WIGS

The Water Drinking Test in Glaucoma Study: *WIGS*

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Protocol authorised by:

Name & Role	**Date**	**Signature**

Study Management Group

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Clinical Queries

Clinical queries should be directed to Serge Miodragovic who will direct the query to the appropriate person.

Sponsor

Imperial College Healthcare NHS Trust is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Joint Research Compliance Office
Imperial College London and Imperial College Healthcare NHS Trust

Room 215, Level 2, Medical School Building
Norfolk Place
London, W2 1PG
Tel: **0207 594 9459/ 0207 594 1862**
http://www3.imperial.ac.uk/clinicalresearchgovernanceoffice

Funder

WIGS study is not funded.

This protocol describes the WIGS study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATIONS

DTC – Diurnal Tension Curve

GCC – Ganglion Cell Complex

IOP – Intraocular Pressure

MD – Mean Deviation

mDTC – modified Diurnal Tension Curve

NFL – Nerve Fiber Layer

NTG – Normal Tension Glaucoma

OCT – Optical Coherence Tomography

VF – Visual Field

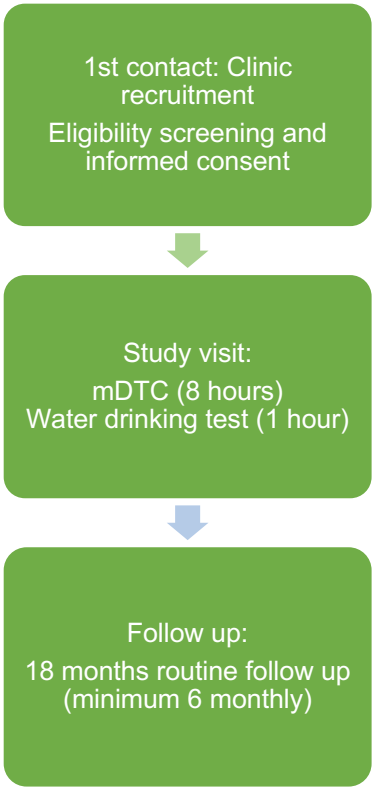
WDT – Water Drinking Test

KEYWORDS
Intraocular pressure, stress test, correlation, water drinking test, modified diurnal tension curve, glaucoma progression, OCT, VF, normal tension glaucoma

STUDY SUMMARY

TITLE	The Water Drinking Test (WDT) in Glaucoma Study: WIGS
DESIGN	Observational cohort study
AIMS	To investigate the correlation and agreement between the intraocular pressure peaks detected during the water drinking test and modified diurnal tension curve in glaucomatous eyes and to analyse whether this is associated with prognostic outcome. We will also measure autonomic nervous system activation during the test to investigate one possible mechanism behind it.
OUTCOME MEASURES	Peak IOP measurements from the two different methods
POPULATION	Primary open-angle and normal tension glaucoma patients
ELIGIBILITY	Primary open-angle and normal tension glaucoma patients, not on anti-ocular hypertensive therapy. - Able to give informed consent to participate in the study - Aged between 18 and 80 years of age - Clear optical media - Spherical equivalent +-10D
DURATION	Single visit

REFERENCE DIAGRAM



1. INTRODUCTION

1.1 BACKGROUND

1.1.1. IOP and glaucoma

Glaucoma is a progressive optic neuropathy characterised by progressive loss of retinal ganglion cells, leading to thinning of the retinal nerve fibre layer and visual field losseS[1]. It is the leading cause of irreversible blindness in the world [2] and affects more than 70 million people worldwide[3].

Intraocular pressure (IOP) is the main risk factor for the development and progression of glaucoma [4] [5]. The gold standard for intraocular pressure (IOP) measurement is applanation tonometry [6]. Routine office measurements may not detect IOP peaks in roughly 30% of patients due to variation throughout the day [7], and this detection failure may be responsible for visual field progression in apparently well-controlled patients [5].

1.1.2. IOP measurement methods

To provide more reliable data, twenty-four hour diurnal tension curves (DTC) can be measured. However, 24-hour IOP monitoring is unfeasible and time consuming in the majority of circumstances. The modified diurnal tension curve (mDTC) involving IOP measurements every 2 or 3 hours during office hours is therefore often used as a shorter alternative.

The water drinking test (WDT) is a tool that aims to indirectly evaluate the eye's aqueous humor outflow facility[8] [9] by putting the drainage system under 'stress' in a test similar to that which may be used in cardiology or endocrinology. More recent research has suggested that water overload with the WDT may correlate well with the IOP peaks detected during a 24-hour intraocular pressure measure[10].

It remains unclear as to the physiological mechanism behind this observed IOP rise. Several hypotheses exist including increases in outflow resistance[11], episcleral venous pressure [12], choroidal expansion [13] and change in blood osmolality. However, it has been observed in one study that 20% of subjects developed change in IOP before change in osmolality could be detected.

Centrally mediated causes, possibly triggered by gastric expansion have been postulated with regards to activation of the autonomic nervous system[14], but this has mainly been characterised in terms of cardiovascular physiology as oppose to intraocular pressure rise. Some evidence has been published to suggest the time course of the autonomic changes observed (rise in blood pressure, reduction in heart rate) are not consistent with reflex activity[15], however in this study only 500mls of water was ingested over 3-4 minutes. This aspect of the test requires further characterisation in relation to the time profiles of the IOP rise.

1.1.3. The role of the WDT in glaucoma

The WDT has been described as an independent risk factor for the development and progression of a glaucomatous field defect in patients with OAG [9,16]. In a prospective study of 5000 patients with open angle glaucoma, the authors found five potential risk factors for the development of glaucomatous visual field lesion: outflow facility, age, IOP, cup/disk ratio

and change in IOP after water ingestion[17]. These data have changed the concept of the WDT, which is now used as a useful tool to assess IOP peaks. Furthermore, the WDT is a reproducible [18,19] low-cost and feasible test in the clinical practice.

1.1.4. OCT and glaucoma progression

OCT has been widely used to measure the thickness of the NFL and GCC, which have strong correlation with glaucoma disease stages[20]. OCT can assist in the diagnosis of glaucoma to a certain extent, with faster rates of OCT progression associated with a higher risk of VF progression[21] . OCT is thought to be more sensitive than VF in detecting progression in the earlier stages of the disease, hense the term 'pre-perimetric glaucoma' [22]. Since OCT measurements have good repeatability and reproducibility, [23] it is clinically advantageous to monitor glaucoma progression using objective OCT structural measurements in the early stages prior to visual field defects appearing.

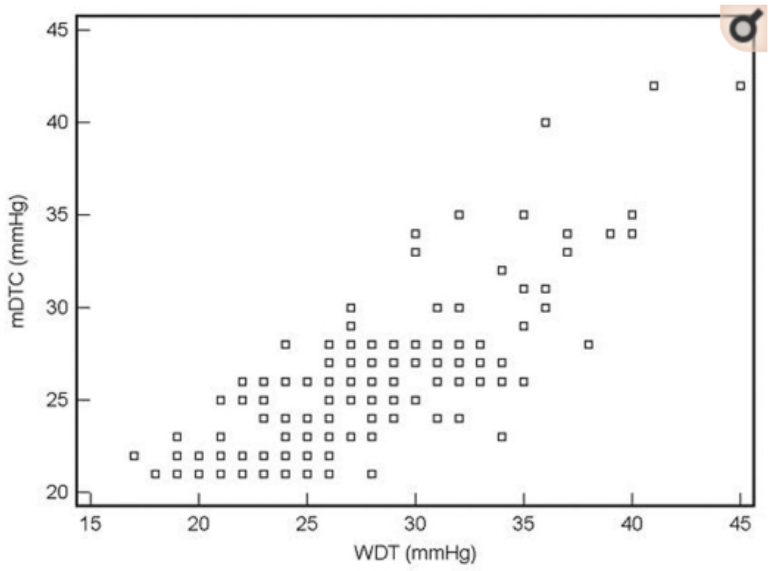
1.1.5. Safety

The water drinking test (WDT) is a safe test for the majority of the population since its intervention is drinking water. However, there are individual cases where it may be harmful; any person with contra-indication of drinking large amounts of water in a small amount of time should be excluded. This includes patients with heart or kidney failure, or those with swallowing difficulties associated with neurological disorders or gastrointestinal strictures or stasis.

1.1.6. Previous studies

Previous studies have shown correlation between the water drinking test and the modified diurnal tension curve [24]. Vasconcelos-Moraes CG et al. [24] showed that the WDT peak was significantly correlated with the mDTC peak (Person's Correlation Coefficient r=0.780 for a 95% confidence interval between 0.716 to 0.831, $p<0.0001$), however this has not yet been widely reproduced. However, this study was conducted on POAG patients who were on topical therapy for raised intraocular pressure, and therefore were required to undergo a washout period of no medication.

Figure 2



Correlation between IOP peaks during the WDT and mDTC

This study showed 95% limits of agreement between the WDT and mDTC IOP peaks ranging from −3.9 mmHg to 8.2 mmHg. In 52.5% of the tests, the agreement was within ± 2 mmHg.

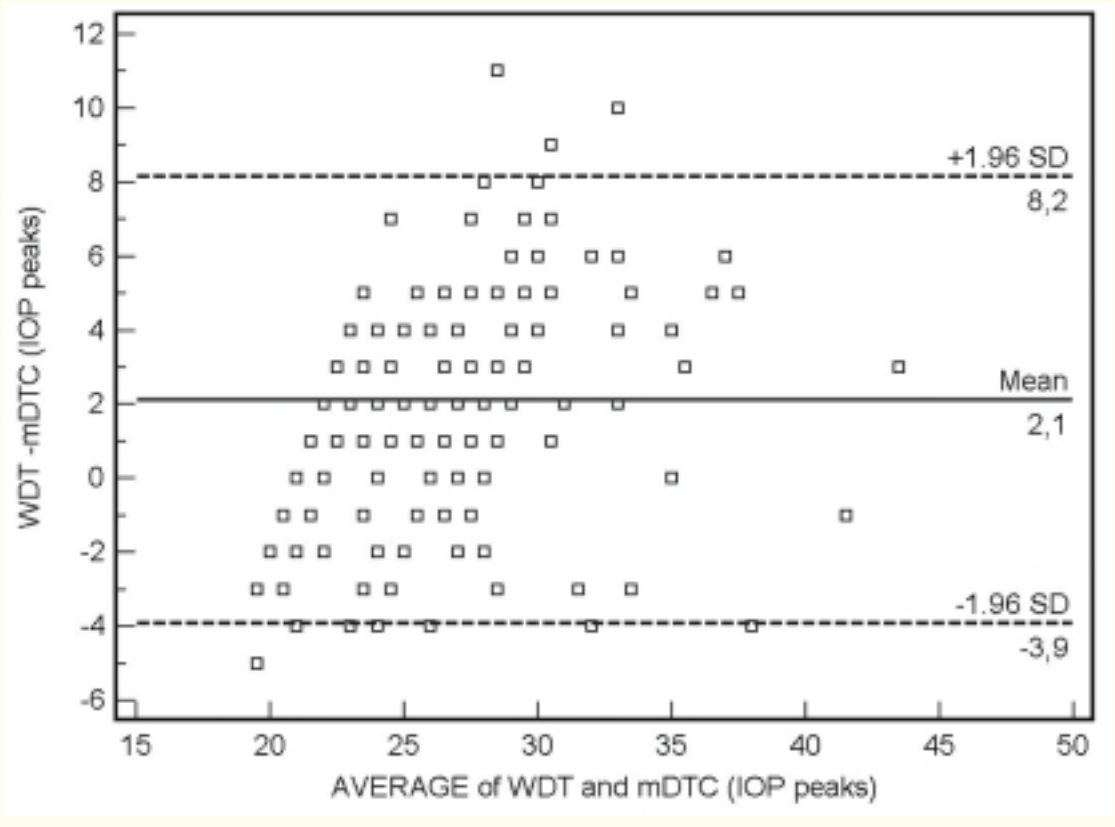


Figure 3

Agreement between the WDT and mDTC peaks

Eighty-two percent of eyes showed higher IOP peaks during the WDT than the mDTC (95% confidence interval between 0.0 and 6.99 mmHg).

When analysing glaucomatous progression De Moraes et al. [9] showed that higher IOP peaks during the WDT were predictive of future visual field progression (hazard ratio=1.11; 95% confidence interval, 1.02 to 1.21; P=0.013), but also that the average and peak IOP during office hours over the same follow-up period were not significantly associated with progression (P=0.651 and 0.569, respectively). This study showed that IOP peaks detected with the WDT were predictive of future visual field progression in a treated POAG population, while office hours measures were not.

Another study performed by Yoshikawa *et al*. [16] in normal tension glaucoma patients showed that the maximum IOP levels after the water drinking test in patients with progressive visual field loss was significantly greater than the levels observed for the non-progressive group. Given that a common indication for referring patients for the mDTC is disease progression despite normal pressures off-treatment ('normal-tension glaucoma'), the agreement of the two tests in this specific cohort is currently under-documented.

1.2 RATIONALE FOR CURRENT STUDY

The current method of using the mDTC is time consuming, labour intensive, and incomprehensive. Not only does the WDT have the potential to improve upon the time consuming and labour intensive nature of the test, but given the active element may improve diagnostic pickup and sensitivity for disease progression, given that the mDTC is only feasibly conducted during office hours.

Further work comparing the currently used mDTC and the WDT to assess IOP peak and fluctuation is necessary. The study mentioned above [24] showed strong evidence of the clinical applicability of the WDT and its correlation with the mDTC. Furthermore, the IOP peak obtained by the WDT has been proved to be an independent risk factor for the development and progression of glaucoma [5,8]. However, to date, there are no studies focusing on OCT data that will indicate progression of 'pre-perimetric' glaucoma, or any studies focusing on the most commonly referred group of patients referred for the test. This will aid us to discern the best way to assess IOP peaks and manage glaucoma treatment and progression.

Our hypotheses are:

- The peak IOP during the WDT correlates with mDCT
- Peak IOP during the WDT is associated with rate of glaucoma progression as measured with OCT
- Changes in autonomic variables associated with IOP rise are consistent with a autonomic reflex as the physiological mechanism behind the test.

2. STUDY OBJECTIVES

- **Primary research objective** is to investigate the correlation and agreement between the intraocular pressure peaks detected during the water drinking test and the standard phasing test.

  Secondary research objective is to correlate the IOPs obtained with both tests and prognostic outcome of the patients enrolled in the study to see whether these methods have predictive value for glaucoma progression. We will also measure autonomic nervous system activation (pupil size, heart rate and postural BP) during the test to investigate one possible mechanism behind it.

Lay summary

Raised intraocular pressure (IOP) is the main risk factor for the development and progression of glaucoma. The mDTC is a test that consists of four to five eye pressure measurements taken thoughout office hours to check for rises in pressure that may be missed during their clinic appointment. To better try to assess the IOP peaks in a more time-efficient way, the water-drinking test has been developed. This involves the patient drinking a weight-adjusted volume of water within 5 minutes which has the effect of testing the ability to cope with increased demand for fluid to leave the eye. It is unclear as to the physiological mechanism by which this occurs. In this study we aim to compare the eye pressure measurements with both tests, and to see if either have any bearing on whether the patient's disease is getting worse. We also aim to show the changes in blood pressure and heart rate throughout the test.

3. STUDY DESIGN

As described below active participation in the study (involving a single visit to the hospital) will last a total of 1 day, while the access (and analysis) of follow-up data generated as part of routine care pathway will go on for a period of 18 months in total. Participants are not required to do anything during this segment of the study.

- Observational cohort study
- 40 Primary open-angle and normal tension glaucoma patients will be attending a single visit lasting 9 hours.
- Their usual follow-up data will be tracked for 18 months

3.1 STUDY OUTCOME MEASURES

- **Primary outcome measure**:

  Intraocular pressures measured during the mDTC
  Intraocular pressures measured during the WDT

- **Secondary outcome measures**: postural blood pressure, heart rate, pupil diameter, pulse oximetry, OCT imaging parameters (angiography and anterior segment angle size) including current and future rates of progression using nerve fibre layer thickness on optical coherence tomography (OCT) and visual field testing.

3.1.1. Premedication

No premedication is required in this study; however, the assessment of the intraocular pressure requires the surface of the eye to be anaesthetised by means of topical drops.

Proxymetacaine hydrochloride 0.5% drops are used for that purpose; the drops have been in approved use for a number of years and are part of standard of care.

3.1.2. Interventions

Baseline and qualification assessments will take place on the day of the study. These include a medical, ophthalmic and drug history, ophthalmic examination, postural blood pressure measurement, testing of visual acuity, OCT/OCTA of the optic disc and macula and then IOP assessment. All ophthalmic assessments will be done on both eyes using the Heidelberg Spectralis® imaging system. The mDTC will be conducted as part of patient's regular visit and is standard of care which consists of 5 IOP measurements beginning at 8am and 2 hourly afterwards (+/- 15min) . Following completion of mDTC patients will have their WDT as detailed below.

The water drinking test will occur following the mDTC and will involve the patient drinking 800mL of water at room temperature, within a maximum of five minutes, after a period of no fluid intake of at least 2 hours. This will come after a period of no fluid intake of at least 2 hours (2pm onwards). For the WDT, the first IOP measure will correspond to the last mDTC measure, and three IOP measurements will be made after water intake with a 15-minute interval between each. IOP measurements will be recorded using Goldmann Applanation Tonometry (GAT). At each 15 minute interval, postural blood pressure, heart rate, oxygen staurations and pupil diameter will be measured. The ambient light conditions will be monitored with a light meter. Imaging will then be repeated after one hour of the test.

4. PARTICIPANT ENTRY

After the fully informed consent has been obtained in writing with the opportunity to ask questions, patients' participation will begin with the visit to the hospital where they will attend their phasing test, as part of their standard care. Following completion of the phasing they will proceed to do their water drinking test which will be followed by several measurements of their IOP and other relevant outcomes. Once they have completed the water drinking test and all necessary measurements their participation in the study will end and their care will continue as normal. Participation in this (active) part of the study will only last 1 day (single visit to the hospital).

4.1 INCLUSION CRITERIA

- Able to give informed consent to participate in the study
- Aged between 18 and 80 years of age
- Clear optical media
- Spherical equivalent +-10D
- Primary open-angle glaucoma or normal tension glaucoma proven by visual field testing or OCT imaging combined with clinical assessment.

4.2 EXCLUSION CRITERIA

- Have any other known ocular disease (except glaucoma)
- Have serious cardiac or kidney disease (WDT contra-indication)
- Have swallowing difficulties associated with either a neurological or gastrointestinal condition.

- Patients with any contra-indication of drinking large amounts of water in a small period of time e.g. swallowing impairment, oesophageal stricture, gastric banding.
- Have secondary or narrow/closed angle glaucoma
- Patients submitted to any surgical procedure or laser intervention during the evaluation period
- Participants who are involved in other current research

4.3 WITHDRAWAL CRITERIA

Participants who lose mental capacity and those who may find it difficult to adhere to the study protocol will be withdrawn. Due to the short duration and low risk-profile of the study there are no stopping criteria.
If a participant loses capacity to consent during the course of the study, they would be withdrawn from the study, while the identifiable data already collected with consent would be retained and used in the study. No further data would be collected or any other research procedures carried out on or in relation to the participant.

5. ADVERSE EVENTS

5.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*

- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.3 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.3.1 Non serious AEs

All such events, whether expected or not, should be recorded.

5.3.2 Serious AEs

All SAEs should be reported to the <name of REC> where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and

- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs
jrco@imperial.ac.uk
CI email (Francesca.cordeiro@nhs.net)
Fax: 0203 312 4388, attention Serge Miodragovic
Please send SAE forms to: ICORG CTU Western Eye Hospital, Marylebone Road London NW1 5QH
Tel: 0203 312 3206 (Mon to Fri 09.00 – 17.00)

6. ASSESSMENT AND FOLLOW-UP

Following completion of the study, participants will be followed up in their usual clinic as part of their regular care. The participants' follow-up data such as OCT scans, Visual Field tests, mDTCs and WDTs, which is routinely generated as part of the glaucoma care pathway will be accessed for 18 months following completion of participation with a view of correlating initial results with possible disease progression and other related outcomes. This segment of the study is purely data-based and does not require any active involvement from patients Participation is optional, and patient's decision (whether or not to grant access to the data) will be documented in the informed consent form.

End of study is defined as last patient last visit (LPLV)

7. STATISTICS AND DATA ANALYSIS

7.1 Sample size

In this pilot study we aim to recruit a total of 40 glaucoma patients.
This is based on a power calculation of of giving 80% power to detect a 2 mmHg difference in IOP peak (sd 2 mmHg) with $\propto$ = 5%.

7.2 Recruitment

Recruitment sources will include:
- opportunistic recruitment in glaucoma clinics at ICHNHST
- electronic search of the patient database at the ICHNHST. The search criteria will include patients with a diagnosis of 'Primary open-angle glaucoma'. Potential patients will be contacted by telephone by a member of the usual care team and given the opportunity to receive more information about the research that we are undertaking.

Study data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study.

7.3 Follow-up

Data generated as part of patients' routine clinical care in their usual clinic will be accessed for 18 months following the study. We will include for OCT scans, Visual Field tests, mDTCs and WDTs, with a maximum interval of 6 months each. Permission to access the relevant data will be documented in the informed consent form; patients will be informed that this is optional.

7.4 Data analysis

7.4.1. Data Collection

Data collection will occur solely on the premises of ICHNT and stored on secure Trust computers.

7.4.2 Data Management

. All identifiable study data will be pseudonymised by way of assignment of Study ID to each participant. Electronic data will be housed on trust protected dedicated servers while any hard copy data e.g. consent forms will be kept in dedicated locked cabinets at the ICORG Clinical Trials Unit at the Western Eye Hospital.

7.4.3 Statistical analysis

No interim analyses will take place as part of this pilot study. Data will be acquired using integrated Heidelberg® software packaged with the Heidelberg® Spectralis OCT system. Data for this initial pilot study will be collected using Microsoft® Excel, and analysed using R and GraphPad prism to compare IOPs between the mDCT and WDT.

Specific analyses will include:

- Generation of baseline data including mean and standard deviation of baseline characteristics
- Bland-Altman agreement analysis of the primary outcome
- Correlation analysis between WDT and rate of progression.
- Analysis of change in OCT measurements
- Change over time analysis for secondary outcomes compared to baseline

8. REGULATORY ISSUES

8.1 ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the xxx Research Ethics Committee (REC) and Health Regulator Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted 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.

8.2 CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and a minimum of 24 hours time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

8.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

8.4 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

8.5 SPONSOR

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6 FUNDING

This study is not funded. Participants will not receive any payments, reimbursement of expenses or any other incentives for taking part in this research.
No payments will be made to investigators not any members of the research team.

8.7 AUDITS

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research.

9. STUDY MANAGEMENT

The day-to-day management and coordination of the study will be done through Trial Manager Serge Miodragovic,Dr Timothy Yap and Research Coordinator Jessica Bonetti..

10. PUBLICATION POLICY

The study results will be published in peer reviewed scientific journals and presented at conferences. Participants' anonymity will be fully respected as no identifiable information will be used in any of the publications or presentations. As stated in the participant information sheet, participants who express interest in finding out about the results will be contacted once the results are made available

Appendix 1. Participant timeline

Type of procedure	Procedure	Clinic recruitment	Study visit	Fr
Consent	PIS & Written consent	x		O
Screening	Inclusion criteria assessed	x		O
Screening	Exclusion criteria assessed	x		O
Baseline assessment	History (medical, ophthalmic, drug, allergy)		x	O
Baseline assessment	Slit-lamp examination		x	O
Baseline assessment	Visual acuity		x	O
Baseline assessment	Visual field test		x	O
Study Procedure	IOP measurements (phasing / mDCT)		x	2
Study Procedure	Water drinking (800mls in 5 minutes)		x	16
Study Procedure	IOP measurements (WDT)		x	15
Study Procedure	Postural blood pressure (BP) / Heart rate / pupil diameter		x	14
Study procedure	OCT scan		x	15

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Imperial College London

Imperial College Ophthalmology Research Group

Participant Identification Number for this trial:

CONSENT FORM

Study Title: ***The Water Drinking Test In Glaucoma Study: WIGS***

Name of Principal Investigator: Prof Francesca Cordeiro Please initial box

1. I confirm that I have read the information sheet dated..... (Version.....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from Imperial College London, from ICORG, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
4. Optional: I agree to grant access to my follow-up data as specified in the patient information sheet. ☐
5. I consent to being contacted regarding potentially taking part in other research studies ☐
6. I give/do not give (delete as applicable) consent for information collected about me to be used to support other research in the future, , including those outside of the EEA. ☐
7. I consent to my GP being informed about my participation in the study ☐
8. I consent to take part in the above study ☐

Name of Participant	Date	Signature
Name of Person taking consent (If different from Principal Investigator)	Date	Signature
Principal Investigator taking consent	Date	Signature

You will be given a copy of this consent form to keep; one copy will be filed in your medical notes, and one will be filed with the study records within the research folder at the Western Eye Hospital.