may affect the efficacy of ocular eye drops are still a subject of speculation. However, there have been a number of studies in recent years that have put forward some potential theories linked to blood flow and ocular surface temperatures. Li et al (2018) proposed that blood vessel ischaemia in Glaucoma was a contributing factor to the disease pathway and using a novel temperature-measuring device on rabbits concluded that the retrobulbar blood flow was increased significantly following heat application to the ocular surface. They stated that since Glaucoma sufferers have a lower-than-normal blood supply (Garhofer et al., 2010) the approach of heating the eyelids could provide a convenient and non-invasive technique with no systemic side effects in which to aid the treatment of Glaucoma (Li et al., 2018). The ocular surface temperature in general has been recorded as lower when compared to healthy subjects. Garcia-Porta et al (2019) demonstrated cooler central corneal temperatures and on eye opening (following a period of eye closure) a significant cooling of the ocular surface in glaucoma sufferers compared to the control. The group concluded that both ocular blood supply and tear film stability are important factors in the make-up of Glaucoma disease. Ambient temperatures have also been documented to influence the IOP of glaucoma patients. A significant reduction in IOP was measured in Glaucoma patients during the summer (13.9 ± 11.1°C) compared to the winter (3.28 ± 4.8°C). The group purported that this effect was due to the cooling of the aqueous humour which in turn reduced its fluidity and circulation, contributing to the increased IOP measure (Krebs et al., 2019). It is clear that temperature does have an influence on the IOPs and ocular surface in general in Glaucoma patients and warrants further investigation.

1.5 Effect of heat on the cornea

There is a possibility that the application of heat to the eye could affect corneal hysteresis. This is defined as the difference in pressure when the cornea bends inwards and then outwards during and following air non-contact applanation. The difference in millimeters of mercury (mmHg) can be used to gauge the elasticity of the cornea, specifically its ability to absorb pressure. Corneal thickness and hysteresis are both important factors in the management of Glaucoma and the former has been revealed to be a strong independent risk factor for Glaucoma progression following the results of the Ocular Hypertension study (Gordon et al., 2002). Several studies have also confirmed that low corneal hysteresis also correlates with an increased risk of Glaucoma progression as evidenced by visual fields outcomes (Congdon et al., 2006; DeMoraes et al., 2012). Lower corneal hysteresis has also been shown to be associated with optic nerve damage (Vu et al., 2013). Unlike corneal thickness, hysteresis is often different between the two eyes and can vary with IOP changes and responses to anti-hypotensive medications are likely to be more significant with lower corneal hysteresis (Agarwal et al., 2012). It is likely that corneal hysteresis could also explain the often-asymmetric presentation of Glaucoma with damage often being worse in the eye that has lower hysteresis (Radcliffe, 2014). To detect any changes to corneal hysteresis by the application of heat during this study the IOPs will be measured using the Ocular Response Analyser (ORA) tonometer which will give the average value of hysteresis after three measures in each eye.

1.6 Reducing the burden on patients and NHS finances

Currently the annual mean cost per patient for Glaucoma treatment in the UK is £475 (Rahman et al., 2013) with increasing costs being incurred if an individual progresses on to require Glaucoma surgery (Traverso et al., 2005). If the efficacy of the drops currently being used by patients could be enhanced with the addition of heat to the eye lids, it may reduce the need for increasing a patient's treatment to dual therapy drops reducing the lifelong burden of extra drop instillation on the patient (Nordstrom et al., 2005) and even improving compliance. In addition, it could eliminate the potential need for progressing to surgery, which would lessen the risk of a secondary infection (Ang et al., 2010) due to the invasive nature of the procedures and in both cases would reduce the overall financial burden for the NHS (Fiscella et al., 2009; Tham et al., 2014; Varma et al., 2011).

Along with the day-to-day costs to the NHS of Glaucoma treatment (topical and surgical) the condition also puts sufferers at an increased risk of falls due to their compromised field of vision. A recent study by McGinley et al (2020) estimated that the cost of admissions for falls where the patients also had a diagnosis of glaucoma was £28.6 million annually in the UK. This was extrapolated from data collected at Maidstone and Tunbridge Wells NHS trust where 11.7% of admissions for falls in a calendar year involved the aforementioned patient group (McGinley, et al., 2020).

Glaucoma is a chronic condition that once diagnosed will generally require some form of treatment for the remaining lifetime of the patient. Rahman et al (2013) conducted a study to calculate the average annual mean cost based on patients at the Glasgow Royal Infirmary. The yearly cost of non-drug and drug therapies for each patient averaged at £475 (Rahman, et al., 2013). In a more recent study analysing the costs of Glaucoma clinics in the UK Fu, et al., reported that the annual cost of a Glaucoma patient to the NHS between 2013-2018 ranges from £352-£512 depending on disease severity (Fu, et al., 2023). The annual cost of Glaucoma medication in England in 2018 was 114.2 million and represented the costliest indication within ophthalmic prescriptions (Hogg and Connor, 2020).

This disease contributes to a significant proportion of the NHS expenditure annually with one study reporting that the UK spent £300 million on Glaucoma care in 2002, with a noticeable increase in the new cases of glaucoma receiving treatment these costs are likely to escalate further (Rouland et al., 2005).

The economic burden in terms of additional treatments that are required and hospital visits, to the personal burden of living with the condition of glaucoma will increase as the disease progresses and the glaucomatous damage worsens and in general has an impact on the quality of life for the patient even in the early stages.

As the glaucomatous damage worsens for the patient, the burdens in terms of economics and the need for additional treatments and close monitoring via hospital visits to personal in terms of quality of life will continue to impose increasing costs on the NHS costs and resources. This cost increases incrementally by approximately £58 for each stage that the disease becomes more severe, and this does not take into account the vision rehabilitation and low vision service costs (Traverso et al., 2005).

2 RATIONALE

To investigate whether applying heat to the eyelids in combination with ocular hypotensive eye drop instillation, can enhance the efficacy of ocular glaucoma medication and lead to a further lowering of IOP. Although there is anecdotal evidence that ocular drug can be enhanced with the application of heat in combination with mydriatics in acute uveitis patients, this theory has not been studied in any detail and is a new approach for hypotensive therapy in POAG and OHT. The prediction is that applying heat to the eyelids will increase the efficacy of instilled drops and result in a further lowering of IOP in individuals diagnosed with POAG/OHT. In this study we aim to use commercially available goggles used to heat the eyelids up to a temperature of 42.5˚C for a period of ten minutes. This approach has been recommended by the DEWS II for the treatment of meibomian gland dysfunction (MGD) and when combined with lid massage aids in the unblocking of the Meibomian glands (Jones et al., 2017). Several studies have shown the safety and efficacy of these devices (Pult et al., 2012; Castillo et al., 2014; Villani et al., 2015). Pending the results of this feasibility study, we would aim to provide proof of concept that the addition of heat to the eyelids enhances the

efficacy of anti-hypotensive eye drops with a view to using this as a basis for a larger scale study in the same field. From this approach we hope to start providing information and scientific basis for the use of existing therapies in this new patient group to help enhance the treatment for this chronic sight threatening disease.

2.1 Background to the proposed research

1) What clinical unmet need are you addressing with the proposed research?

To investigate whether the efficacy of the Glaucoma eye drops to reduce IOPs can be made more effective. This would reduce the burden to the patient in terms of side effects and drop frequency and reduce the cost to the NHS.

2) What novel solution / technology are you proposing to meet the clinical need identified?

The eyelids will be heated using Blephasteam® or an equivalent device, a medical device consisting of a pair of goggles designed to relieve the symptoms of Meibomian Gland Dysfunction (MGD). The eyepieces of the goggles provide latent heat without pressure and once the moistened insert is included provides a high humidity environment (Jones et al., 2017). These eyepiece chambers promote fluidisation of the secretions in the glands. The alternate current supplied wireless device will be plugged in for 3-4 minutes to reach temperature, a light indicates when it is ready for use. A water carrier will be filled with drinking water will be inserted into the mask, the goggles are worn for 10 minutes, which is timed by the device. It has been reported that moist and non-moist lid-warming devices are equally efficient at improving the symptoms of MGD (Arita, et al., 2015). In this study we are repurposing this piece of equipment to investigate whether it can enhance the effect of the eye drops and further reduce IOP when used in conjunction with hypotensive eyedrops. Each patient will have their own water carrier for hygiene purposes.

3) Are there competing solutions / technologies that are already available in the clinic or are currently being developed?

We have performed an extensive literature search in conjunction with our library service to determine whether there are currently any other studies or similar approaches being employed in a manner that we have put forward in this feasibility study. There is anecdotal evidence that the application of heat can enhance the effectiveness of mydriatric drops. There have been no studies that have tested the concept of applied eyelid heat in combination with anti-glaucoma medication in humans.

4) What is the advantage of your proposed solution compared to solutions / technologies that are already available in the clinic or are currently being developed?

The advantage of the approach proposed in this study is to utilise an existing medical device

that would be readily available to patients and can be reused. By using this device in conjunction with their hypotensive eye drops it is hoped that the effectiveness of their current treatment will be enhanced and as a secondary action may also improve any MGD which is frequently reported in patients medically managed for Glaucoma.

3 THEORETICAL FRAMEWORK

There is a lack of evidence that applying heat to the eyelids may improve ocular drug delivery in all areas of Ophthalmology. This feasibility study has chosen to focus on the hypothesis that the addition of heat will enhance the efficacy of ocular hypotensive eye drops used in the treatment of POAG and OHT will result in a significant reduction in IOPs when compared to the use of ocular hypotensive eye drops alone. There is a great potential use for a favourable outcome from this study in that it could reduce the need for additional eye drops or progression to surgery. It is currently well accepted that applying heat to the eyelids is a safe procedure and is a mainstay of treatment for MGD and it is this approach that will be used in this study to determine whether ocular drug delivery can be enhanced. The clinic at Hinchingbrooke (HH) and Peterborough City Hospital (PCH) runs regular Glaucoma clinics with a large number of these patients who have an active diagnosis of POAG or OHT. Patients will be approached that currently use their eye drops in the morning as it is thought that this in combination with the heat will enhance the effect further. If proof of concept is realised through this feasibility study, then a larger scale project will be put forward to investigate whether the effect is demonstrated in all Glaucoma hypotensive eye drops and whether it is also effective if patients instil their drops in the evening. It is acknowledged that the effectiveness of the glaucoma eyedrops could be increased with heat alone and/or with the additional beneficial effects imparted on the ocular surface by virtue of improving any underlying MGD condition. As such the baseline MGD status of all patients will be recorded to determine to what level the improvement of this condition may affect the overall outcome.

4 RESEARCH QUESTION/AIM(S)

To investigate whether applying heat to the eyelids of patients with POAG or OHT in combination with ocular hypotensive eye drops results in further lowering of IOP.

Primary objective
The primary objective of the study is to demonstrate that heat applied directly to the eyelids in combination with the instillation of anti-Glaucoma eye drops induces a further lowering of IOPs when compared to the use of anti-Glaucoma eye drops alone.

Secondary objective
The secondary objective of the study is to determine whether there is a timepoint during the

course of the day (phasing) that demonstrates the largest difference in IOP following heat and hypotensive eye drop combination.

4.1 Objectives

4.1.1 Primary objective:

1. The mean difference of IOP in the same eye (right eye) from the baseline IOP and after the bilateral heat intervention.

4.1.2 Secondary objectives:

1.Adverse events

2.QoL questionnaires

4.2 Outcome

Should this study confirm the proposed hypothesis it would be the intention of the researchers to expand the scope of the study by collaborating with other NHS trusts to increase subject recruits, include broader patient demographics and a wider range of anti-hypotensive eye drops to investigate whether a particular class of drug would be more sensitive to temperature and whether gender or race has an effect on the IOP. Although it is not within the scope of the current budget applied for, future studies would also include a non-glaucomatous control group who would undergo the same IOP phasing protocol with and without the heated goggles to establish whether heat alone would be sufficient to reduce the IOP in comparison to the combination of heat and anti-hypotensive eye drops in Glaucoma patients. It would be the intention of this research team to apply for further funding to support this action from charities such as Glaucoma UK which encourage applications from Optometrists to the open call Glaucoma care grant.

5 STUDY DESIGN and METHODS of DATA COLLECTION AND DATA ANALYIS

This is a feasibility single-centred, interventional study that will evaluate the impact of using heat applied to the eyelids in reducing IOP measured over the course of a day (phasing) in POAG and OHT patients. The trial will involve 24 patients with a diagnosis of POAG with IOPs ≤24mmHg or OHT with IOPs ≤ 30mmHg. Participants would already be using a prostaglandin analogue (PGA) eyedrop monotherapy instilled in the morning-this approach has been adopted to reduce the variability of the results. Before the baseline visit the principle

investigator (PI) or research optometrist will receive consent from the patients, who will then undergo a visual fields test (Humphrey sita fast 24-2) if one has not already been completed in the previous three months.

One week prior to the baseline visit and whilst participating in the study the patients will be asked to complete a 'drop compliance diary' documenting when and how frequently they are using their Glaucoma medication. This is to ensure that they are adhering to their advised schedule of drop regime beforehand and that taking part in the study is not influencing their habitual drop routine. This approach is to help confirm that the reason for any reduction in IOP over the course of the study can be more confidently attributed to the intervention of heat rather than a possible phenomenon that being part of the study might naturally improve compliance with their eyedrops and hence IOP would be reduced in this manner.

The patient will attend the clinic for three separate visits each approximately one week apart, starting with phasing 'without heat', then phasing 'with heat' and lastly phasing wearing the Blephasteam mask but with no heat as a control. The Blephasteam mask will only be used on the days of the clinic visits, the participants will not be required to use the device at home. The water carrier inserts for the masks will be designated to the same patient throughout the study for hygiene reasons. The inserts for the mask will be moistened and fitted according to the manufacturers' instructions. The wireless device will be left to reach temperature for 3-4 minutes then the patient will be asked to wear the mask and be instructed to keep their eyes closed, this occurs once at the start of each visit. The device warms the ocular surface for a set time of 10 minutes, after which the participants will remove the mask and instil their habitual Glaucoma eyedrops. They will be instructed to close their eyes and apply light pressure on the inner corner of the eye for 30 seconds. The IOP will then be measured at the first time point with the ORA and Goldman devices. Although both eyes will be treated with the heat mask only the right eye results (to eliminate bias) will be used for the statistical analysis. During the visits the patients' will have their best corrected visual acuity (BCVA) reviewed before and after measurements are taken. IOPs are measured first using the ORA tonometer (Reichert Inc., Germany) followed by the Goldman tonometer (Haag-Streit AG, Switzerland) five minutes later as per previous studies measuring IOP with the sequential use of tonometers (Tejwani et al., 2015). These IOP measures are taken at five set time points during the day called 'phasing': 08:30 +/- 30 mins, 10:30 +/- 30 mins, 12:30 +/- 30 mins, 14:30 +/- 30 mins and 16:30 +/- 30 mins. An average of three measures will be taken using the ORA machine, when using the Goldman tonometer three measures will only be taken if the first two are not within >2mmHg of each other. The procedure for the Goldman tonometer will be as follows: Two individuals (an operator and a reader) will perform the readings for the study visits. The operator will be responsible for operating the slit lamp, tonometer, and the instrument dial, while the reader will read and record the results. A full anterior segment slit-lamp examination will be performed at the end of each phasing visit to ensure there are no adverse effects experienced following the treatment, including grading of the Meibomian glands (Efron scale). Additional assessments include adverse events and quality of life and ocular questionnaires.

One to two weeks after completion of the study the patients will undergo a further visual

fields test (Humphrey sita fast 24-2) to ensure no significant progression of their disease has occurred as a result of the study regime. All data will be recorded and stored for analysis at the end of the trial and made available to the standard of care treating clinician. At the end of the trial the patients will continue their Glaucoma visit schedule as requested by their treating Ophthalmologist.
All attempts will be made to have participants complete the study by organising visits that fit in with their timetable and offering further appointments should the participant not be able to attend on a certain day. Participants will be offered reimbursement for travel and refreshments on the day of their study visits. In the case of participant 'drop-outs', the research team will attempt to recruit further participants otherwise patients on whom all the tests could not be performed will be excluded from analysis.

When designing this trial, it was important for us to ensure that the comments and suggestions of the public and patients were taken on board, so that we could confirm that this trial was suitable for people with POAG or OHT. To do this, a patient and public involvement (PPI) forum was be organised on 30th May 2023 and the trial subsequently developed with the help of people diagnosed with Glaucoma in the Cambridgeshire area who agreed that the tests and procedures included in this study were practical and acceptable to patients.

It is the intention of the research team that the results of the study will be disseminated in peer-reviewed articles and at ophthalmic conferences.

5.1 Data collection and recording

Baseline and follow-up data will be recorded on a Case Report Form (CRF). All CRFs will be stored in a secure cabinet and the data will be inputted into a password protected database. The names of patients who decline to take part or those who do not meet eligibility criteria will also be recorded in a secure database to ensure that they are not re-approached. Each participant will be assigned a unique trial ID number at the start of the assessment process. This number will be written on all clinical assessment forms, datasheets and databases used to record participant data. A hard copy of a record sheet linking patient identity, contact details and trial ID number for all participants will be kept at the sponsor site (North West Anglia Foundation Trust). This will be placed securely in a locked filing cabinet separate from datasheets. All data will be kept secure at all times and maintained in accordance with the requirements of the Data Protection Act and archived locally according to clinical trial good clinical practice (GCP) regulations and the host institutions additional procedures.

5.2 Statistical Methods

5.2.1 General:

Data will be presented using descriptive statistics; continuous data will be summarised using means & standard deviations if normally distributed otherwise using median and interquartile

range. For categorical data frequencies and percentages will be reported. Missing data will be reported.

Primary analysis:

1. Mean difference of IOP will be analysed using paired t-test if normally distributed or using Wilcoxon signed rank test for pared cases if not normally distributed.

Secondary analysis:

1. Adverse Events will be analysed using Chi-squared test or a summary by presenting full listing and frequencies & percentages.
2. Quality of Life (QoL) questionnaires will be analysed using normality tests, descriptive statistics and reliability tests.

5.2.2 Datasets

To determine whether there is a significant change in IOP in each participant, the IOP measured with and without the addition of heat over the five time points will be used in a one-way repeat measure ANOVA test will be completed for each day of phasing. A paired t-test will be used to establish significance between an individual's IOP measure at a certain time point with or without the addition of heat. A difference of 1.5mmHg in IOP mean deviation would be considered a significant change of IOP. This value has been used in previous Glaucoma studies (Allergan Bimatoprost SR and Thea In-Sight) to provide a 95% confidence interval. A paired t-test will be used to establish any significant change in BCVA at baseline and exit visit based on a mean SD change of 0.1 logMAR or 5 ETDRS letters. Ocular safety parameters, QoL (EQ-5D-5L) and OSDI questionnaires, visual fields and slit-lamp exam measures will be summarised for the cohort by mean, standard deviation (SD), median, minimum and maximum values. A non-parametric analysis (Wilcoxon signed rank test) will be used if the data is found to not be normally distributed. Ocular adverse events and safety variables will be tabulated by whether the participant has received heat treatment or not before instilling their anti-hypotensive eye drops. Normality of the data will be checked by plotting histograms of the data (separately before and after the heat) and not using stats tests. Differences will be considered statistically significant P values less than 0.05.

6 STUDY SETTING

The data will be collected at the sponsor site of Hinchingbrooke and Peterborough City hospitals both part of NWAFT. The patients that will be recruited for the study will normally attend the Glaucoma clinic at this site so this will ensure continuity for them. At both hospitals an ophthalmology research team member will conduct the collection of data along with the PI. This will be a single centre pilot study that will not require any specific requirements; most of

the equipment for the study is already available within the eye clinic. The heat masks will be purchased specifically for the study from the grant awarded by Sight Research UK.

7 SAMPLE AND RECRUITMENT

7.1 Eligibility Criteria

7.1.1 Inclusion criteria

Patient fulfilling all of the following criteria will be eligible:

- Informed consent signed and dated
- Patients diagnosed with bilateral POAG or OHT
- Patient aged ≥ 18 years old
- Both eyes with a central corneal thickness of between 500-600 µm
- Both eyes with a diagnosis of POAG or OHT, initially treated and controlled for at least six months by a prostaglandin analogue monotherapy (mane instillation)
- IOP ≤ 24 mmHg in at least one eye POAG
- IOP ≤ 30 mmHg in at least one eye OHT

7.1.2 Exclusion criteria

Patient will NOT be eligible if ONE or MORE of the following criteria is met:

- ➢ Fundus examination not performed or not available within 12 months
- ➢ Visual field not performed or not available within 12 months
- ➢ Advance stage of Glaucoma, defined by at least one of the following criteria:
- ➢ Absolute defect in the ten degrees central point of the visual fields
- ➢ Severe visual field loss: MD < -18 dB
- ➢ Risk of visual field worsening as a consequence of participation in the study according to the investigator's best judgment
- ➢ Far best corrected visual acuity ≥ +0.7 logMAR
- ➢ History of trauma, infection, clinically significant inflammation within the previous three months
- ➢ Ongoing or known history of ocular allergy and/or uveitis and/or viral infection Clinically significant or progressive retinal disease (e.g. retinal degeneration, diabetic retinopathy, retinal detachment)
- ➢ Presence of at least one severe objective sign among the following:
  - ➢ Conjunctival hyperaemia (Grade 5 - Efron scale)
  - ➢ Superficial punctate keratitis (Grade 4/5 – Oxford scale)
  - ➢ Blepharitis (Grade 3 – Efron scale)
  - ➢ Severe dry eye as assessed by the investigator
  - ➢ Corneal ulceration
  - ➢ Any palpebral abnormality incompatible with a good examination
  - ➢ Any other abnormality preventing accurate assessment e.g. reliable tonometry measurement, visual field examination, fundus examination.
  - ➢ A patient judged to have poor compliance with their glaucoma drops according to the investigator's best judgement

7.2 Sampling

POAG and OHT patients will be recruited for the study since this represents the largest percentage of Glaucoma diagnoses. Regarding medication, only patients using eye drops in the mornings will be recruited since it is hypothesised that this regime combined with heat will show better IOP lowering response over the day that can be demonstrated during phasing.

7.2.1 Size of sample

This is a feasibility study and as such a sample size of 24 participants has been selected for this quantitative research and this has been based on the figures previously cited by Sim and Lewis (2012) and Julious (2005) and also taking into account the budget available for equipment. The average of the IOPs measures taken at each time point with the ORA or Goldman tonometer and with and without the addition of heat will be used for statistical analysis.

7.2.2 Sampling technique

Potential participants will be identified from the Glaucoma clinics at Hinchingbrooke and Peterborough City hospitals. This approach will be used to ensure that the most appropriate patients are approached for the study and will allow a greater number of potential participants to be pre-screened. Only patients fluent in English will be invited to take part in the study as there are no multi-language documents available. This is a study to demonstrate proof of concept with a small budget for running the project and as such resources are limited. However, should the research be expanded in the future it will include the provision of multi-language paperwork to include develop inclusivity.

7.3 Recruitment

Pre-screening of the Glaucoma clinics will be undertaken by the Ophthalmology research team to identify any possible candidates using Medisoft (an electronic medical records system for ophthalmology); they will be diagnosed with POAG or OHT and have been on hypotensive ocular eye drops for the past six months. Potential participants will need to be using prostaglandin analogue (PGA) as a monotherapy with patients using their eye drops in the morning. Those identified as suitable for the study will then be approached by Mr S. Alam or Dr C. Willshire when they attend for their clinic appointment. Prospective participants will be fully informed as to what participation involves during their consultation with a clinician or a member of the study team. They will be provided with all the relevant information that they need to make an informed decision whether or not to participate. The study will be discussed with the patient at their appointment and if they are interested to be screened for the study will be given a patient information sheet (PIS). After giving the patient sufficient amount of time to read the PIS they will be contacted by the Ophthalmology research team by phone to answer

any questions that they have and then a convenient appointment arranged for the baseline appointment. When the patient attends for their first visit Mr S. Alam or Dr. C Willshire will receive informed consent before baseline measurements are undertaken including a baseline visual fields test (Humphrey sita fast 24-2 if this has not been completed in the previous three months). Following this, successful patients will schedule have an appointment arranged for the first day of phasing. Full explanation of how to use the Blephasteam® device will be given to the patient before commencing the study. On the second visit of phasing the patient will be asked to wear the mask and be instructed to keep their eyes open. The device warms the ocular surface for a set time of 10 minute, after which the participants will remove the mask and instil their habitual Glaucoma eyedrops. They will be instructed to close their eyes and apply light pressure on the inner corner of the eye for 30 seconds, any excess eye drop will be wiped away from the external adnexa using a tissue. The first IOP measurements will then be taken at 08:30 +/- 30 minutes. There will then be four other subsequent IOPs measures taken at approximately two hour intervals +/- 30 minutes (10:30, 12:30, 14:30 and 16:30).

7.3.1 Sample identification

Dr C.Willshire and Miss J. Williams will identify potential participants for the study by reviewing medisoft notes for upcoming Glaucoma clinics at Hinchingbrooke and Peterborough City hospitals. Once a potential patient has been identified the PI (Mr S. Alam) will be informed as to when they will be attending for their normal appointment, at this visit the patient will be informed about the study and asked by the PI as to whether they would like to receive any more information, a PIS will be given to the patient at this visit. After a sufficient amount of time has elapsed for the patient to read the PIS Dr C.Willshire or Miss J. WIlliams will contact the patient by phone and enquire as to whether they have any questions about the study and if they would like to proceed. If the patient agrees to participate in the study they will be booked in for a baseline visit at their convenience. Patients may also be sent an invitiation letter to the study through the post. The pack would include the PIS and an opt-out slip that they can return to the research team in a stamp addressed envelope if they did not want to contact the research team directly. Posters advertising the study will also be displayed in the waiting area of the eye clinic any patients that are interested in receiving more information about the study will be given a contact telephone number for the ophthalmology research clinic. Only members of the ophthalmology research which form part of the patient's existing clinical care team will have access to patient records without explicit consent in order to identify potential participants, and check whether they meet the inclusion criteria. Patients will be offered expenses to cover reasonable travel costs up to £20 per visit and the cost of a meal-up to £15 for each visit. Funding will also be applied for to cover the cost of the lid warming devices (Blephasteam®). The Goldman pressure machine and ORA tonometer will be used to measure the IOPs on patients when they attend for the phasing visits. These machines are currently available in the eye clinic and forms part of the patient's normal standard of care.

7.3.2 Consent

Patient information leaflets and consent forms will be designed so that the patient can understand the purpose and nature of the research. Individuals will be supplied with as much information as they require in order to make an informed decision about participation in this study including what the research involves, its benefits (or lack thereof) and any risks and burdens. It will be made clear that the decision whether or not to participate will not affect any on-going or future treatment within each trust. It will be made clear that participation is voluntary and that they can withdraw at any time and for any reason. They will be assured that confidentiality will be maintained at all times.

Having agreed to participate in the study, informed consent will be received from the patient by the PI prior to the patient entering into the screening phase. The patient will be given the opportunity to ask questions and these will be recorded along with answers.

They will then undergo a screening assessment, where, if eligible, they will then be booked in for continuation of the study.

7.4 Summary

POAG and OHT patients using a prostaglandin analogue monotherapy will be recruited to undergo a series of IOP phasing visits with and without heat applied to the eyelids.
There will also be a 'control' phasing visit whereby the participant will wear the mask but the heat aspect will not be activated. The study will measure the change in IOP (using the Goldman and ORA tonometers) to establish whether there is any significant difference in IOP with or without the heat when combined with the patient's habitual glaucoma drop therapy, and at which time point during the day displays the maximal effect.

8 ETHICAL AND REGULATORY CONSIDERATIONS

The conduct of this study will be in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

This protocol and related documents will be submitted for review to the National Research Ethics Service Committee. Local approval will be sought before recruitment may commence at a study site. The Study Coordination Centre will require a written copy of local approval documentation before initiating each centre and accepting participants into the study.

Prior to any study procedures information sheets will be provided to all eligible subjects and written informed consent obtained. This study will not enrol subjects who cannot consent for themselves.

General

There are four visits that the participants need to undergo in excess of standard of care. Standard care of clinic appointments in the Glaucoma clinic will be continued as normal. The

precise risks and benefits of participating in the study will be outlined in patient information sheets.

Ongoing treatment if the study is successful

All participants will be made aware of the results of the study and a letter thanking them for taking part in the study. If the study successfully establishes efficacy, the patients will be informed that these masks can be purchased but will not automatically be available in the NHS.

8.1 Assessment and management of risk

In terms of benefits to participants, the heat masks may result in a significant and meaningful effect by reducing the IOP in combination with their ocular hypotensive eye drops. A secondary effect may be to improve any existing MGD for which the device is usually indicated. Heat therapy is the standard treatment regime for obstructive meibomian gland dysfunction (MGD). This would increase the quality of the tear film, by enhancing the meibum supply from the glands situated on the upper and lower eye lids. If clinical effectiveness is shown, the Blephasteam® would provide a non-invasive treatment option for one of the most common causes of reversible blindness (Blomdahl et al., 1997). This would also reduce the chance that patients would need to progress to dual eye drop therapy or surgical intervention.

The risks of wearing the masks are negligible; a recent study stated that the Blephasteam® device provided safe and effective warmth to the ocular area without any adverse effects on the ocular surface in this study (Purslow et al., 2010; Villani et al., 2012). Each patient will receive their own insert for the Blephasteam® device to use throughout the study to ensure there will be no cross contamination between patients.

Compliance with the heat-masks may be an issue but all site personnel will stress optimal compliance with all patients and ensure that instructions are followed by helping the patient use the device at the time of the visit.

Blephasteam ® CE certified medical device.

8.2 Research Ethics Committee (REC) and other Regulatory review & reports

Before the start of the study, a favourable opinion will be sought from a REC (researchers should check if they are required to gain a favourable opinion from the UK Health Departments Research Ethics Service NHS REC) or other REC approval) for the study protocol, informed consent forms and other relevant documents e.g. advertisements.

For NHS REC reviewed research

- Substantial amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement at site.
- All correspondence with the REC will be retained.
- It is the Chief Investigator's responsibility to produce the annual reports as required.
- The Chief Investigator will notify the REC of the end of the study.
- An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended.
- If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.
- Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

Regulatory Review & Compliance

Before the site can enrol patients into the study, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place. Specific arrangements on how to gain approval from participating organisations are in place and comply with the relevant guidance.

For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

Amendments

For studies involving the NHS:

If the sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the sponsor must submit a valid notice of amendment to the REC for consideration. The REC will provide a response regarding the amendment within 35 days of receipt of the notice. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC.

If applicable, other specialist review bodies (e.g. Confidentiality Advisory Group (CAG)) need to be notified about substantial amendments in case the amendment affects their opinion of the study.

Amendments also need to be notified to the national coordinating function of the UK country where the lead NHS R&D office is based and communicated to the participating organisations (R&D office and local research team) departments of participating sites to assess whether the amendment affects the NHS permission for that site. Note that some amendments that may be considered to be non-substantial for the purposes of REC still need to be notified to NHS R&D (e.g. a change to the funding arrangements).

8.3 Peer review

The protocol has been reviewed by Mr Richard Wormald who is an indepdendent expert researcher and Ophthalmologist in the field of Glaucoma based at MEH.

8.4 Patient & Public Involvement

A patient and public involvement (PPI) forum was organised on 30th May 2023 to assess the feasibility of the intervention i.e. how the patient would feel about the study protocol and using this approach to Glaucoma treatment on a regular basis. The protocol and patient information leaflet have been amended in accordance with the feedback from the comments provided by the attendees.

8.5 Protocol compliance

Accidental protocol deviations can happen at any time. Should they occur, the episodes will be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately. The Ophthalmology team will work to ensure that protocol deviations are kept to a minimum, by liaising closely with the participants to increase adherence to the protocol.

8.6 Data protection and patient confidentiality

The Chief Investigator will act as custodian for the trial data. Personal data will be regarded as strictly confidential. To preserve anonymity, any data leaving the site will identify participants by their initials and a unique study identification code only. No identifiable patient data will leave the study site. The study will comply with the GDPR, 2018. All study records and Investigator Site Files will be kept at site in a locked filing cabinet with restricted access. Any breach of confidentiality will be minimised by adherence to the European Data Protection Act, with reassurance stated on the consent form to minimise any potential distress.

8.6.1 Data Management

Data management will be consistent with MRC Guidelines for Good Clinical Practice in Clinical Trials and the Data Protection Act. Centre PIs will ensure that all personnel are familiar and

comply with these guidelines. Data management procedures for the trial will be developed and overseen by the Contract Research Organisation (CRO).

8.7 Indemnity

Specific trial insurance for the **HALO** study will be provided by the Sponsor (NWAFT). This will provide compensation for negligent harm arising from the design and management of the study with the limit of insurance set at £5M per patient with an aggregate value of £5M.

Negligent harm arising from the conduct of the study at the participating NHS sites will be covered by NHS Indemnity.

8.8 Access to the final study dataset

The study may be subject to an audit by the sponsor, and other regulatory bodies to ensure adherence to GCP. The investigator(s) / institutions will permit study-related monitoring, audits, REC review and regulatory inspection(s), providing direct access to source data/documents. The Investigator(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing the Sponsor(s), Regulators and REC direct access to source data and other documents (e.g. the patients' case sheets).

9 DISSEMINATION POLICY

9.1 Dissemination policy

The data will be owned by the study sponsor (NWAFT). On completion of the study the data will be analysed and tabulated, and a Final Study Report prepared. This will be available in digital form or as a paper version for the participants to view the outcome of the study. The participating investigators will have the rights to publish study data in appropriate journals and the intention is to submit results to an Optometric conference. Any funding or supporting body will be acknowledged within the publications.

9.2 Authorship eligibility guidelines and any intended use of professional writers

The PI and Ophthalmology research team involved in this study will be granted sole authorship.

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11.1 Appendix 2 – Schedule of Procedures

Procedures	Visits					
	Identification and consent	Visit 1- phasing without heat	Visit 2- phasing with heat	Visit 3-phasing with mask but no heat	Visit 4 – safety check	
Informed consent	x					
Demographics	x					
Medical and ocular history	x					
QoL questionnaires		x	x	x		
OSDI questionnaire		x	x	x		
Visual fields	x				x	
Drop compliance diary	x	x	x	x		
Slit-lamp examination		x	x	x		
Corneal fluorescein stain (Oxford grading)		x	x	x		
Meibomian gland dysfunction (Efron grading)		x	x	x		

Conjunctival hyperaemia (Efron grading)		x	x	x		
Application of Blephasteam®			x			
Instillation of habitual hypotensive eye drops		x	x	x		
IOP @ 08:30 +/- 30 mins		x	x	x		
IOP @ 10:30 +/- 30 mins		x	x	x		
IOP @ 12:30 +/- 30 mins		x	x	x		
IOP @ 14:30 +/- 30 mins		x	x	x		
IOP @ 16:30 +/- 30 mins		x	x	x		
Adverse events		x	x	x		
Far best corrected visual acuity (BCVA)		x	x	x	x	
Verification of inclusion and exclusion status	x					

13.3 Appendix 3 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC.