Academic and Clinical Central Office for Research and Development

Non-CTIMP Study Protocol

REtinaL Imaging & Ambulatory BLood PrEssure: validating ultra-widefield retinal imaging derived biomarkers against ambulatory blood pressure

THE RELIABLE STUDY

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Funder	**Insert name of Funder (if applicable)**
Funding Reference Number	**Insert funding reference before finalisation**
Chief Investigator	**Dr Iain MacIntyre**
Sponsor number	**AC18080**
REC Number	**Insert REC number before finalisation**
Project registration	**If applicable trials should be registered on a publically accessible database. ACCORD can provide log-in credentials for clinicaltrials.gov. Please email resgov@accord.scot to arrange**
Version Number and Date	**Draft Version 1.0 24th September 2018**

Amendment classification and number: **E.g. non-substantial amendment 01 Jan 2000** **Or** **Substantial amendment 01: 01 Jan 2000**	**Summary of change(s)** **Please supply a brief summary of the change to the protocol**

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LIST OF ABBREVIATIONS

Insert abbreviations as required

LIST OF ABBREVIATIONS

This is not an exhaustive list.
Any additional abbreviations used within the protocol must also be added here.

ABPM	Ambulatory Blood Pressure Monitoring
ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
AE	Adverse Event
AR	Adverse Reaction
AUC	Area Under the Curve
AVR	arteriolar-to-venular-width-ratio
BP	Blood Pressure
CI	Chief Investigator
CRF	Case Report Form
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
PI	Principal Investigator
QA	Quality Assurance
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SLO	scanning laser ophthalmoscope
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
UWF	ultra-widefield

1 INTRODUCTION

1.1 BACKGROUND

Hypertension, defined as a blood pressure (BP) of ≥140/90 mm Hg, is a common, generally asymptomatic condition that is reported to be the leading risk factor for death and disability world-wide[1]. It is estimated that approximately 30% of adults in England have hypertension[2] with similar rates in Scotland[3]. Despite its high prevalence around 30% of adults in the UK with hypertension remain undiagnosed[4], leaving them at increased risk of cardiovascular disease and stroke. An opportunistic method for detecting people with hypertension may therefore improve detection across the population with significant health and economic benefit.

An image of the human retina reveals one of the best views of the body's microcirculation that can be achieved without an invasive procedure. Evidence suggests that features measured from retinal imaging such as the arteriolar-to-venular-width-ratio (AVR), which is a combination of measurements of vessel diameters near the optic nerve head, and vessel tortuosity are biomarkers of hypertension as well as early indicators of increased risk of developing hypertension[5-7]. Development of a robust clinical test for hypertension around non-invasive retinal imaging would enable opportunistic detection of hypertension in people attending routine check-ups at the high-street optometrist or ophthalmic clinics for eye care appointments.

1.2 RATIONALE FOR STUDY

We hypothesise that AVR measured using the arterioles and venules seen in the retina is an indicator for the presence of hypertension.

A pilot study has been performed using a scanning laser ophthalmoscope (SLO) to acquire ultra-widefield (UWF) retinal images and BP measurements from 500 subjects aged 50-59 years recruited to the Northern Ireland Cohort for the Longitudinal Study of Aging (www.qub.ac.uk/sites/NICOLA). Automated detection of the retinal vasculature was performed. The optic disc boundary and fovea were located to establish a measurement zone in each retinal image which encompassed a sector subtending 180 degrees on the nasal side of the optic nerve head. Manual correction to the automatically detected vessel segments and classification as artery or vein was performed within this sector. A computerised method was used to measure AVR and an area under receiver operator characteristics curve (AUC) of up to 0.720 was found for the diagnosis of hypertension, as established from clinic-based BP measurement. While this demonstrated diagnosis of hypertension from AVR, the method was limited by the accuracy of the BP measurement. A recent study has shown that clinic based BP measurement has an AUC of 0.806 for diagnosis of hypertension compared to ambulatory BP monitoring (ABPM), the current reference standard[8].

To determine the true accuracy of AVR for hypertension diagnosis a further study is now required where participants have UWF retinal imaging and a gold standard diagnosis of hypertension made using ambulatory BP measurement.

2 STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

- To show whether computational measurements made of the retinal vascular widths in UWF images can be used as a surrogate for clinical measurements to detect people with high BP.

2.1.2 Secondary Objectives

- To determine the ability of semi-automated analysis of UWF retinal images to predict untreated hypertension as established through ambulatory BP measurement.
- To determine the ability of a single clinical BP measurement taken in the clinic to predict untreated hypertension as established through ambulatory BP measurement.
- To determine the ability of semi-automated analysis of UWF retinal images to monitor change as established through ambulatory BP measurement in people receiving BP lowering medication.

2.2 ENDPOINTS

2.2.1 Primary Endpoint

- Is it possible to establish a cut-point in AVR as measured using UWF retinal images that will allow us identify people with hypertension? Where hypertension will be clinically defined using the standard ABPM.

2.2.2 Secondary Endpoints

- Is it possible to establish a cut-point in a single clinical BP measurement that will allow us identify people with hypertension?
- Is there a relationship between AVR and its component parts with the continuous outcome from ABPM?

3 STUDY DESIGN

This is a single centre, prospective, non-interventional, exploratory study examining if there is an association between AVR measurements using UWF retinal images and blood pressure measured by ABPM .

After screening and recruitment participants attending the ambulatory blood pressure clinic at the Western General Hospital will be invited to have retinal images taken using a scanning laser ophthalmoscope to acquire UWF retinal images. A semi-automatous method will then be used to calculate the AVR and this will then be compared to blood pressure recordings.

As this is an exploratory study there in no intention to commercialize or apply for CE marking of any device or software used in this study.

4 STUDY POPULATION

Participants attending a hypertensive clinic at the Western General Hospital in Edinburgh will be asked to consent to UWF retinal imaging, subject to the inclusion and exclusion criteria below. It is expected that between 25 and 50 participants per week attend the clinic, of which approximately 50% are attending without a known diagnosis of hypertension.

4.1 NUMBER OF PARTICIPANTS

For the required statistical power (see Section 8.1 for more detail) the number of required participants is 502. Taking into consideration that no more than 10% of participants are difficult to image, the target for recruitment is 550. With an estimated number of patients attending the hypertension clinic of 25 per week and taking in to consideration patients declining to participate in the study (estimated to be no more than 10%), the total required number of weeks of recruitment will be 30 factoring in staffing needs such as holidays and fluctuating numbers attending the hypertensive clinic.

4.2 INCLUSION CRITERIA

- Attending ambulatory blood pressure clinic
- Able to undertake ambulatory BP measurement
- Able to undertake single clinic-based BP measurement
- Able to undergo UWF retinal imaging with a SLO
- Aged 18 to 90
- Able to give informed consent

4.3 EXCLUSION CRITERIA

- People with known history of retinal surgery
- People under the age of 18 years.
- People that cannot: manoeuvre themselves to the SLO unaided, sit upright in a chair or wheelchair or position themselves comfortably for imaging.
- People with epilepsy

4.4 CO-ENROLMENT

Since the impact on patients by taking part in this study is minimal co-enrolment will be permitted with other interventional and non-interventional studies. Details of co-enrolment will be recorded at the time of screening.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

- All Patients receiving an appointment at the ambulatory blood pressure clinic will receive a Patient Information Sheet regarding the study from their usual care team.
- On attendance at clinic, the patient will again be offered a Patient Information Sheet and the opportunity to ask questions of a member of our research team.
- If the patient would like to participate then he or she will be asked to sign and date the approved version of the consent form before any study specific procedures are performed.

5.2 CONSENTING PARTICIPANTS

If a patient agrees to partake, informed consent will be received by a trained member of our team who takes them through the consent form and obtains their signature. One copy of the signed consent form will be given to the participant, the original will be retained at the study site in the Investigator Site File.

5.3 SCREENING FOR ELIGIBILITY

A member of the research team will screen for eligibility based on the study inclusion / exclusion criteria.

5.4 WITHDRAWAL OF STUDY PARTICIPANTS

Participants are free to withdraw from the study at any point or a participant can be withdrawn by the Investigator. If withdrawal occurs, the primary reason for withdrawal

will be documented in the participant's case report form, if possible. The participant will have the option of withdrawal from
(i) all aspects of the trial but continued use of data collected up to that point
(ii) all aspects of the trial with removal of all previously collected data.
(iii) all aspects of the trial with removal of previously collected and stored participant samples.

Randomised patients who wish to be withdrawn from the study before they have undertaken any study related procedures will be withdrawn from the study and another participant will be recruited to replace them. Data on the original participant will be kept on the CRF/database if the participant agrees to this.

6 STUDY ASSESSMENTS

6.1 STUDY ASSESSMENTS

Imaging of each eye with a SLO will be performed by:

- Adjusting the table or seat height so that the patient's eyes are slightly above the eye piece.
- Ask the patient to
  - i. Move in close to the device
  - ii. Hold the grips on the side of the device
  - ii. Rest their forehead on the top of the face pad
  - iii. Turn their head slightly so that their nose is on the outside of the face pad

The patient will see a flash of light as a photograph is taken. At least 2 pictures of each eye will be taken in this way. The typical time required to complete this imaging sessions is 10 minutes.

Blood pressure measurement will be taken as part of normal routine clinical care and as such will be dealt with in the normal way by the participant's clinical team.

6.2 SAFETY ASSESSMENTS

Local policy is that all research imaging must take into account the possibility incidental findings. The consent process for retinal imaging is designed to ensure that participants are aware of this. At least two images per eye will be captured to distinguish eye "floaters" from other potentially clinically relevant incidental findings. These "floaters" are specks of debris in the vitreous fluid within the eyeball.

All retinal images will be reviewed by trained members of the study team within 14 days of acquisition. This will be in an anonymised format and governed by Data Protection. There is a small chance (<1%) of an incidental finding being significant and urgent[9]. The consent process is designed to ensure participants understand this

and to give the opportunity to discuss with the research team if desired. A requirement of being included in the research is agreement by the participant for their GP to be informed of any incidental findings that are found. This is to allow the GP to put the participant onto an appropriate track for medical treatment should the incidental findings indicate this is required.

6.3 LONG TERM FOLLOW UP ASSESSMENTS

Not Applicable

6.4 STORAGE AND ANALYSIS OF SAMPLES

Not Applicable

7 DATA COLLECTION

Each consenting participant will undergo retinal imaging using SLO. It will take approximately 5-10 minutes for the consenting process and for a member of the research team to answer questions that the participant may have. A member of the team appropriately trained in the use of the SLO will escort each participant to the room for retinal imaging. The operator will position the participant by asking them to sit in a seat, place their chin on a chin rest and look into the aperture of the SLO. At least two images of each eye will be captured by the operator. After imaging, the participant will be escorted back to the clinic reception area.

Data will be analysed by members of our research team who are NHS and University of Edinburgh staff. Anonymised participant data including retinal images will also be available to Optos PLC for additional computational analysis.

Each participant will be assigned a unique anonymised code. This will be used on the study case report form and as the subject ID in the retinal imaging software. A master list linking participants to their codes will be kept secure in a password protected file accessible by only the chief investigator and the member of the research team taking informed consent.

The following data will be collected and entered in the study case report form:

- Demographic data including; Age, sex, weight, height, dominant arm and smoking history
- Past medical history
- Current medications
- Clinic blood pressure x 2 (both arms)
- Ambulatory blood pressure results

All anonymised demographic and clinical data will be share with Optos at the end of the study.

7.1 Source Data Documentation

Subjects electronic medical notes along with information from their GP (referral letter) will be used to collect source data. This will only be collected once subjects have given their consent.

7.2 Case Report Forms

A case report form and electronic case report form will be used with data also being inserted into a simple database

8 STATISTICS AND DATA ANALYSIS

8.1 SAMPLE SIZE CALCULATION

To determine the sample size required we refer to a previous study comparing the effectiveness of clinic based BP measurement versus ambulatory BP monitoring at diagnosis of hypertension (the current reference standard)[8]. The AUC for clinic versus ambulatory BP for diagnosis of hypertension was 0.81 with range 0.69-0.89. To be confident that AVR for diagnosis of hypertension is at least equivalent to clinic BP measurement we would need 502 participants with 0.05 probability of a type-1 error and 90% power.

UWF retinal imaging was exceptionally well tolerated in the CArdiovascular & Retinal Morphology EyescaN (CARMEN) study conducted by members of the research team (MacGillivray, Dhillion, Robertson). This study (REC reference: 12/SS/0022) added UWF retinal imaging to CT coronary angiography to investigate possible retinal vascular markers of coronary heart disease. Within CARMEN the percentage of gradable images, where the optic disc and main retinal vessels were clearly visible, was 93.3%[10]. We anticipate that this will be similar in the proposed study. Over 500 participants (median age 58 years, range 27-75 years) were imaged at the Clinical Research Imaging Centre at the Edinburgh Royal Infirmary site over a 18 month period, and 92% of those invited to participate consented to eye imaging[10]. We anticipate a similar acceptance rate for the proposed study.

Taking into consideration the likely number of participants with ungradable images, we would need an additional number of participants for the required statistical power. An extra 10% will mitigate against ungradable images, which gives a target recruitment figure of 553 participants.

The estimated number of patients attending the hypertension clinic is 25 per week. Taking in to consideration patients declining to participate in the study (estimated to be <10%), the total required number of weeks for recruitment will be 23. A more conservative estimate is 30 weeks, factoring in staffing needs such as holidays and fluctuating numbers attending the hypertensive clinic.

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8.2 PROPOSED ANALYSES

The methods of computational analysis to measure retinal features will primarily be performed at Optos using software that has been developed from previous studies[11, 12]. The software implements computational post-processing to identify blood vessels in UWF retinal images and quantifies vessel widths.

BP as measured by ambulatory measurement will be used to establish the presence and severity of hypertension.

AVR, established through retinal image analysis, will be compared the classification of hypertension (i.e. presence and severity) through analysis of the AUC.

AVR will also be compared to BP through regression analysis to look for general terms.

Significance of difference between groups (i.e. hypertensive vrs. normotensive) will be investigated through the student's T-test.

9 ADVERSE EVENTS

Imaging of the retina will be performed with a Daytona plus SLO (Optos plc, Dunfermline, UK). Imaging is non-invasive and has no known harmful effects. The device is CE marked. No adverse events are expected. If one occurs, it will be fully investigated by the study team and reported to study sponsor in line with ACCORDs standard operating procedure CR006 (Identifying, Recording and Reporting Adverse Events and Urgent Safety Measures for Non-CTIMPs) & CR012 (Identifying, Recording and Reporting Adverse Events for Clinical Investigations of Medical Devices). Optos will also be notified within 24 hours of any Serious Adverse Device Effect or Adverse Device Effect.

10 OVERSIGHT ARRANGEMENTS

10.1 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

10.2 RISK ASSESSMENT

A study specific risk assessment will be performed by representatives of the co-sponsors, ACCORD monitors and the QA group, in accordance with ACCORD governance and sponsorship SOPs. Input will be sought from the Chief Investigator or designee. The outcomes of the risk assessment will form the basis of the monitoring plans and audit plans. The risk assessment outcomes will also indicate

which risk adaptions (delete if no adaptations were possible) could be incorporated into to trial design.

10.3 STUDY MONITORING AND AUDIT

The ACCORD Sponsor Representative will assess the study to determine if an independent risk assessment is required. If required, the independent risk assessment will be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and, if so, at what frequency.

Risk assessment, if required, will determine if audit by the ACCORD QA group is required. Should audit be required, details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed.

11 GOOD CLINICAL PRACTICE

11.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

11.2 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

11.2.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be

given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s).

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant's medical notes (if applicable).

11.2.2 Study Site Staff

The Investigator must be familiar with the protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their trial related duties.

11.2.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

11.2.4 Investigator Documentation

- The Principal Investigator will ensure that the required documentation is available in local Investigator Site files ISFs.

11.2.5 GCP Training

For non-CTIMP (i.e. non-drug) studies all researchers are encouraged to undertake GCP training in order to understand the principles of GCP. However, this is not a mandatory requirement unless deemed so by the sponsor. GCP training status for all investigators should be indicated in their respective CVs.

11.2.6 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

11.2.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the UK 2018 Data Protection Act & EU General Data Protection Regulation (GDPR) with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles Access to collated participant data will be restricted to individuals from the research team treating the

participants, representatives of the sponsor(s) and representatives of regulatory authorities.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

12 STUDY CONDUCT RESPONSIBILITIES

12.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments will be submitted to a sponsor representative for review and authorisation before being submitted in writing to the appropriate REC, and local R&D for approval prior to participants being enrolled into an amended protocol.

12.2 MANAGEMENT OF PROTOCOL NON COMPLIANCE

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation. All protocol deviation logs and violation forms should be emailed to QA@accord.scot

Deviations and violations are non-compliance events discovered after the event has occurred. Deviation logs will be maintained for each site in multi-centre studies. An alternative frequency of deviation log submission to the sponsors may be agreed in writing with the sponsors.

12.3 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (seriousbreach@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to research ethics committees as necessary.

12.4 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 3 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

12.5 END OF STUDY

The end of study is defined as the last participant's last visit.

The Investigators or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, and R+D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@accord.scot.

A summary report of the study will be provided to the REC within 1 year of the end of the study.

12.6 CONTINUATION OF TREATMENT FOLLOWING THE END OF STUDY

Detail if intervention will be continued to be provided following the end of the study. If not provide justification

12.7 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the NHS Lothian. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.

- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.

13 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

13.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team.

14 REFERENCES

1. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2224-2260
2. Joffres M, Falaschetti E, Gillespie C, Robitaille C, Loustalot F, Poulter N, et al. Hypertension prevalence, awareness, treatment and control in national surveys from England, the USA and Canada, and correlation with stroke and ischaemic heart disease mortality: a cross-sectional study. *BMJ Open*. 2013;3:e003423
3. Observatory TSPH. High Blood Pressure. http://www.scotpho.org.uk/clinical-risk-factors/high-blood-pressure/key-points. 2016
4. Knott C, Mindell J. Hypertension. *Health Survey for England*. 2011
5. Wong TY, Mitchell P. Hypertensive retinopathy. *N Engl J Med*. 2004;351:2310-2317
6. Ikram MK, Witteman JC, Vingerling JR, Breteler MM, Hofman A, de Jong PT. Retinal vessel diameters and risk of hypertension: the Rotterdam Study. *Hypertension*. 2006;47:189-194
7. Cheung CY, Zheng Y, Hsu W, Lee ML, Lau QP, Mitchell P, et al. Retinal vascular tortuosity, blood pressure, and cardiovascular risk factors. *Ophthalmology*. 2011;118:812-818
8. Hodgkinson J, Mant J, Martin U, Guo B, Hobbs FD, Deeks JJ, et al. Relative effectiveness of clinic and home blood pressure monitoring compared with ambulatory blood pressure monitoring in diagnosis of hypertension: systematic review. *BMJ*. 2011;342:d3621
9. Boucher MC, Desroches G, Garcia-Salinas R, Kherani A, Maberley D, Olivier S, et al. Teleophthalmology screening for diabetic retinopathy through mobile imaging units within Canada. *Can J Ophthalmol*. 2008;43:658-668
10. Robertson G, Peto T, Dhillon B, Williams M, Trucco E, van Beek E, et al. Wide-field Ophthalmic Imaging for Biomarker Discovery in Coronary Heart Disease *ARVO ISIE*. 2013
11. Pellegrini E, Robertson G, Trucco E, MacGillivray TJ, Lupascu C, van Hemert J, et al. Blood vessel segmentation and width estimation in ultra-wide field scanning laser ophthalmoscopy. *Biomed Opt Express*. 2014;5:4329-4337
12. Robertson G, Peto T, Williams M, Dhillon B, Houston G, Newby D, et al. Ultra-Widefield Ophthalmic Imaging for Biomarker Discovery in Hypertension. *ARVO ISIE*. 2016