Tele-opHthalmology-enablEd and ARtificial Intelligence-ready referral pathway for coMmunity optomEtry referralS of retinal disease: a Cluster Randomised Superiority Trial with a linked Observational Diagnostic Accuracy Study

The HERMES Study

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Sponsor – Moorfields Eye Hospital NHS Foundation Trust

Collaboration with Kings CTU Trial Statistician and Methodologist Team & Newcastle Health Economics.

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Moorfields Eye Hospital NHS Foundation Trust

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Table 1: Abbreviations

AMD	Age-related Macular Degeneration
BMJ	British Medical Journal
BRC	Biomedical Research Centre
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trial Unit
CCA	Cost-Consequence Analysis
DCE	Discrete Choice Experiment
DMC	Data Monitoring Committee
DoH	Department of Health
eCRF	electronic Case Report Form
ETDRS	Early Treatment Diabetic Retinopathy Study
FTP	File Transfer Protocol

GDPR	General Data Protection Regulation
GAMP	Good Automated Manufacturing Practice
HES	Hospital Eye Services
HCI	Human-Computer Interaction
ICC	Intraclass Correlation Coefficient
ICF	Informed Consent form
ID	Identifier
IT	Information Technology
KCTU	King's Clinical Trial Unit
MEH	Moorfields Eye Hospital NHS Foundation Trust
nAMD	Neovascular Age-related Macular Degeneration
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NIHR HTA	National Institute for Health Research Health Technology Assessment Programme
OCT	Optical coherence tomography
PI	Principal Investigator
PIS	Patient Information Sheet
PPI	Patient and Public Involvement
PSS	Personal and Social Services
QALY	Quality Adjusted Life Year
RCOphth	Royal College of Ophthalmologists
RCT	Superiority Cluster Randomised Trial
STARD	Standards for Reporting Diagnostic Accuracy

SQL	Structured Query Language
TSC	Trial Steering Committee
UCL	University College London
UK	United Kingdom
USA	United States of America
WTP	Willingness to Pay

1. Definitions

a. **Unnecessary referral**: An erroneous referral from community optometry to Hospital-based Eye Services (HES) with suspicion of retinal disease that requires monitoring or treatment in HES (at the opinion of the referring optometrist). This includes both cases where no retinal disease is identified and cases where retinal disease is present but does not require monitoring or treatment at HES-level and can be safely managed at community optometry level. The latter category includes conditions that don't require HES-level management on the basis of professional guidelines by the Royal College of Ophthalmologists and the College of Optometrists, predominantly cases of dry Age-related Macular Degeneration.

b. **Full range of standard of care**: Current models of patient referral from community optometry to HES are not digitalized and predominantly involve paper-based referrals sent by post. Minor variations exist with respect to the type and speed of the postal service, the inclusion of print-outs of scans with the referral letter and the experience/expertise of the referring optometrists. Available audit data from HES in England indicate similar rates of unnecessary referrals to HES from community optometry indicating that the above variations don't affect the overall performance of the standard of care.

c. **Tele-Ophthalmology**: A digital link between community optometry practices and HES to allow transfer of clinical data and full volume of the OCT scans (that are reviewed remotely by clinicians in HES).

2. Study Synopsis

Brief title:	The HERMES study
Official title:	Tele-opHthalmology-enablEd and ARtificial Intelligence-ready referral pathway for coMmunity optomEtry referralS of retinal disease
Sponsor reference number:	BALK1006
Public database identifier	
Study type & Phase	A Cluster Randomised Superiority Trial with a linked Observational Diagnostic Accuracy Study
Study design	An interventional superiority cluster randomised trial (RCT) will be performed comparing standard practice for referral of suspicious retinal disease with tele-ophthalmology digital link between community optometry and HES. Additionally, a prospective observational study will be conducted integrating the data of the RCT to assess the diagnostic (referral) accuracy

	of an advanced AI DSS (the Moorfields-DeepMind algorithm) for the automated diagnosis and referral recommendation for retinal disease. A pragmatic, post-implementation, observational sub-study will be conducted to evaluate the corporation of the tele-ophthalmology pathway within a real-life setting. A within trial and model based economic evaluation will estimate the efficiency of alternative referral models for retinal disease. A HCI analysis using qualitative methods will assess feasibility of implementation of both digital technologies.
Study Population/disease condition	All people attending for an eye examination at the participating community optometry practices who undergo an OCT will be considered for participation in the study. Only people with a suspicion of retinal disease in the opinion of the community optometrist will be recruited in the RCT and observational diagnostic study. As entire optometry practices (clusters) will be randomised into standard care or tele-ophthalmology, patients who are approached and agree to take part in the study will consent to data collection and analysis - there will not be patient-level randomisation. For the pragmatic sub-study all people diagnosed with a suspicious retinal disease in the opinion of the community optometrist and need to be referred to HES will be recruited on the study.
Eligibility criteria:	***Inclusion criteria:*** • Adults (≥18) attending the involved community optometry practices who underwent an OCT • People who at the opinion of the community optometrist have any suspicion of a retinal condition (including dry AMD, wet AMD, diabetic retinopathy, macular oedema, macular holes, epiretinal membranes, central serous chorio-retinopathy, genetic eye disease) • Macular OCT scan performed at community optometry
	Exclusion criteria: • People with known retinal co-morbidities in either eye triggering the referral • People with media opacities, inability to position or fixate or any other reason that prevents acquisition of good quality OCT scans (at the discretion of the community optometrist)
Target number of participants	340 people randomised 1:1 in the intervention and control arms
Criteria for evaluation	• **Primary outcome measure(s):** **Primary Outcome Cluster RCT**: Proportion of false positive referrals (unnecessary HES visits) in the current referral pathway and the tele-ophthalmology referral pathway (against the Reference Standard). The primary endpoint selected is patient-centric as unnecessary visits to HES are associated with significant anxiety and inconvenience for patients as demonstrated by our pre-application PPI work, while at the same time having significant implications for NHS services in terms of costs and relative efficiency. **Primary Outcome AI study**: Diagnostic accuracy of the referral decision made by the Moorfields-DeepMind AI (Dichotomous analysis:

	refer to HES, do not refer to HES) - please see STARD flowchart under APPENDIX
	Secondary outcome measure(s): **Secondary Outcomes Cluster RCT:** • Proportion of wrong diagnosis and wrong referral urgency in standard and tele-ophthalmology pathways against the reference standard • Proportion of false negative referrals (patients that would have benefited from a HES review) as well as sensitivity and specificity in standard and tele-ophthalmology pathways against the reference standard • Time from referral to consultation for urgent and routine referrals in standard and tele-ophthalmology pathways • Time from referral to treatment for urgent maculopathies (wet AMD and Retinal Vein Occlusions) in standard and tele-ophthalmology pathways • Number of uncommon referrals (rare disease) that can be safely triaged in the tele-ophthalmology pathway • Within trial cost-effectiveness and cost-consequences of the tele-ophthalmology digital pathway compared with standard care • Modelled cost-consequences and net benefits of alternative diagnostic and referral strategies **Secondary Outcomes AI study:** • Diagnostic accuracy of Moorfields-DeepMind AI for the diagnosis of retinal disease • Diagnostic accuracy (sensitivity and specificity) of Moorfields-DeepMind AI for referral urgency (routine or urgent referral) • Proportion of false positive referrals (unnecessary HES visits) in the standard and tele-ophthalmology pathways when human assessors are replaced by the AI DSS • Proportion of wrong diagnosis and wrong referral urgency in the standard and tele-ophthalmology pathways when human assessors are replaced by AI DSS • Uptime and end-to-end inference speed of technical infrastructure supporting the AI DSS • Average time of end-to-end output (referral recommendation) by the AI DSS • Modelled cost-consequences and net benefits of AI-enabled digital referral pathway using the same model as for the RCT to compare alternative diagnostic and referral strategies **Secondary Outcomes Pragmatic Sub-Study:** • Proportion of false positive referrals (unnecessary HES visits) in the tele-ophthalmology referral pathway against the Reference Standard and the intervention arm in the main RCT. • Proportion of wrong diagnosis and wrong referral urgency in the tele-ophthalmology pathway compared against the Reference Standard and the intervention arm in the main RCT study • Proportion of false negative referrals (patients that would have benefited from a HES review) compared against the Reference Standard and the intervention arm in the main RCT study

Sources of funding	NIHR HTA
Anticipated start date:	September 2020
Anticipated primary completion date:	August 2023
Timelines	**Months 1 to 3**: Study set-up, ethics **Months 4 to 9**: Introduction of digital platform in intervention cluster **Months 10 to 21**: Patient recruitment in community optometry and implementation of intervention (tele-ophthalmology), data collection for HCI analysis and economic analysis, AI DSS analysis of OCTs **Months 22 to 27**: Patient recruitment continuation in post-implementation sub-study **Months 28 to 33**: Reading Centre analysis, Economic, Qualitative and Statistical analysis, AI diagnostic accuracy analysis Months 34 to 36: Reporting and dissemination of results
Anticipated impact and dissemination	The output of this program has the potential to influence the healthcare market by validating digital care pathways for patients with retinal disease. The outcomes of this research will be communicated to NHS England and the Department of Health to inform policy on the role of digital technologies, including tele-medicine and AI DSS. The Research team and the sponsor organisation will actively approach and engage key parties such as the College of Optometrists, stakeholders in the community optometry market and Clinical Commissioning Groups. A detailed engagement plan will be formulated to disseminate the results of this research in order to inform policy decisions for optimising patient care. The proposed route to market will involve commissioning arrangements for the adoption of tele-ophthalmology referral pathways between community optometry and HES.
Sponsor/Co-Sponsor	Moorfields Eye Hospital NHS Foundation Trust
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3. Background

Ophthalmology outpatient attendances account for 10% for all outpatient activity in the United Kingdom (UK), more than any other individual medical speciality other than orthopaedics (RCOphth, Way Forward report, 2016). Modern ophthalmic practice in the UK is faced by the challenges of an ageing population, increasing prevalence of degenerative disease, and emergent treatments that are revolutionary but dependent on timely diagnosis. This represents a huge strain on diagnostic services and adversely impacts on timely access to care. Concurrently, there have been exponential increases in computing power and artificial intelligence, expansions in the strength and ubiquity of communications technologies, and developments in imaging capabilities, including in the community optometry setting (Dabasia PL et al, 2014).

In the UK primary care for ophthalmology is delivered by community-based optometry practices (High Street Opticians). A large proportion of patients diagnosed with a suspicion of retinal disease, including common conditions such as Wet Age-related Macular Degeneration (wet AMD), are referred to Hospital Eye Services (HES) for diagnostics and disease management (Looker HC et al, 2014 Konstantakopoulou E et al, 2018). The referral process results in unnecessary referrals, erroneous diagnoses, miss-classification in terms of urgency, duplication of imaging tests and delays in access to treatment.

An increase of 30% in eye clinic attendances has been observed within the last 5 years throughout the UK (MacEwen C, 2017). Further increases are likely because of the increasing availability of imaging technology, and especially Optical Coherence Tomography (OCT), which is becoming ubiquitous in community optometry practices (AOP OCT Roll Out, 2017). OCT is a non-invasive imaging modality that uses light to generate micrometre-resolution three-dimensional images of the retina, and provides the best way to diagnose a number of common retinal pathologies including wet AMD.

There is an urgent need for a better way of managing this surge in demand in order to both minimise the false-positive rate of referrals to HES and to optimise use of available resources (RCOphth, Way Forward report, 2016). This research proposal focuses on two potentially complementary digital technologies that have the potential to revolutionise the interface between community optometrists and hospital-based eye clinics; the tele-ophthalmology

platform and the Moorfields-DeepMind Artificial Intelligence Decision Support System. The technologies will be assessed through two complementary and linked quantitative studies:

1. *Cluster superiority randomised controlled trial (RCT) comparing standard practice to tele-ophthalmology digital referral model for the identification of suspicious eye disease in community optometry practices.*
2. *Prospective, observational, diagnostic accuracy study of an Artificial Intelligence (Machine Learning) Diagnosis Support System (the Moorfields-DeepMind algorithm) compared to expert human review for the identification of suspicious eye disease from the imaging data (OCTs) available from the RCT.*

1. Cluster Superiority Randomised Trial (RCT) of tele-ophthalmology; Tele-medicine in Ophthalmology can help face this challenge of provision of optimal and expert care to people attending for eye tests in community optometry practices, through a digital referral pathway relying on a tele-ophthalmology link between community optometry and HES. This could optimise the referral process by allowing remote review of imaging and clinical data captured at the community level, by human experts based in HES. Pilot data produced by our research team has demonstrated the potential of tele-ophthalmology to drastically improve the efficiency of the referral pathway between community optometry and HES (Korteum K et al, 2018) but definitive evidence garnered from more than one HES is required before evidence based recommendations could be made.

We will perform a cluster randomised superiority trial to assess the impact on service delivery metrics (such as proportion of unnecessary referrals and time from referral to treatment for urgent maculopathies) of a digital link between community optometry practices and HES using a tele-ophthalmology platform. We will use a device-agnostic, tele-ophthalmology platform to enable a digital referral pathway of patients with a suspicion of retinal disease. The pilot data demonstrated the potential of tele-ophthalmology to drastically reduce unnecessary referrals to HES (Korteum K et al, 2018) and hence we propose a randomised trial powered to demonstrate superiority of the digital referral pathway against standard care.

2. Prospective, observational, diagnostic accuracy study of Artificial Intelligence (Machine Learning) Diagnosis Support (the Moorfields-DeepMind algorithm); Artificial Intelligence Decision Support Systems (AI DSS) have recently been developed and shown to have good diagnostic accuracy against human experts in interpreting ocular imaging tests, such as OCT (De Fauw et al, 2018). The collaboration between Moorfields Eye Hospital and Google DeepMind produced the arguably most advanced Deep Learning decision support system in Ophthalmology, capable of interpreting OCT scans, providing diagnosis for retinal disease and suggesting urgency of referral (De Fauw et al, 2018). In silico analysis using retrospectively collected data has validated the tool against human experts for the diagnosis of retinal disease and referral recommendations and it has been shown to be non-inferior. While such work is important, a prospective study is required to demonstrate its value in practice. The Moorfields-

DeepMind AI DSS that we propose to use is not commercialised but is uniquely available to Moorfields Eye Hospital to be used independently for research purposes.

We will perform a prospective, observational study to assess diagnostic (referral) accuracy of the Moorfields-DeepMind AI DSS when applied on the OCT scans collected in the context of the tele-ophthalmology RCT. This will allow maximum utilisation of collected data from the trial and will provide estimates and confidence intervals of diagnostic (referral) accuracy. All cases included in the RCT will be reviewed by the Moorfields-DeepMind AI DSS within 48 hours of uploading the OCT scans to the AI system and a referral decision (refer routinely, refer urgently, don't refer) will be made by the algorithm for each case and recorded. The referral decisions made by the AI DSS will not be implemented in practice, yet data of the time required to obtain these decisions and any technical issues encountered with its use will be captured. These data will be incorporated into the model based economic evaluation to show the economic case for adoption (or not) of the Moorfields-DeepMind AI DSS.

Impact of the Covid-19 pandemic
Post-implementation Observational Pragmatic Sub-Study

NHS services underwent rapid and significant adjustments across the board in response to extreme challenges presented by the Covid-19 pandemic. Changes to healthcare services driven by necessity are not always underpinned by a robust evidence base for efficiency and safety. In Ophthalmology, as a response to the need for social distancing and minimising unnecessary hospital visits, tele-ophthalmology pathways were commissioned recently in some areas of England using a digital links to facilitate referrals between community optometry and Hospital Eye Services. Greater Manchester was an early adopter of this approach and a majority of the optometry practices in that area are now referring to NHS eye units via a tele-ophthalmology link. This local change in standard care provides a unique opportunity to examine whether tele-ophthalmology works under usual conditions within the NHS. This sub-study will allow us to measure and visualise variation in quality of health care within a local region to inform our inferences from the RCT on how the tele- ophthalmology pathway will perform within a real-life setting. We will thus perform a pragmatic, observational, post-implementation study involving community optometry practices in the Greater Manchester area. This will also serve as a safety analysis allowing identifying potential safety signals of the tele-ophthalmology pathways and adding granularity to the economic and qualitative evaluations of the RCT.

4. Trial aims and objectives

4.1 Aims

There are two complementary aims (aims 1&2) pertaining to the linked quantitative studies assessing the two digital technologies ('tele-Ophthalmology' and the 'Moorfields-DeepMind'

AI). The qualitative research element (aim 3) using Human Computer Interaction methodology will run across both studies to provide evidence on implementation.

1. To assess the effectiveness and efficiency of a digital referral pathway between community optometry (High Street Opticians) and Hospital Eye Services for referral of retinal disease enabled by a device-agnostic, tele-ophthalmology platform (Interventional cluster superiority RCT).

2. To estimate the diagnostic (referral) accuracy and assess the 'real-life' performance of an Artificial Intelligence Decision Support System (the Moorfields-DeepMind AI) in the context of referral pathways between community optometry and HES. This will utilise a state of the art Deep Learning decision support system for retinal referrals (the Moorfields-DeepMind AI) and model its relative efficiency when used in this referral pathway (based on an observational, prospective diagnostic accuracy study).

3. To assess patient and healthcare professional acceptability as well as the barriers and enablers for the adoption of these digital technologies in the context of referral pathways between community optometry and HES through a Human-Computer Interaction approach.

4. To estimate the effectiveness and efficiency of a digital referral pathway between community optometry (High Street Opticians) and the Hospital Eyes Services for referral of retinal diseases enabled by a tele-ophthalmology platform in a real-life, observational post-implementation sub-study.

4.2 Objectives associated with Aim 1

Tele-ophthalmology Cluster Randomised Superiority Trial

Primary Objective: To compare the proportion of referrals classified as unnecessary (cases that can be safely managed without a HES consultation) between current standard care and tele-ophthalmology digital referral pathway.

Secondary Objectives:

1. To estimate the relative efficiency of the tele-ophthalmology digital pathway compared with standard care in both within trial and model based evaluations.

2. To compare the rate of inappropriate referrals (defined as wrong diagnosis or wrong level of urgency) between standard care and the tele-ophthalmology digital pathway.

3. To capture the number of uncommon/complex retinal referrals to secondary care and the proportion that can be safely triaged through the tele-ophthalmology platform.

4. To compare time from referral to review and/or treatment in HES for urgent referrals (such as Wet AMD and Retinal Vein Occlusions) between standard care and tele-ophthalmology digital pathway.

5. To assess the number of false negatives (number of patients that would have benefited from a HES consultation but were deemed suitable for continued care in the community) (Safety assessment).

4.3 Objectives associated with Aim 2

Artificial Intelligence prospective, observational diagnostic accuracy study:

1. To estimate the diagnostic (referral) accuracy of the Moorfields-DeepMind AI for recommending referral to HES from community optometry practices.

2. To estimate the diagnostic accuracy of the Moorfields-DeepMind AI for the diagnosis of retinal disease.

3. To model the efficiency of the introduction of the DeepMind algorithm in the referral pathway between community optometry and HES. This will be integrated as comparators within the economic model outlined for Aim 1 above.

4. To assess the technical feasibility of utilising the Moorfields-DeepMind AI for real-time analysis of retinal OCT images.

5. To assess real-time operational performance of the Moorfields-DeepMind AI in the tele-ophthalmology referral pathway.

4.4 Objectives Associated with Aim 3

Human Computer Interaction analysis

1. To understand current workflows and practices of staff and patients in community optometry and HES so as to identify key user requirements for tele-ophthalmology tools from the perspectives of both practitioners and patients (working with care settings with diverse established practices).

2. To oversee the deployment of a digital referral platform' at selected participating sites to ensure acceptability and acceptance by all user groups, and to understand the adoption process.

3. To identify factors that shape professionals' and patients' attitudes to, and trust in, the Moorfields-DeepMind AI, and how to present information in ways that instil appropriate confidence.

4. To observe workflows and practices of staff and patients in community optometry practices and HES with already established tele-ophthalmology pathways to identify technical, logistical and human factors affecting implementation of tele-ophthalmology in real-life (pragmatic sub-study).

4.5 Objectives Associated with Aim 4

Pragmatic Sub-Study

1. To compare the proportion of referrals classified as unnecessary (cases that can be safely managed without a HES consultation) against Reference Standard and the intervention arm of the RCT.
2. To compare the rate of inappropriate referrals (defined as wrong diagnosis or wrong level of urgency) against the Reference Standard and the intervention arm of the RCT.
3. To assess the number of false negatives (number of patients that would have benefitted from a HES consultation but were deemed suitable to continued care in the community) (Safety assessment).
4. To compare time from referral to review and/or treatment in HES for urgent referrals (such as Wet AMD and Retinal Vein Occlusions) between post-implementation real-life tele-ophthalmology digitial pathway and the intervention arm of the RCT.
5. To estimate the relative efficiency of the real-life tele-ophthalmology digital pathway compared with the RCT tele-ophthalmology pathway

5. Study Design and Patient Population

5.1 Study Design

- *Interventional cluster superiority RCT*; Community optometry practices will be randomised to either continue with standard care for referral of retinal disease to hospital-based eye clinics or move to the tele-ophthalmology digital referral pathway. Referral recommendations made in either arm of the RCT will be assessed against a reference standard provided by the Moorfields Reading Centre to inform the between arms comparison (standard care vs tele-ophthalmology). – *Please see CONSORT flowchart under APPENDIX*
- *Observational prospective diagnostic accuracy study*; OCT scans transferred to the Moorfields Reading Centre in the course of the study will be assessed by the DeepMind algorithm in 'real-time' and its referral recommendations will be recorded and analysed for diagnostic (referral) accuracy and compared against the performance of human experts in the standard care and tele-ophthalmology arms of the RCT.- *Please see STARD flowchart under APPENDIX*
- *Observational, post-implementations, pragmatic sub-study;* Community Optometry practices in the Greater Manchester area will continue to refer patients with suspicious retinal disease to HES using the locally established tele-ophthalmology digital pathway. Referral recommendations will be compared against a reference standard provided by Moorfields Reading Centre to infrom the assessment of real-life effectiveness and efficiency of the tele-ophthalmology referral pathway.

5.2 Setting

Patients will be recruited at 24 optometry practices (clusters) in the catchment areas of 4 HES sites: Moorfields Eye Hospital NHS Foundation Trust (8-12 practices), Birmingham University Hospitals NHS Foundation Trust (4-8 practices), North Middlesex NHS Foundation Trust (4-8 practices) and North West Anglia NHS Foundation Trust (4-8 practices). 12 clusters (each cluster is an optometry practice) will be randomised to standard care and 12 clusters to the intervention (tele-ophthalmology). This selection of sites includes urban, sub-urban and rural locations within the UK allowing the inferences made from this study to be applicable to more of the UK population. 2 additional optometry practices (clusters) will be randomised (1:1) in a reserve capacity in case of a cluster drop-out or in order to accelerate the recruitment process. – *please see sample size section.*

Eligible practices need to have an OCT devices and the activity volume and track record of referral to HES that will allow achieving the per practice recruitment target.

Patients will be recruited at 12 optometry practices (clusters) in the catchment area of Manchester University NHS Foundation Trust. These practices have adopted a tele-ophthalmology referral pathway as standard practices. Recruitment from these clusters will inform the pragmatic, observational, post-implementation sub-study.

All OCTs and clinical vignettes from each case will be transferred to the Moorfields Reading Centre that will provide the reference standard (diagnosis and referral recommendation). All suitable OCTs will be processed by the DeepMind algorithm at the Moorfields Reading Centre in 'real-time' for the AI observational diagnostic study.

5.3 Patient Population

Adults (≥18 years) attending for an eye examination at the participating community optometry practices who undergo an OCT will be considered for participation in the study. Only people with a suspicion of retinal disease at the opinion of the community optometrist will be recruited in the RCT and observational diagnostic study. As entire optometry practices (clusters) will be randomised into standard care or tele-ophthalmology, patients who are approached and agree to take part in the study will consent to data collection and analysis - there will not be patient-level randomisation. The detailed approach to patient information and consent for this study will be developed in close collaboration with our PPI group contributors

5.4 Inclusion Criteria

- Able to give consent and understand the study
- Able to cooperate by following study specific instructions

- Adults (≥18 years) attending the involved community optometry practices who underwent an OCT
- Individuals who at the opinion of the community optometrist have any suspicion of a retinal condition (including dry AMD, wet AMD, diabetic retinopathy, macular oedema, macular holes, epiretinal membranes, central serous chorio-retinopathy, genetic eye disease)
- Macular OCT performed at community optometry

5.5 Exclusion Criteria

- Individuals with known retinal co-morbidities in either eye triggering the referral
- Individuals with media opacities, inability to position or fixate or any other reason that prevents acquisition of good quality OCT scans (at the discretion of the community optometrist)

5.6 Allocation to trial groups

Simple randomisation will be performed for involved optometry practices into the intervention and control arms. Randomisation will be performed with the unit of allocation being the cluster rather than the individual and allocation concealment will be at the cluster level. Optometry practices will be randomised 1:1 to standard care or tele-ophthalmology stratified by the hospital site. Optometry practices are committed to the allocated study arm for the duration of the recruitment period or until they have recruited the minimum of the per cluster recruitment range (10 patients).

5.7 Control Pathway RCT – Standard Practice

The control pathway is standard practice for referral of patients with suspicion of retinal disease from community optometry to HES. Patients who attend a participating community optometry practice will undergo a clinical assessment and OCT scan. Patients with a suspicion of any retinal disease at the opinion of the community optometrist will be included in the study and will receive a referral decision by the community optometrist. The decision by the optometrist can be:

1) Refer urgently to HES

2) Refer routinely to HES

3) Don’t refer to HES

When a decision to refer is made, the referral will be sent as per standard practice to the corresponding HES (Moorfields Eye Hospital, Central Middlesex Hospital, Peterborough City Hospital, Stamford and Rutland Hospital, Hinchingbrooke Hospital and Queen Elizabeth Hospital Birmingham) to be processed.

All OCTs and a clinical vignette from each case will be transferred to the Moorfields Reading Centre that will provide the reference standard for referral recommendations.

5.8 Intervention Pathway RCT - Digital Pathway)

The intervention pathway is the tele-ophthalmology model for referral of patients with suspicion of retinal disease from community optometry to HES using a digital referral platform. Patients who attend at participating community optometry practices will undergo a clinical assessment and OCT scan. Patients with a suspicion of any retinal disease at the opinion of the community optometrist will be included in the study and their OCT and clinical information will be transferred via the digital referral platform to corresponding HES.. In each case, human experts based in HES will make a referral decision remotely ('tele-HES') after review of OCT and clinical information on the digital referral platform. The referring community optometrist will also make their own referral recommendation independent of HES. In each case both the decision made by the community optometrist and the one made by remote review in 'tele-HES' will be recorded but the decision made by 'tele-HES' will be the one implemented. The following scenarios can occur in the intervention arm

1) Community optometrist decision: Refer urgently to HES—> OCT scan and clinical data are transferred to 'tele-HES' and reviewed within 2 business days remotely by human expert —> Referral Decision is made in 'tele-HES' (refer urgently, refer routinely, don't refer) and fed-back to the community optometry practice to be implemented.

2) Community optometrist decision: Refer routinely to HES—> OCT scan and clinical data are transferred to 'tele-HES' and reviewed within 2 business days remotely by human expert —> Referral Decision is made in 'tele-HES' (refer urgently, refer routinely, don't refer) and fed-back to the community optometry practice to be implemented.

3) Community optometrist decision: Don't refer to HES—> OCT scan and clinical data are transferred to 'tele-HES' and reviewed within 2 business days remotely by human expert —> Referral Decision is made in 'tele-HES' (refer urgently, refer routinely, don't refer) and fed-back to the community optometry practice to be implemented.

The decision made in 'tele-HES' will be the one implemented in every case in the intervention pathway. The remote review of OCTs and clinical data at 'tele-HES' will be performed by expert clinicians (medics or specialist optometrists) experienced in retinal clinics (minimum of two years' experience of independent practice in the context of retinal clinics in HES) based at Moorfields Eye Hospital, Central Middlesex Hospital, North West Anglia NHS Foundation Trust Hospitals or Queen Elizabeth Hospital Birmingham with access to senior advice by Consultant Ophthalmologists specialising in retinal disease.

5.9 Safety Net

In cases 'tele-HES' decision is 'don't refer', the patient will be provided with additional information and alerts for clinical symptoms that should prompt a visit directly to the A&E department of the corresponding secondary care site (Moorfields Eye Hospital, Central Middlesex Hospital, North West Anglia NHS Foundation Trust Hospitals or Queen Elizabeth Hospital Birmingham). Additionally, in cases where a disagreement is found between the decision by the community optometrist and the one made in 'tele-HES', patients will be offered a follow-up appointment at the community optometry practice within 4 weeks. .

5.10 Control and Intervention pathways: DeepMind observational diagnostic study - data collection and processing

All referred and non-referred cases from the standard care and tele-ophthalmology arm will be included in the AI diagnostic study. All suitable OCTs will be transferred prospectively on a weekly basis to the Moorfields Ophthalmic Reading Centre as described in the data collection plan. OCTs will be processed by the Moorfields-DeepMind AI and end-to-end timing of the process will be captured for each case. For each case the Moorfields-DeepMind AI will provide a:

- Diagnosis
- Decision to refer or not
- Urgency of referral (routine or urgent)

5.11 Reference Standard

OCTs from the standard care and tele-ophthalmology arms will be transferred to the Moorfields Ophthalmic Reading Centre. The reference standard will be provided by the expert Ophthalmic Reading Centre for the Cluster RCT and observational AI study and the Pragmatic sub-study. The reference standard will be the referral decisions and disease diagnosis made at the Reading Centre on the basis of review of images and clinical history and will apply to the RCT, the AI Diagnostic Accuracy study and the Post-implementation, Pragmatic sub-study. Specifically, for each patient the OCT (including b-scans and colour fundus image) and a clinical vignette including visual acuity, age, symptoms, ocular and systemic history will be reviewed by two expert graders. The process to be followed is double-grading with adjudication by a senior retinal specialist at the Moorfields Reading Centre.

Table 2: Schedule of Assessments

Data Collection	
	Referral Visit
Medical History	✓
Consent	✓
Clinical Pro-Forma	✓
Visual Acuity (ETDRS) with habitual correction	✓
Optical Coherence Tomography	✓
Referral Decision and Urgency (community optometrist)	✓
Referral Decision and Urgency (HES)	✓
Referral Decision and Urgency (DeepMind AI DSS)	✓
End-to-end processing time for DeepMind algorithm	✓
Time from referral to assessment for routine referrals	✓
Time from referral to assessment and treatment for urgent maculopathies	✓
OCT device used	✓

Please refer to ANNEX A for further details

5.12 Outcomes

5.12.1 Primary Outcome Cluster RCT:

Proportion of false positive referrals (unnecessary HES visits) in the current referral pathway and the tele-ophthalmology referral pathway (against the Reference Standard). The primary endpoint selected is patient-centric as unnecessary visits to HES are associated with significant anxiety and inconvenience for patients as demonstrated by our pre-application PPI work, while at the same time having significant implications for NHS services in terms of costs and relative efficiency.

5.12.2 Secondary Outcomes Cluster RCT:

1. Proportion of wrong diagnosis and wrong referral urgency in standard and tele-ophthalmology pathways against the reference standard
2. Proportion of false negative referrals (patients that would have benefited from a HES review) as well as sensitivity and specificity in standard and tele-ophthalmology pathways against the reference standard
3. Time from referral to consultation for urgent and routine referrals in standard and tele-ophthalmology pathways
4. Time from referral to treatment for urgent maculopathies (wet AMD and Retinal Vein Occlusions) in standard and tele-ophthalmology pathways
5. Number of uncommon referrals (rare disease) that can be safely triaged in the tele-ophthalmology pathway

6. Within trial cost-effectiveness and cost-consequences of the tele-ophthalmology digital pathway compared with standard care
7. Modelled cost-consequences and net benefits of alternative diagnostic and referral strategies

5.12.3 Primary Outcome AI study: We will adhere to the STARD publication standard in reporting the outcomes of the observational diagnostic accuracy study. The primary endpoint is diagnostic accuracy of the referral decision made by the Moorfields-DeepMind AI (refer to HES, do not refer to HES) against the Reference Standard (Moorfields Reading Centre).

5.12.4 Secondary Outcomes AI study:

1. Diagnostic accuracy of Moorfields-DeepMind AI for the diagnosis of retinal disease
2. Diagnostic accuracy (sensitivity and specificity) of Moorfields-DeepMind AI for referral urgency (routine or urgent referral)
3. Proportion of false positive referrals (unnecessary HES visits) in the standard and tele-ophthalmology pathways when human assessors are replaced by the AI DSS
4. Proportion of wrong diagnosis and wrong referral urgency in the standard and tele-ophthalmology pathways when human assessors are replaced by AI DSS
5. Uptime and end-to-end inference speed of technical infrastructure supporting the AI DSS
6. Average time of end-to-end output (referral recommendation) by the AI DSS
7. Modelled cost-consequences and net benefits of AI-enabled digital referral pathway using the same model as for the RCT to compare alternative diagnostic and referral strategies

5.12.5 Secondary Outcomes Pragmatic Sub-study:

1. Proportion of false positive referrals (unnecessary HES visits) in the tele-ophthalmology referral pathway against the Reference Standard and the intervention arm in the main RCT.
2. Proportion of wrong diagnosis and wrong referral urgency in the tele-ophthalmology pathway compared against the Reference Standard and the intervention arm in the main RCT study
3. Proportion of false negative referrals (patients that would have benefited from a HES review) compared against the Reference Standard and the intervention arm in the main RCT study
4. Time from referral to review and/or treatment in HES for urgent referrals (such as Wet AMD and Retinal Vein Occlusions) in the post-implementation real-life tele-ophthalmology digitial pathway

Trial Documents and Subject Records

6.1 eCRFs and Source Document Identification

We will establish a hub and spoke structure, where each community optometry practice liaises with its local hospital site (Moorfields Eye Hospital, Central Middlesex Hospital, North West Anglia NHS Foundation Trust, Queen Elizabeth Hospital Birmingham) for the day-to-day operation of the trial, through the site coordinator located at each site. 8-12 optometry practices will be located in the catchment area of Moorfields Eye Hospital NHS Foundation

Trust (5-6 control and 5-6 intervention), 4-8 in the catchment area of North West London NHS Foundation Trust (Central Middlesex Hospital) (2-4 control and 2-4 intervention), 4-8 in the catchment area of North West Anglia NHS Foundation Trust (2-4 control and 2-4 intervention) and 4-8 in the catchment area of Birmingham University Hospitals NHS Foundation Trust (2-4 control and 2-4 intervention). All sites, including community optometry and hospital sites transfer data (OCT and clinical data) to Moorfields Reading Centre. The digital referral platform will be used in the 12 intervention optometry practices and the 4 HES; OCTs and clinical data from patients in the intervention optometry practices will be transferred to HES via a digital referral platform for remote review ('tele-HES') by local human experts.

Both the control arm and interventional arm will use the trial database to complete the eCRF and securely upload OCT scans. The interventional arm also transfers OCT's to the patient's hub hospital via a secure tele-ophthalmology platform. The scans and data will then be matched with the relevant trial data in the eCRF database.

For the AI Diagnostic Accuracy study, the pseudonymised OCT scans will be securely transmitted from the Moorfields Reading Centre to a secure Google Cloud Healthcare DICOM store over an encrypted connection, where it will be analysed by the DeepMind algorithm. Results from this analysis will be logged in the eCRF database. The study's use of cloud computing infrastructure adheres to January 2018 guidance from NHS Digital regarding cloud computing for health and social care. All data will be handled in accordance with the Data Protection Act 2018.

6.2 Confidentiality of Trial Documents and Subject Records

Identifiable patient data will not be accessed outside the care team without prior consent at any stage of the project. The OCT scans will be pseudoanonymised and no personal data will be included on the scans. No personal identifiers such as the patients name will be sent to the Sponsor and a unique identification code will be assigned to each OCT scan. This log of subject codes will be kept at each research site but not shared with the Sponsor.

The eCRF will not bear the subject's name or other personal identifiable data. A trial number will be used for identification on the eCRFs. A separate log file which links the study ID and the patient's details, screening log and recruitment information will be kept on a protected NHS computer at hub sites. The key log will be kept at the recruitment site and will not be shared with the Sponsor. It will be the responsibility of the chief investigator or delegated trial member to ensure the accuracy of all data recorded on the eCRFs. eCRFs will be completed and signed off by the Chief Investigator or delegated/authorised individual as outlined in the delegation log, the completed eCRFs will be checked for accuracy and completion by the trial co-ordinator..

6.3 Procedures for validation and securing of electronic clinical data systems

The eCRF will be developed by the Moorfields Eye Hospital database development team. The front end will use a bespoke web application and the back end (data storage) will be hosted on Moorfields Eye Hospital Research Database SQL servers. All servers are backed up daily and with multiple restore points every day and backup copies exist in more than one All MEH clinical trial databases are part of the MEH disaster recovery strategy and have a 5 day Recovery Time Objective.

6.4 Data handling and record keeping

With respect to data handling, the senior data manager in Moorfields Eye Hospital CRF will independently ask the IT applications team to run missing data query and perform range check, logic check and data quality checks of the Electronic Database on a monthly basis.

Data queries will be sent to trial co-ordinators for clarification and confirmation whenever picked up.

After all data queries are resolved and all errors are corrected, the database will then be locked with the agreement of King's CTU statistician and data will be exported by the applications manager and sent to trial statistician for data analysis. Pre-existing mechanisms for data transfer between Moorfields Eye Hospital CRF and King's CTU will be utilised.

Active project data is stored in the dedicated secure Reading Centre drive with appropriate back up arrangements. Access to the drive is restricted only to Reading Centre staff with permission and access will be monitored, granted, revoked on a per user basis. This means that only individuals with prior authorisation can access the data

7. Compliance and withdrawal

7.1 Withdrawal / dropout of subjects

Participants are free to withdraw at any time. Data collected up to the point of withdrawal will still be included in data analysis.

7.2 Protocol Compliance

Protocol compliance will be monitored by the Trial Steering Committee and reported to the Sponsor and NIHR.

7.3 Interim analysis and data monitoring

Interim analysis of data could be considered at the recommendation of the Data Monitoring Committee.

7.4 Stopping / discontinuation rules and breaking of randomisation code

Stopping/Discontinuation rules will be developed and implemented by the Trial Steering Committee.

8. Human-Computer Interaction Analysis

As noted above, the aims of the HCI analysis are to assess the barriers and enablers for the adoption of the proposed digital technologies in the context of referral pathways between community optometry and HES through a Human-Computer Interaction approach.

In order to capture patient and staff perspectives of tele-ophthalmology models of care as well as AI DSS, we will take a qualitative approach, conducting interviews and observations in both community optometry and HES. We will compare people's expectations (what they believe they will want and use) with their experiences when they have access to the relevant technology. In order to compare expectations against experiences, we will gather data in a variety of settings over the course of the project:

- *In the first six months* of the project we will work with two optometry practices that are adopting tele-ophthalmology at this time, and also with the Birmingham HES (which will be adapting its practices to accommodate tele-ophthalmology in this period). At these three sites, longitudinal data will be gathered (pre-, during and post-implementation), as described below.
- *Over the subsequent 12 months* (months 7-18), we will also work with two optometry practices that are already experienced in using tele-ophthalmology (sites that have already adopted tele-ophthalmology in the Greater Manchester area),; two practices that are not using tele-ophthalmology and have no immediate plans to transition (control sites for the quantitative studies described above); and a second HES (Moorfields Eye Hospital).

8.1 Data Collection

Data gathering will be based on interviews (to identify perceptions) and observations (to identify behaviours). In the first six months (following ethical approval), the focus will be on objective 2 (understanding the adoption process and factors that contribute to success in adoption). Longitudinal data will be gathered at the three selected sites, focusing on the perspectives of key informants (professionals) involved in the implementation process. This will involve a mix of interviews and observations, including work shadowing of key personnel

during implementation. The aim will be to interview and observe key informants before, during and after implementation at each site (interleaving data gathering across the sites to maximise value). Data gathering will focus on expectations and current work practices before implementation; barriers, facilitators and experiences during implementation; and perceptions and practices post-implementation. See below for more details on methods.

Similar data gathering and analysis methods will be adopted for the main study period (months 7-18), where the focus will be on objectives 1 (understanding workflows, practices and user requirements, including facilitators and barriers to adoption) and 3 (identifying factors that shape attitudes to the AI DSS, and how to present information to instil appropriate confidence) – *see HCI objectives, page 14*. In this period, participants will include clinicians and patients.

8.2 Sampling, Recruitment and Analysis Methods

Purposive sampling techniques will be applied to recruit participants who are representative of all key patient and professional groups across all sites, including both “power users” and reluctant users. In each setting, the aim will be to interview 15 patients and up to 10 clinicians and other professionals (settings: secondary care clinics; pre-; and post-transitioning optometry practices), depending on the sizes of the clinics selected for inclusion. The interviews will be conducted by a Process Evaluation Specialist, they will be semi-structured and will be designed to address the research objectives outlined above. Probes such as anonymised screenshots from the digital referral platform and illustrative information presentation prototypes from the DeepMind algorithm will be used in interviews to support the exploration of the themes. Interview data will be transcribed and analysed by a qualitative methods expert under the supervision of Prof Ann Blandford at UCL using inductive Thematic Analysis, with a particular focus on facilitators and barriers to change, and the factors that contribute to successful change. These will include questions around trust in technology and data privacy as well as efficiency and effectiveness and changes in clinician workflow and patient experience. Data gathering and analysis will be interleaved, so that later data gathering is informed by the findings from earlier analysis.

Small-scale ethnographic observations will be conducted in all settings, observing both selected clinician-patient interactions around the diagnostic process (community optometry and HES) and clinician tele-care practices (HES). 3-5 clinician-patient consultations will be observed per setting; debrief interviews with patients will cover the same themes as the interviews with practitioners, but be sensitive to the different perspectives of patients and professionals. Detailed field notes will be kept of all observations. This data will also be subjected to thematic analysis, focusing on workflows, variability in workflows, and any problems experienced during the interaction (particularly related to technology use).

Patients will be invited to participate at the time that they receive their appointment letter, so that they have time to consider whether they wish to do so (for informed consent), and to plan their clinic visit time to accommodate a short interview (15 mins approx.) after their appointment. On the day of the visit the investigator will provide the patient information leaflet

(PIS) to the patient and go through it highlighting what the purpose of the study is, what it entails if the patient decides to take part and possible advantages and disadvantages and risks of taking part. When the patient has had amble time to read the PIS and ask questions regarding the study, the patient will be asked to sign an informed consent form (ICF). Once the informed consent process is complete a copy of the ICF will be provided to the participant, and the signed form will be filed in the participant's study records. Once the informed consent process is complete, the investigator will record the decision in the case history form.

As this is a cluster randomised clinical trial, randomisation applies at the level of entire community optometry practices. The practices randomised to the intervention arm (tele-ophthalmology) will adopt this pathway for all patient referrals to secondary care as standard practice. Patient-level consent for this study pertains to allowing use of collected data for analysis but participation in the study will not affect patient-level care. Given the urgent presentation of the patient population we will approach for participation in this study and the fact that patient management will not be influenced by randomisation as described above, a 24-hour minimum period of consideration for patient participation is not warranted. Patients approached for participation will be given the study-specific PIS and adequate time to have any queries addressed by the clinical team before deciding on participation to the study.

8.3 Focus of Analysis

The primary focus for analysis will be on facilitators and barriers to implementation of the tele-ophthalmology system and the introduction of Artificial Intelligence Decision Support across clinical contexts, along with accounts of how it changes workflow and patient experience. Evaluation will be formative, so as to inform future implementations and also to contextualise the analyses of clinical effectiveness and cost effectiveness. For the AI DSS, questions to be included in interviews will involve whether the AI is to be used as decision aid (e.g., as a filter for disease/no disease) or as a completely independent decision making tool, issues around trust in the technology, perceptions of medicolegal concerns (who is responsible for the decisions?), the optimal place in the care pathway for positioning the AI (high street optician or hospital-based eye services or both), concerns such as de-skilling of practitioners (as diagnostic decisions may be devolved to AI), reduced employment opportunities, the need for a 'safety net'/quality check to oversee and 'sanity check' the performance of the AI system, and impersonal care for patients, and perceived benefits such as more efficient and appropriate care, greater confidence in the process, etc. We will also particularly focus on the question of 'interpretability' of AI DSS and the 'black box' phenomenon and whether it influences trust and potential uptake of this technology. The 'interpretability' of AI DSS is a major factor in technology uptake and may influence the direction of AI DSS developers towards more interpretable technologies.

The data collected from sites with established tele-ophthalmology pathways (Greater Manchester) will be particularly valuable for identifying barriers to implementation in a real-life context that wouldn't be picked up in the controlled environment of the RCT such as technical,

staffing, training and human factors. Such barriers can be consequential with respect to patient safety as they have the potential to lead to delays in clinical review or missed cases and will therefore the post-implementation sub-study offers an opportunity to explore potential safety signals of the tele-ophthalmology pathways not typically observable in the context of RCT trials.

8.4 Dissemination of Results

Findings will be reported through academic journals in ophthalmology, health services research and HCI; some will focus on findings from the HCI studies, and some will relate findings to those of the parallel studies covering other themes. PPI workshops will be organised in Birmingham and London before the main study period, with a focus on designing the study adapting the model from an earlier project (the “before” study is reported by Furniss et al, 2016).

9. Statistical considerations

The trial statisticians based at King’s Clinical Trial Unit will write the statistical analysis plan before database lock and will perform the analysis using the Stata software (StataCorp, College Station, TX, USA).

9.1 Sample size calculation

The primary outcome is the proportion of false positive referrals. Under the current system an audit conducted at Moorfields Eye Hospital NHS Foundation Trust in September 2018 showed that 70 % of retinal referrals were false positive (Korteum et al BJO 2018) A pilot study on 40 patients conducted in three optometry practices showed that this could be reduced by 60 % (Korteum et al, BJO 2018). A 95 % confidence interval computed by the modified Wald Method as advised by Agresti and Coull (The American Statistician. 52:119-126, 1998) would extend 44.6% to 73.7%. There is consensus amongst clinicians however that given the savings to the NHS and benefit to patients, slightly smaller differences would be important to detect and we have powered the study to examine a reduction to 40 % false referrals. Whilst smaller differences might yet be important it would seem unethical to power for lower than 40 % based on the observed data and clinical expertise in this area.

Although decisions for patients are made on an individual basis each patient cannot be assumed to generate independent information since they will be clustered within optometry practices. The correlation of information from patients within a cluster (the intracluster correlation) is estimated to be 0.15. We have based this intracluster correlation on previous

work conducted in ophthalmology (Day AC et al, 2015, Theodossiades J et al, 2004) with a clinical outcome similar to this study. Since this is an estimate we have increased the intracluster correlation slightly to allow for the potential that patients within the same optometry practice may be more similarly managed than patients within different practices although clinical consensus is that clinical signs are more likely to impact upon decision making for referral than individual optometrist attitudes. Using nQuery software version 8.3.10, a hierarchical 2-level mixed effects model was used to calculate the required sample size. 24/26 clusters split between the study arms in a 1:1 ratio need to recruit an average of 12/10 patients per clusters (12 patients if 24 clusters, 10 patients if 26 clusters) in order to achieve 89.27% power to detect a difference in the proportion of false positive referrals of 30% (a drop from the current rate of 70% to the clinically relevant rate of 40%). This calculation assumes an intracluster correlation of 0.15 and the test is performed at the 5% significance level.

A total of 288 patients (based on an average of 12 patients recruited at 24 clusters, 144 per study arm) would therefore be needed to complete the data analysis with sufficient statistical power. To allow for an anticipated 15% drop our rate (patients are likely to be elderly and have comorbidity causing motion artefacts and some images may be ungradable), the total sample size is 340 patients (170 per study arm).

The sample size of the RCT and pragmatic sub-study combined will also enable the AI observational diagnostic accuracy study to obtain robust estimates of sensitivity and specificity. All 500 patients (accounting for the anticipated drop-out rate) will be included in the AI study. Classifications will be made without additional clinical information. Research from our group suggests that the diagnostic accuracy of the Moorfields-DeepMind AI will be as high as 95% (De Fauw et al, 2018). This combined sample of 500 patients with 475 patients being correctly diagnosed would produce a two-sided 95.0% confidence interval with a width of 0.039. The sample from the RCT alone -288 patients with 274 being correctly diagnosed - produce a two-sided 95.0% confidence interval with a width of 0.052. PASS has been used to calculated these widths.

9.1.1 Recruitment plan

On the basis of feedback provided by optometry practices already identified and interested in participating in the study, an average of 3 eligible patients can be approached to consider participation in the study per month per cluster, with a range of 2-5 patients based on the size of the optometry practice. However, it is also expected that 35% of potential patients will decline to participate. Currently, different sites are at different stages of readiness for commencing recruitment and therefore a staggered start to recruitment over 3 months is embedded in the recruitment plan. Based on these conservative estimates a recruitment period of 12 months with a staggered initiation over the first 3 months will be sufficient to approach 521 patients, of whom it is expected that 340 patients will be recruited to the study. A smaller practice only approaching 2 patients per month will require 11 months to recruit 12 patients (accounting for drop out and decline to participate). If the practice was one of the last to start recruitment and so started 3 months into the recruitment window, they would still

manage to recruit 10 patients in 9 months (accounting for drop out and decline to participate). A larger practice in the same catchment area will be able to compensate by over-recruiting up to a set maximum of 16 patients. The range of cluster size will thus be 10-16 patients. Optometry practices that have reached their maximum cluster size of 16 patients before the end of the 12 - month recruitment period and can no longer recruit to the main RCT study can continue to recruit patients to the AI observational diagnostic accuracy study.

The 2 additional randomised community practices allow the potential to increase the number of clusters to 26 if further acceleration of recruitment is required. 26 clusters will be required to recruit 306 patients overall with an average of 10 patients per cluster (and a minimum of 8 patients per cluster) in order to achieve 89.27% power to detect a difference in the proportion of false positive referrals of 30% - using the same parameters as the sample size calculation for the 24 clusters.

9.1.2 Pragmatic Sub-Study

Manchester Eye Hospital and its local area, a site included in the original protocol, has already moved to a tele-ophthalmology referral pathway as part of a commissioning change across the local region. This change in standard care provides a unique opportunity to examine whether tele-ophthalmology works under usual conditions within the NHS. This sub-study will allow us to measure and visualise variation in quality of health care within a local region to inform our inferences from the RCT on how the tele- ophthalmology pathway will perform within a real-life setting.

From this study, key estimate statistics will be calculated including the overall rate of referral to HES, the false positive (referral) and false negative rate against the Reference Standard and the proportion of wrong diagnosis and wrong referral urgency. These shall be compared to the rates found for the intervention arm of the main RCT.

Recruiting 18 patients from each of 12 tele-optometry practices (for a total of 216 patients) will allow the proportion of false positive referrals to be produced with a 95% confidence interval with a width less than 0.187. This was calculated based on confidence intervals for one proportion within a cluster-randomised design with an intracluster correlation of 0.15. A total of 216 patients (based on an average of 18 patients recruited from 12 clusters) would therefore provide a certain degree of precision. To allow for an anticipated 15% drop our rate (patients are likely to be elderly and have comorbidity causing motion artefacts and some images may be ungradable), the total sample size is 254 patients. It is expected that 35% of participants will decline to participate and so 390 patients would need to be approached. These patients can be recruited over a period of 18 months with an average of 3 patients approached by each practice per month.

9.2 Statistical analysis

The primary analysis will be conducted following an intention to treat principle where all randomised patients are analysed in their allocated group whether or not they receive their randomised management plan. Baseline characteristics will be summarised for each management group (standard care or tele-ophthalmology). We will report the number of clusters in each group and the size of clusters. Continuous data will be summarised using means and standard deviations if data appear Gaussian or medians and interquartile ranges. Categorical data will be reported as proportions and percentages. The primary outcome is the proportion of false referrals. The outcome is measured at the patient level. This will be compared between management groups using logistic regression adjusting for clustered centres. Outcomes will be reported as adjusted odds ratios. We will also report the difference in proportions with a 95 % confidence interval as per the Consort extension for cluster randomised controlled trials. We will report false referral rates with 95 % confidence intervals computed by the exact binomial method by diagnosis and by level of urgency. The results will be presented at the cluster level and overall.

Secondary outcomes such as time from referral to review in HES and treatment will be analysed in a similar fashion. The percentage of patients experiencing adverse events in the two groups will be reported with 95 % confidence intervals computed by the exact binomial method.

Loss to follow-up will be examined by study arm. Reasons for missingness may be important and these will be investigated using logistic regression of covariates based on an indicator of missingness. An available case analysis will be reported along with an analysis using imputed data based on best and worst case scenarios. Since this is a cluster RCT we will also examine and report missingness by cluster.

No formal interim analysis is planned but reports concerning patient safety will be prepared for review by the Independent Data Monitoring Committee. All tests will be two sided and will be assessed at the 5 % significance level unless otherwise specified. All confidence intervals will be 95 % and two sided. A detailed statistical analysis plan will be agreed with the Trial Steering Group prior to any analysis of locked data. All statistical analysis will be performed using Stata (StataCorp, College Station, TX, USA). Statisticians analysing the data will be masked to the management group status of the practise and patient.

In the AI diagnostic accuracy study, we will report estimates of sensitivity and specificity of the DeepMind algorithm for referral decisions with 95 % confidence intervals. Our primary analysis will combine urgent and standard referral to HES and compare against no referral to HES but a sensitivity analysis will be conducted to evaluate urgent referrals. The referral outcome (refer routinely, refer urgently, don't refer) will be cross tabulated for the DeepMind algorithm and each of the RCT treatment arms (community optometry and 'tele-HES'), the pragmatic sub-study, and for the Reference Standard.

10. Economic analysis

The economic evaluation will comprise a within trial cost-consequence analysis (CCA) directly comparing the interventions from the trial. A cost-benefit analysis will also be included where the consequences from the CCA are valued using a discrete choice experiment (DCE) comparing tele-ophthalmology digital pathway compared with usual care with additional comparators defined by the addition of the use of the Moorfields-DeepMind Algorithm to assess OCT scans.

10.1 Cost-Consequence Analysis

This analysis highlights the choices and trade-offs between the modalities of care provision without an explicit synthesis of data into a single measure of efficiency. The results for the cost-consequence analysis will be presented as a balance sheet, which will include point estimates and appropriate measures of variance. Deterministic sensitivity analysis e.g. variations in unit costs, will also be conducted. The consequences for each of the comparators will be based upon a further consideration of outcomes (for example necessary referrals missed, correct referrals, individuals correctly not referred). The likelihood of these different outcomes (given as percentages) will be described.

Costs that will be included will be those that fall on the NHS and community optometry practices. Currently community optometrists review OCT scans in their practice to assess the health of the retina and refer any potential pathology for assessment at the hospital eye service. Costs will be explored from different perspectives, names an NHS perspective and an NHS & Community optometry perspective. From an NHS perspective, costs such as hospital visits, medications and community GP visits will be costed. Unit costs for resource use will be derived from published sources e.g. NHS Reference Costs and Unit Costs of Health and Social Care (Personal Social Services Research Unit, 2019, NHS England, 2018). When considering the addition of the community optometry perspective, the costs to purchase and maintain an OCT scanner will be considered. The costs of acquisition will be derived from market prices and converted in a cost per patient using standard economic methodology (Drummond et al 2005). In addition to this, the costs of the Moorfields-DeepMind algorithm will be considered in the within trial analysis. We will base this cost on advice from the algorithm owners as well as consideration of analogous algorithms. We expect there to be considerable uncertainty around the price to the NHS as a market price is not available. Therefore, we will explore the impact on efficiency of a range of prices. This will help decision-makers consider the maximum price they might be willing to pay for this algorithm given the benefits it may provide.

In addition to the costs of running the algorithm in terms of hardware, software and staff, required will be considered. This will be based upon its use within the study and advice from members of the study. A sensitivity analysis will be carried out to explore how the adoption of

different perspectives (i.e. who is bearing the costs) will affect the cost effectiveness of the intervention.

The consequences of the CCA will include a number of factors rather than a single discrete outcome as the algorithm has a number of different goals, including the reductions of false positive referrals and the prioritisation of the true positives. Outcomes which may be included in this CCA are; false positives, false negatives, unnecessary hospitalisations and duration of the time spent with an untreated macular disorder. These will be compared to the costs of provision and of the intervention and with the results of the Discrete Choice Experiment (DCE) described below.

10.2 Discrete Choice Experiment

The DCE will be used to value in monetary terms the relative importance of the different consequences included in the CCA. To do this it will use methods previously successfully used in other NIHR funded studies (Burr et al., 2012, McCormack et al., 2005). A DCE is an attribute-based survey method for measuring benefits. It offers participants at least two alternative choices which vary across several attributes of interest. These can include several attributes of how the intervention is provided and its effect on health and other outcomes. Each of these attributes can vary over a range of levels. The choice of DCE attributes for this intervention will be informed from existing literature on macular disease and provision of eye care service. The output of the qualitative study will also be examined for any attributes which could affect the preferences of the users of the service. Examples of the potential attributes are described in Table 1.

Table 1: Examples of potential attributes for the DCE

	Attribute	Description
1	Risk of mild central vision loss	Risk based on late diagnosis, based on literature. Presented as number of people in 10,000
2	Risk of moderate central vision loss	Risk based on late diagnosis, based on literature. Presented as number of people in 10,000
3	Risk of severe central vision loss	Risk based on late diagnosis, based on literature. Presented as number of people in 10,000
4	Time spent until medical assessment (if required)	Same day, six weeks, three months, None until symptoms worsen
5	Unnecessary distress	None, hospital visit when eye is healthy, being told no problem and them symptoms worsen
6	Cost per year	10, 25, 20 40, 60, 80, 100 (other)

The cost attribute will be included, as this will allow willingness to pay for a unit change in the level of each of the other attributes to be estimated. The values for the cost attribute will be based on pilot work and reviews of prior studies in this area for example Burr et al. (2012) valued an intervention to monitor ocular hypertension to prevent glaucoma using a DCE. The range of values was between £15-70 (GBP 2012). Similarly, Shih et al. (2007) assessed the WTP for a diabetic retinopathy screening service and reported a narrower range of between

$4-$24 (USD 2007). After the attributes have been established then the piloting stages will occur. A survey company will be utilised to gain a large enough sample (www.researchnow.co.uk). The participants will be offered a small incentive (£1-£2) to complete the survey. The overall sample will be representative as closely as possibly for factors such as age, sex and ethnic background for the UK population. Optimal sample size requirements for the limited dependent variable models estimated in DCEs depend on knowledge of the true choice probabilities, which are not known prior to undertaking this research. However, previous DCE studies have shown that robust choice models can be estimated from sample sizes between 50-100 respondents. As such, a small pilot sample of 100 participants will be used as a sample to monitor the rate of completion and to carry out preliminary analysis and change any parts of the survey that are necessary. After the preliminary analysis is carried out, then a further sample of 300 participants will be surveyed which will be sample size comparable to other HTAs in this area. The results of the DCE will be analysed using conditional logit regression analysis, which will measure the direction and strength of the participant preferences. Sub group analysis will also be carried out to see if factors such as age, sex or ethnic background have any effect on the resulting preferences.

To capitalise on the opportunity afforded by the pragmatic post-implementation study, the economic evaluation will provide the following additional elements:

1. The Manchester sub-study group will inform estimates of the cost of the intervention, as delivered in a 'real world' application which may be more realistic than those estimated from a trial setting.
2. Secondly the Manchester sub-study group will be used to inform an exploratory analysis. In this the costs and consequence of the real life sub-study group will be compared to the results from the trial group to identify if there is any meaningful difference between the two sets of data and if there are what the driving factors are. As a safety analysis will be carried out as part of a sub-study, the cost and consequences of any unexpected adverse events that are recorded will be included in the cost consequence analysis. If any safety events become apparent during the design of the Discrete Choice Experiment then these may be used as the basis of different attributes and levels in the study design.

10.3 Data analysis

As noted above, the results of the DCE will be used to value the 'consequences' described in the cost-consequence analysis. Outcomes will also be expressed as a net benefit by combining the differences in each outcome by the willingness to pay for a unit change in that outcome (derived the discrete choice experiment described above). This WTP values will be subtracted from the costs to express the net benefit of the intervention in monetary terms. Probabilistic and deterministic sensitivity analyses will be carried out to vary parameter uncertainty in for the both the costs and the effects. Results of the probabilistic sensitivity analysis will be presented as point estimates of net-benefits, plots of costs and benefits net

benefit curves, which show the likelihood of each intervention being most likely to be have the highest net benefit.

11. Monitoring and Quality Assurance

11.1 Project management

The overall management structure of this study will consist of **Executive Group (EG), Trial Management Group (TMG), Trial Steering Committee (TSC)** including a TSC Independent chair, an independent statistician, two clinicians and a representative of the Macular Society (the CI, study statisticians, health economists and the project manager will attend as observers) and **a Data Monitoring Committee (DMC)** including a statistician and two clinicians independent of the study team**.**

The **TMG** will be responsible for the day-to-day running and management of the trial. The Group will meet formally and informally regularly to discuss progress with trial and examine mitigating strategies in case of issues arising. The Trial Manager and CI will also send regular progress reports to all site PIs.

The **TSC** will ensure the overall integrity of the study by monitoring its progress, investigating any serious adverse events, and taking account of regular reports from the **DMC**.

The **EG** will meet every four weeks to discuss the practicalities of the study.

The **TSC** and the **DMC** have formal Charters which describe the Committee Members, the frequency of the meetings and the remit of the Committees. These Charters are reviewed annually.

The **TSC** is expected to meet annually (or more often, if determined by the Chair). The **DMC** will monitor the trial data to ensure that the trial is being implemented in accordance with the highest standards of patient safety and ethical conduct. Throughout the trial, the **DMC** will monitor data on recruitment, emerging external evidence, sample characteristics and primary outcomes and make recommendations on whether an interim analysis is required.

12. Ethical considerations

The research project will adhere to the UK Framework for Health and Social Care research. Ethics approval will be sought for this project. No particular challenges are expected given the low risk nature of the intervention of the RCT, the safety net arrangements for cases not referred to HES from community optometry, the observational design of the AI diagnostic

accuracy study, and the relatively low personal sensitivity of the topics to be investigated in the HCI studies.

Patients lacking capacity or unable to understand the study will not be eligible. A record will be kept at each optometry site that captures reasons for patients not recruited on the study. As recruitment will take place at community optometry practices, translator services will not be provided.

13. PPI Involvement

13.1 Pre-application phase

In preparation for this proposal, we collected opinions from patients involved in the pilot phase of the tele-ophthalmology model in Moorfields Croydon in September 2018. This process was organised and delivered by members of the clinical team piloting the tele-ophthalmology pathway. Questionnaires were handed to 18 patients with closed and open-ended questions. These included: general perceptions of 'tele-ophthalmology', questions around trust in technology, potential concerns about impersonal care or reduced opportunities to interact with healthcare professionals. Patients overall felt positively about the prospect of avoiding unnecessary visits to the eye hospital and improved experience of care in the community. General perception of the central concept of the project was very positive and surveyed patients expressed contentment that tele-ophthalmology could reduce waiting times, curtail unnecessary hospital visits and alleviate anxiety from prolonged uncertainty around diagnosis. In the open-ended question 'what would help you gain greater trust in the tele-ophthalmology clinics' several patients placed emphasis on patient information to be provided during attendance at community optometry practices to offer adequate understanding of the pathways, the experience to be expected during their visit and the timescale for obtaining feedback. Patients also wanted to have a point of contact for questions and clarifications on any letters they may receive from secondary care.

In light of these comments, information material on tele-ophthalmology will be produced and offered to potential participants alongside the patient information sheet for the specific study. Captured comments from patients will be crucial for ensuring that information material is appropriate and suitably worded to inform on the proposed pathways while alleviating any concerns. Patient input also helped reinforce the importance of introducing a comprehensive qualitative element to this research project thorough the Human Computer Interaction analysis to capture patient perceptions around digital models of care, including Artificial Intelligence, such as issues around data privacy, impersonal care, trust in the technology, confidence in the quality of care provided through digital means.

13.2 Development phase

Taking on board recommendations the patient feedback collected during the tele-ophthalmology pilot, a study-specific PPI group will be recruited at Moorfields Eye Hospital, where the study principle investigators are based. A meeting of the PPI group is planned at the onset of the development period of the study (first 6 months of the study) either face-to-face or via teleconference. The PPI group will help consider potential barriers to recruitment and advise on wording of patient information material, advise on issues around location and geographical spread of community optometry practices and transport arrangements, review the tele-ophthalmology platform interface and advise on elements that would enhance patient trust. This input will be critical in finalising the protocol for the main study, especially on selection of sites for the qualitative elements of the study.

13.3 Main Study

The study-specific PPI group will also transition to the main study and will meet at least once a year with provision for additional face-to-face or 'virtual' meetings when input is required for potential protocol amendments or issues arising during the course of the study. An end of study debrief is planned with all PPI contributors which will include discussions of the prioritisation and dissemination of study results both to the public as well as relevant healthcare professionals. The Eye Charities and especially the Macular Society will be involved throughout the study and, if approved by the NIHR will be represented in the Steering Committee and will assist with dissemination of trial results to patients and healthcare professionals.

14. Financing

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15. Archiving and data retention

A single file with research data will be maintained and stored in a secure NHS computer at the Moorfields Reading Centre with restricted access by the Chief Investigator only. Data will be destroyed after the retention period. The retention period is for 15 years.

16. References

Apple Watch AFib (Atrial Fibrilation app) FDA approval https://www.accessdata.fda.gov/cdrh_docs/pdf18/DEN180044.pdf

Braun, V., & Clarke, V. (2006). Using thematic analysis in psychology. Qualitative research in psychology, 3(2), 77-101.

Burr J et al. 2012. Surveillance for ocular hypertension: an evidence synthesis and economic evaluation. In: NATIONAL INSTITUTE FOR HEALTH REASEARCH (ed.) Health Technology Assessment. Basingstoke.

Cameron JR, Ahmed S, Curry P, Forrest G, Sanders R. Impact of direct electronic optometric referral with ocular imaging to a hospital eye service. Eye (Lond). 2009;23(5):1134-1140.

Chee RI, Darwish D, Fernandez-Vega A, Patel S, Jonas K, Ostmo S, et al. Retinal Telemedicine. Curr Ophthalmol Rep. 2018;6(1):36-45.

CLARKE, P. M., SIMON, J., CULL, C. A. & HOLMAN, R. R. 2006. Assessing the impact of visual acuity on quality of life in individuals with type 2 diabetes using the short form-36. Diabetes Care, 29, 1506-11.

Craig, P., Dieppe, P., Macintyre, S., Michie, S., Nazareth, I., & Petticrew, M. (2008). Developing and evaluating complex interventions: the new Medical Research Council guidance. Bmj, 337, a1655.

Dabasia PL, Edgar DF, Garway-Heath DF, Lawrenson JG.
A survey of current and anticipated use of standard and specialist equipment by UK optometrists. Ophthalmic Physiol Opt. 2014 Sep;34(5):592-613.

De Fauw J, Ledsam JR, Romera-Paredes B, Nikolov S, Tomasev N, Blackwell S, et al. Clinically applicable deep learning for diagnosis and referral in retinal disease. Nature medicine. 2018;24(9):1342-50.

Esteva A et al. Nature. 2017 Feb 2;542(7639):115-118.

Elwyn G, Kreuwel I, Durand MA, Sivell S, Joseph-Williams N, Evans R, Edwards A. How to develop web-based decision support interventions for patients: a process map. Patient education and counseling. 2011 Feb 28;82(2):260-5

FDA News Release. FDA permits marketing of artificial intelligence-based device to detect certain diabetes-related eye problems. 11 April 2018.
Gulshan V, et al. JAMA 2016;316(22):2402−10.
Health Quality O. Optical coherence tomography for age-related macular degeneration and diabetic macular edema: an evidence-based analysis. Ont Health Technol Assess Ser. 2009;9(13):1-22.
Heeks, R. (2006). Health information systems: Failure, success and improvisation. International journal of medical informatics, 75(2), 125-137.J
Johnson, J., & Henderson, A. (2002). Conceptual models: begin by designing what to design. interactions, 9(1), 25-32. Jones L, Bryan SR, Miranda MA, Crabb DP, Kotecha A. Example of monitoring measurements in a virtual eye clinic using 'big data'. Br J Ophthalmol. 2018;102(7):911-5.
Kelly SP, Wallwork I, Haider D, Qureshi K. Teleophthalmology with optical coherence tomography imaging in community optometry. Evaluation of a quality improvement for macular patients. Clin Ophthalmol. 2011;5:1673-8
Konstantakopoulou E et al Clinical safety of a minor eye conditions scheme in England delivered by community optometrists BMJ Open Ophthalmology 2018;0:e000125. Kortuem K, Fasler K, Charnley A, Khambati H, Fasolo S, Katz M, et al. Implementation of medical retina virtual clinics in a tertiary eye care referral centre. Br J Ophthalmol. 2018.
Lakhani P et al. Radiology. 2017 Aug;284(2):574-582.
Li B, Powell AM, Hooper PL, Sheidow TG. Prospective evaluation of teleophthalmology in screening and recurrence monitoring of neovascular age-related macular degeneration: a randomized clinical trial. JAMA Ophthalmol. 2015;133(3):276-82.
Lin CT, Albertson GA, Schilling LM, Cyran EM, Anderson SN, Ware L, et al. Is patients' perception of time spent with the physician a determinant of ambulatory patient satisfaction? Archives of internal medicine. 2001;161(11):1437-42.
Looker HC, Nyangoma SO, Cromie DT, Olson JA, Leese GP, Black MW, et al. Rates of referable eye disease in the Scottish National Diabetic Retinopathy Screening Programme. Br J Ophthalmol. 2014;98(6):790-5.
MCCORMACK, K., WAKE, B., PEREZ, J., FRASER, C., COOK, J., MCINTOSH, E., VALE, L. & GRANT, A. 2005. Laparoscopic surgery for inguinal hernia repair: systematic review of effectiveness and economic evaluation. In: REASEARCH, N. I. F. H. (ed.) Health Technology Assessment.
MacEwen C. Increasing demand on hospital eye services risks patients losing vision. BOSU report, 2017
NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE 2014. Developing NICE guidelines: the manual. In: EXCELLENCE, N. I. F. H. A. C. (ed.). UK: NICE.
NHS ENGLAND. 2018. Reference costs [Online]. [Accessed 23/04/2019 2019].
PERSONAL SOCIAL SERVICES RESEARCH UNIT. 2019. Unit Costs of Health and Social Care 2018 [Online]. Kent: PSSRU. [Accessed 23/04/2019 2019].
Preece, J., Rogers, Y., & Sharp, H. (2015). Interaction design: beyond human-computer interaction. John Wiley & Sons.

RCOphth. 2016;https://www.rcophth.ac.uk/2016/03/increasing-demand-on-hospital-eye-services-risks-patients-losing-vision/

OCT Roll Out Specsavers https://www.aop.org.uk/ot/industry/high-street/2017/05/22/oct-rollout-in-every-specsavers-announced

Rathi S, Tsui E, Mehta N, Zahid S, Schuman JS. The Current State of Teleophthalmology in the United States. Ophthalmology. 2017;124(12):1729-34.

Resnikoff S, Felch W, Gauthier TM, Spivey B. The number of ophthalmologists in practice and training worldwide: a growing gap despite more than 200,000 practitioners. Br J Ophthalmol. 2012;96(6):783-7.

Rosson, M. B., & Carroll, J. M. (2002). Usability engineering: scenario-based development of human-computer interaction. Morgan Kaufmann.

Royal College Ophthalmologist: Management of Wet Age-Related Macular Degeneration, 2015 'The Way Forward'

Scanlon PH. The English National Screening Programme for diabetic retinopathy 2003-2016. Acta Diabetol. 2017;54(6):515-25.

SHIH, H., CHOU, P., TUNG, T., CHEN, S., LIU, J., LEE, F. & LIU, C. 2007. A Community-based Study of the Willingness to Pay Associated with Screening for Diabetic Retinopathy among Type 2 Diabetes in Kinmen, Taiwan. Journal of Epidemiology, 17, 186-193. Theodossiades J, Murdoch I, Cousens S. Glaucoma case finding: a cluster-randomised intervention trial. Eye (Lond). 2004 May;18(5):483-90.

Yardley, L., Morrison, L., Bradbury, K., & Muller, I. (2015). The person-based approach to intervention development: application to digital health-related behavior change interventions. Journal of medical Internet research, 17(1).

Wong WL, Su X, Li X, Cheung CM, Klein R, Cheng CY, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health. 2014;2(2):e106-16.

17. Annex A

INSTRUCTIONS AND DETAILS OF ASSESSMENTS
Assessments at community optometry practices:
For each patient, the symptoms at presentation and patient history will be captured on a clinical pro-forma (eCRF) for the control arm and for the intervention arm. Visual acuity with habitual correction will be recorded as per standard practice in community optometry practices. An Optical Coherence Tomography (OCT) scan of both eyes will be performed as per standard practice and the type of OCT device will be recorded. The referral decision by the community optometrist will be recorded.
Assessments at HES:
The referral decision after clinical review at HES will be recorded. The time from referral to assessment and referral recommendation will be recorded. For cases with urgent maculopathies requiring treatment (such as neovascular AMD and Central Retinal Vein Occlusions), the time from referral to treatment will be recorded.
Assessments at Reading Centre:
The referral decision provided by the AI DSS after processing OCT in each case at the Reading Centre will be recorded. The end-to-end processing time of each OCT by the AI DSS will be recorded.

18. Appendix

Figure 1.