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Final Project Report

Implementation of Corneal Confocal Microscopy in Primary Care Optometry Practices for Screening and Early Detection of Diabetic Neuropathy: a Feasibility Study.

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Table of Contents

Glossary

Term	Description
Acceptability	Satisfactory, suitable and capable of being tolerated
ACCMetrics	ACCMetrics, an algorithm to extract and automatically quantify nerve fibres providing an output for all the main nerve parameters either for single images or for multiple images/patient in minutes rather than hours.
Binomial Test	In statistics, the binomial test is an exact test of the statistical significance of deviations from a theoretically expected distribution of observations into two categories.
Blepharospasm	Involuntary tight closure of the eyelids.
Chief Investigator	The person who takes overall responsibility for the research.
Confidence Interval (CI)	The CI is a range of values, above and below a finding, in which the actual value is likely to fall. The confidence interval represents the accuracy or precision of an estimate.
CCMetrics	CCMetrics is image analysis software which was originally developed for semi-automated (manual) quantification of nerve fibre metrics from CCM images. CCMetrics allows quantification of nerve fibre metrics in images obtained using the HRT3 Heidelberg Retina Tomograph with the Rostock Cornea Module (for confocal corneal microscopy).
Corneal Confocal Microscopy (CCM)	Clinical ophthalmic technique for in vivo imaging of the living cornea and its cellular structure.
Diabetic Neuropathy (DN)	Nerve damage that can occur in people with diabetes. There are different types of diabetic neuropathies including small fibre neuropathy, large fibre neuropathy, autonomic neuropathy, peripheral neuropathy etc.
Diabetic Peripheral Neuropathy (DPN)	Nerve damage in the peripheral nervous system that affects people with diabetes. DPN is where small nerve fibres are damaged in patients with diabetes, usually in the legs, feet or hands.
Feasibility	Possible and practical to do easily or conveniently.
Fixation	Fixation or visual fixation is the maintaining of the visual gaze on a single location.
HRT - RCM	The CCM equipment used to conduct CCM testing is a HRT (Heidelberg Retinal Tomography) with a Rostock Corneal Module (RCM) ad on.
Implementation	The process of putting the procedure into effect; carrying it out.
Intraepidermal Nerve Fibre Density (IENFD)	The IENFD test is a simple 3mm punch biopsy of skin from the leg, performed under local anaesthetic. Once the sample is received at the lab, small sensory nerve fibres are stained and easily visualized under a microscope. Results include assessment of IENFD density through a pathological review by neurological experts.
In Vivo (IV)	In vivo refers to a study that is performed in a living organism
Nerve Conduction Studies (NCS)	Is a medical diagnostic test commonly used to evaluate the function, especially the ability of electrical conduction, of the motor and sensory nerves of the human body.
Optometrist	Primary health care specialists trained to examine the eyes to detect defects in vision, signs of injury, ocular diseases or abnormality and problems with general eye health.
Palpebral	Relating to the eyelids or located on or near the eyelids.

Ptosis	A drooping or falling of the upper or lower eyelid.
Quantitative Sensory Testing (QST)	Is a method used to assess damage to the small nerve endings (which detect changes in temperature), and the large nerve endings (which detect vibration).
Quartile	In this study a quartile refers to a division of results into 25% intervals. The patients were tested in consecutive order at each practice. The first quartile represents the results for the first 25% of patients tested. The second quartile represents the results for the next 26-50% of the patients and so on.
Retinopathy	Disease of the retina which results in impairment or loss of vision.
SMDRSS	South Manchester Diabetic Retinopathy Screening Service.
Tomocap	A disposable thin plastic cap which is placed over the microscope lens.

Acronyms and abbreviations

CCM	Corneal Confocal Microscopy
CI	Confidence Interval
DN	Diabetic Neuropathy
DPN	Diabetic Peripheral Neuropathy
HRT – RCM	Heidelberg Retinal Tomograph - Rostock Corneal Module
IENFD	Intraepidermal Nerve Fibre Density
IV	In Vivo
NCS	Nerve Conduction Studies
QST	Quantitative Sensory Testing
SMDRSS	South Manchester Diabetic Retinopathy Screening Service

Executive summary

Background and purpose

Diabetic Neuropathy (DN) is the most common and costly complication of diabetes. Easily performed clinical techniques such as neurological examination, assessment of vibration perception or insensitivity to the 10g monofilament, only assess advanced neuropathy i.e. those at risk of foot ulceration and other complications. There is evidence now that the ophthalmic technique of in vivo corneal confocal microscopy (IVCCM or CCM) might be such an ideal surrogate measure of DPN. At present, CCM is only performed at research centres by experienced operators therefore the primary aim of this study was to investigate the feasibility and acceptability of CCM in optometry practices to screen for DN.

Recruitment

Four community optometry practices in Greater Manchester that were part of South Manchester Diabetic Retinopathy Screening Service (SMDRSS) took part in the study. The practices were selected based on finding maximum variety of the patient population in terms of: age, ethnicity, socio-economic factors and the size of their diabetes population and willingness of optometrists to participate in this research.

During the study period (April-September 2015) 716 patients were approached to take part. Recruitment of patients to the study was more successful than anticipated and the target sample size of 400 patients was exceeded within the recruitment period. Of the 449 patients recruited, 95% had type 2 diabetes mellitus, 38% were female and the mean age was 67 years. 80% of participants were white, 16% black, less than 3% Asian and 1% other ethnic groups, and there was variation between practices, reflecting the different ethnic composition of the practices populations.

We compared the composition of the study population against the UK diabetic population as reported in the National Diabetes Audit (NDA) 2012-2013 (Health and Social Care Information Centre, 2014). Overall, apart from ethnicity, the composition of the study population is similar to the UK diabetic population for age, gender, type of diabetes and duration of diabetes characteristics. The proportions of white and black ethnicities reported in our study sample differed considerably from the UK proportions reported in the NDA; however it was not possible to establish a comparison for this variable because 23% of the NDA respondents did not state their ethnicity.

Methods

Participating optometrists received training during a two day workshop to learn the technique of CCM and to be able to successfully perform the test. A receptionist from each practice was also trained on data collection procedures and patient recruitment. Additionally, in house training was provided for each practice. Tests on the first four to eight patients were supervised by an expert, after these optometrists conducted the test independently. Practices received support throughout the whole recruitment period tailored to their needs.

The test was offered to all adult diabetic patients attending their annual retinopathy screening assessment. Where possible, a double appointment was made for the retinal screening test followed by the CCM test, or alternatively a separate CCM appointment was made. At the CCM appointment, the optometrists obtained informed consent from the patient, carried out the test and completed data collection forms. At the end of the test, patients completed an anonymised satisfaction questionnaire. On a regular basis, optometrists selected six or more of the best images from each patient and transferred them to the Chief Investigator for analysis. Periodically, the images were assessed for quality and feedback was provided to the optometrists.

Following the recruitment period (April to September 2015), individual interviews were conducted with each optometrist in order to capture their views and experience of using CCM. A budget impact analysis was also carried out retrospectively to assess the economic impact of this test.

The key findings of this study are presented in the following linked outputs:

1. Feasibility and acceptability of CCM in optometry practices (this report) which includes a summary of the budget impact analysis report.
2. Budget impact analysis report (Davidson et al., July 2016)
3. Clinical findings of the study. This will also be available soon from Mitra Tavakoli et al.

Results

Training

The optometrists stated that the training and follow-up support was useful, appropriate and sufficient; with the practical elements being highly valued by all. Ongoing support appeared to be critical and they welcomed feedback in relation to the quality of the images provided. They made some suggestions for improvement, which were:

- Additional time hours for practical training during the workshop, and less theory based training
- Additional training in what was an 'adequate' quality image for diagnosis. This is also associated with time implications, as optometrists may be able to take fewer images if they are confident that what they have captured is acceptable for diagnosis.
- Further opportunity for extra training to get familiar with various and more complex cases
- Reducing the time between training and conducting CCM test independently with patients (4-5 weeks during this study, which was due to delivery of CCM equipment (HRT with a Rostock Corneal Module ad-on from Germany).

Patient acceptability

Based on the feedback from questionnaires, the majority of patients reported that the test was pain free (90%), comfortable (87%), and 97% would agree to do the test again in the future. Optometrists reported that some patients mentioned being physically uncomfortable because the test involved touching the eye, and some patients found it difficult to maintain the required position for the duration of the test.

Duration of the test

The average duration of the scan decreased over the course of the study from 16 to 10 minutes. Three of four optometrists indicated that selecting images (after conducting the test) was time consuming.

Performing the test

Optometrists were able to complete the CCM test successfully for 92% of patients. This improved over time from 80% in quartile one to 96% in quartile four. Despite this high success rate, the optometrists stated that conducting CCM was difficult in 36% of tests or impossible for 4% of tests; reasons include: patient characteristics, equipment design, ability to perform the test, or a combination of these issues. However, upon review by an optometrist, it was anticipated that some of these challenges could be overcome. In general, optometrists believed that the CCM equipment was not as 'user friendly' as other ophthalmic instruments. Optometrists commented that if CCM were to become part of routine clinical practice, they recommended that the ergonomic features of the CCM equipment be upgraded.

Images

Despite optometrist-reported difficulties in conducting the CCM test for 40% of patients, they successfully screened and assessed 92% of patients. In relation to the quality of CCM images produced, optometrists rated 78% of the images as having acceptable, good or excellent quality. Those images deemed excellent by optometrists increased from 20% in quartile one to 36% in quartile four. Submitted images were assessed by the Chief Investigator, and this showed that 96% of CCM images were of sufficient quality to permit diagnosis and further evaluation. In terms of grading the quality of the CCM images, an analysis of the level of agreement between the optometrist and the Chief Investigator grading indicates there was a 'fair agreement' as defined by Kappa statistics (Landis and Koch, 1977). The optometrists were more cautious about the quality of the CCM images; which is also reflected in the qualitative data. In addition, a sample of 10% of all CCM images were subsequently re-rated by the Chief Investigator and two other researchers. The level of agreement between two Chief Investigator scores at different time points had a 'moderate rating' using Kappa statistics, whereas the level of agreement between the Chief Investigator and the other two researchers was less consistent (see section 4.6.3).

Budget impact

This section is a summary of the budget impact analysis; a more detailed report on these findings is available by (Davidson et al, 2016). The budget impact was calculated over a 5 year period assuming that diabetic neuropathy screening using the CCM test would be combined with the current retinopathy screening test in the same appointment. There are over 182 retinopathy screening programmes in the UK, which use several models of delivery, therefore two separate models of annual screening were compared:

1) fixed equipment in community optometry practices (assuming all screening in England would be conducted in optometry practices)
2) mobile screening/equipment in roving vans (assuming all screening in England would be conducted in mobile units)

Our economic analysis estimated that current retinopathy screening costs £12 per person screened per year within optometry practices. Introducing the additional CCM test within optometry practices would cost an additional £20 per person per year, or an additional £15 per person per year to deliver if both screening tests were conducted in mobile units. Mobile screening is a cheaper option primarily because they employ designated screeners or technicians rather than optometrists to deliver the service.

Optometrists' perspectives on future implementation

To be implemented in routine practice, optometrists suggested that the following would need further development:

- clinical rationale in practice
- cost and remuneration
- resource implications
- ergonomic features of the CCM equipment

Implications for future studies

Further work is required to determine the accuracy of the CCM test, compared to other available techniques and clinical information. A follow on study could test the sensitivity and specificity of the CCM test in comparison with other established techniques. The benefit of earlier diagnosis on the impact of improved diabetic management (as no treatment for neuropathy is currently available) warrants further investigation.

1. Project overview

1.1 Background

Diabetic neuropathy (DN) is the most common and costly complications of diabetes, leading to painful neuropathy (~21%) (Abbott et al, 2011), and a significant increased relative risk of foot ulceration and amputation (Holman, Young and Jeffcoate, 2012). It has been previously shown that foot ulceration is much more common in patients with diabetic peripheral neuropathy (DPN), with the annual incidence rising from <1% in those without neuropathy to >7% in those with established neuropathic deficits (Abbott et al, 1998; Tavakoli et al. 2013). Nerve damage can lead to major complications affecting the bowel, heart, inability to sense low blood glucose and even amputation. It is hard to identify because often there are no early symptoms and signs and current diagnostic tests are time consuming, technically challenging and uncomfortable. Based on current tests, it is not possible to identify individuals at high risk. Table 1 summarises the advantages and disadvantages of current tests for assessing DN.

Table 1. A summary of advantages and disadvantages of tests to assess diabetic neuropathy

Method	Advantage	Disadvantage
Clinical/Neurological Examination	Simple, easy to perform, does not require special equipment	Not sensitive, not reproducible
Nerve Conduction Studies	Sensitive, objective, currently the gold standard for diagnosis	Assesses only large fibres, requires special equipment
Quantitative Sensory Testing (QST)	Evaluates both large and small nerve fibres, quantitative, relatively easy to perform	Subjective, moderate reproducibility, requires special equipment
Sympathetic Skin Response	Simple, fast, objective	Semi-quantitative, low sensitivity
Quantitative Sudomotor Axon Reflex Test	Sensitive, objective, reproducible	Requires special equipment, time-consuming
Autonomic Testing	Objective, quantitative	Moderate sensitivity, requires special equipment
Neuropad™ (Sudomotor function assessment)	Non-invasive, easy to perform, does not require special equipment	Subjective, expensive, moderate sensitivity, uncertain interpretation
Sural Nerve / Skin biopsy	Quantitative, sensitive, currently the gold standard to quantify small fibres	Invasive, costly, risk of infection at the site of biopsy, requires specialist histological technique to quantify intra-epidermal nerve fibre density
Non-Contact Corneal Aesthesiometry	Non-invasive, quantitative	Subjective, moderate sensitivity
Corneal Confocal Microscopy (CCM)	Reproducible, rapid, sensitive, non-invasive, reiterative and quantitative	Requires special equipment and expertise

Whilst symptoms and neurological deficits have direct relevance to patients, many of the assessments summarised in Table 1 have significant limitations. Neurophysiology is objective and reproducible, but does not assess small fibres, which are the earliest to be damaged and show repair. Small fibres can be assessed objectively by quantifying intra-epidermal nerve fibre density in skin biopsies, however, this is an invasive procedure which requires expert laboratory assessment and has considerable variability even amongst controls. Hence, there is a need for a non-invasive, sensitive test for screening and early detection within clinical trials of diabetic neuropathy. There is strong evidence now that the ophthalmic technique of in vivo corneal confocal microscopy (IVCCM) might be such an ideal test for screening and early detection of DPN (Tavakoli et al. 2013).

1.2 Aim and objectives

The main aim of the study was to investigate feasibility and acceptability of CCM in optometry practices to screen for DN.

In this study, we tried to address the following questions:

- Can trained optometrists capture images of sufficient quality for analysis? How does their ability to capture images change over time?
- What level and type of training do optometrists require to capture images of sufficient quality?
- How long does it take to perform the CCM test? How does this change over time?
- What are optometrists' overall experiences of using CCM?
- Are patients able to tolerate the CCM technique?
- What are patients' overall experiences?

This report contains data about the questions above. In addition, two other reports contain details of

- What is the likely impact on healthcare spending if screening for neuropathy by CCM were implemented? (Please note this question is addressed in brief within this report but in greater detail within a separate report titled: Budget Impact Analysis of Introducing Diabetic Neuropathy Screening in England with Corneal Confocal Microscopy (Davidson, N et al, 2016)
- What proportion of patients with a CCM result indicating neuropathy had clinical symptoms to back up this diagnosis? (Please note this question is being addressed separately by Mitra Tavakoli).

1.3 Optometry practices

Retinopathy is a disease of the retina which results in impairment or loss of vision. As part of the national diabetes eye screening programme[1], South Manchester Diabetic Retinopathy Screening Service (SMDRSS) is one of the providers in the Greater Manchester area delivering retinopathy screening. There are 78 optometry practices in the catchment area of the SMDRSS. Four practices with sufficient numbers of patients to deliver the study within the project timeline were approached and agreed to participate.

Optometry practices were selected for this study that would reflect the different types of optometry practices across Greater Manchester, for instance practices that were part of a chain and those that are independent. Each practice estimated what their typical practice population was in terms of age, gender and ethnicity (see Table 2). For socio-economic factors, data from the national general practice profiles was used (Public Health England, 2015). We assumed that SMDRSS patients would

[1] https://www.gov.uk/guidance/diabetic-eye-screening-programme-overview

approach a practice in the vicinity of their home and therefore recruited patients that would reflect the local population demographics.

Reported practice populations varied in terms of:

1) Diversity and ethnicity
2) Socio-economic status (Public Health England, 2015)
3) Age groups (see Table 2)

Table 2. Practice data collected to select optometry practices

	Practice Identifier*			
	B	**C**	**D**	**E**
Typical no. diabetic patients (over 6 months)	250	318	359	425
Level of social deprivation	High deprivation	Medium-low deprivation	Medium-high deprivation	Medium deprivation
Type 1 diabetes	5%	10%	15%	5%
Type 2 diabetes	95%	90%	85%	95%
Ethnicity				
White	90%	90%	1%	92%
Black$_a$	5%	0%	80%	3%
Asian$_b$	5%	10%	19%	5%
Age in years				
<20	3%	2%	5%	From 3-98 with
20-40	5%	8%	20%	the higher
40-60	15%	20%	30%	proportion
>60	77%	70%	45%	between 55+

a Black includes: Black/ African/ Caribbean/ Black British Asian includes: Asian/ Asian British
b Asian includes: Asian/ Asian British
c Other includes: mixed/ multiple ethnic groups/other
*letters are used to anonymise each practice. Practice A withdrew from the study prior to recruitment.

Each participating practice was asked to offer the test to all eligible patients up to a maximum of 100-125 patients. Practices were reimbursed for their time at a rate calculated based on hourly rate for optometrists, with consideration of the practices involvement, of £60 for each patient who consented to take part in the study. Following the training workshop and before starting recruitment, one practice withdrew from the study due to management obstacles within that practice. However, another practice agreed to participate.

2. Recruitment

2.1 Recruitment of patients

All participants in the study were identified at each practice when they booked their annual retinopathy screening test. Diabetic patients (both type 1 and 2) aged 16 years and over were invited to take part by the practice admin team and there was a poster providing information about the study in each practice. In most cases, CCM was booked alongside their retinopathy screening appointment; and when this was not feasible CCM was scheduled as a separate appointment. A logbook was completed for every patient that was approached and patients could freely decline or withdraw at any point without providing reason. Eligible and interested patients were provided with a participant information sheet and invitation letter at least 24 hours prior to their CCM test. At the

appointment, the optometrist discussed the study with the patient, checked clinical eligibility (see* Table 3) and took written informed consent.

Table 3. Eligibility criteria

Inclusion criteria	Exclusion criteria
Aged 16 years and over	Patients under the age of 16
Signed written informed consent	Patients unable to consent for themselves
Have Type 1 or 2 diabetes	Concurrent ocular disease, ocular infection or inflammation which may affect the cornea*
Participant in SMDRSS	History of ocular disease or systemic disease that has affected the cornea (e.g. keratoconus, corneal dystrophies, refractive surgery)*
	Wearing hard contact lens (Rigid gas permeable)*

* The asterisked exclusion criteria are applied because they affect the natural structure/function or cause damage to the cornea.

Between April and September 2015, 716 patients were approached to take part in this study. Of these, 449 (63%) agreed to take part and met the eligibility criteria. Figure 1 shows the recruitment progress throughout the study. The recruitment target was over-achieved, ahead of schedule.

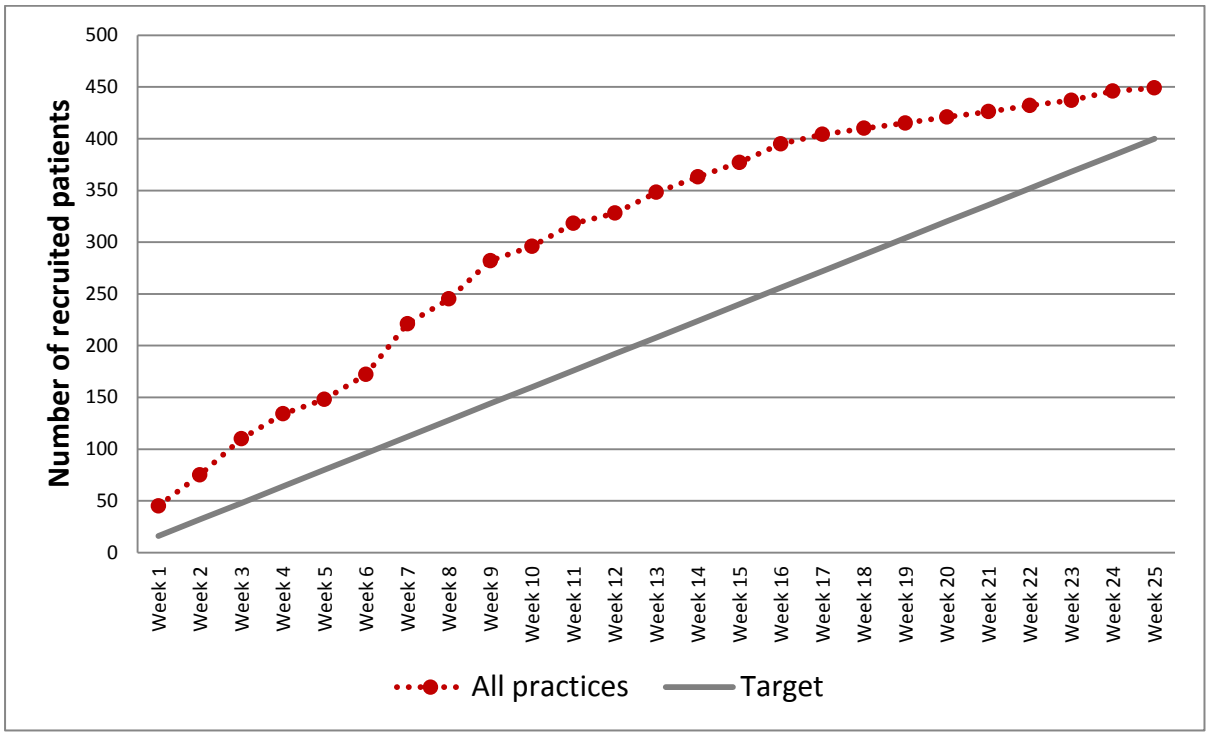

Figure 1. Recruitment of patients throughout the course of the study. The dotted line indicates the number of patients recruited across all practices during the recruitment period. Week 1 is relative to each practice; it corresponds to the first week each practice started recruitment, which varied at each practice.

Factors which the research team deemed important to successful recruitment include:

- Participating practices had a willingness to learn about research, a keenness to participate in the study, and a high proportion of potentially eligible diabetic patients.

- The additional CCM test was offered in three of the four practices as a double appointment alongside routine retinopathy testing. This meant most patients did not need a separate visit to take part in the study.
- Selected practices had no other research activity being undertaken in their practice during the course of this study. This meant each optometrist could solely focus on this study.
- Receptionists received training and support on how to introduce the study and ensure consistency of approach.
- Regular visits to the practice by the study team focussed on recruitment progress, support with any issues, collection and review of forms, and provision of study specific supplies. This helped keep up the momentum with recruitment, particularly for practices that had a slower pace of study activity.
- A graph, showing recruitment figures of all 4 practices over time, was shared with the practices to demonstrate individual progress towards the recruitment target.
- When practices raised a query, the query and resolution was anonymised and shared with all practices to ensure consistency and share best practice.

2.2 Sample size

A sample size of 400 patients with a 95% confidence interval of ±5%, was calculated to allow estimations of the proportions on study outcomes, these being; image quality and proportions of patients who are eligible, consent, undertake successful screening. The sample size decision was primarily based on equipment availability, and feasibility for the practices to recruit sufficient numbers during the course of the study.

Practices were part of SMDRSS and based in different areas of Greater Manchester, with varying social-economic status, adequate number of patients in the retinopathy screening programme, and wide ethnic background.

Table 4 presents these factors. Practice A withdrew from the study prior to participant recruitment, therefore data for practice A is not reported.

2.3 Patient population

Among the 449 patients who participated in the study (

Table 4), 38% were female and the mean age was 67 years. There was some small variation between practices on gender and age. Overall 80% of the recruited sample were white, 16% black, 3% Asian and 1% other ethnic groups, and there was variation between practices, reflecting the different ethnic composition of the practice populations. In all four practices, the proportion of white patients in the study sample was higher than expected, and in two of the practices (D and E) these differences were statistically significant (at the $p<0.05$ level, binomial test). This could be in part, due to the study information only being available in English. 95% of participants had type 2 diabetes. The mean duration of disease was 8 years, with 35% having a history of retinopathy and 6% a history of diabetic neuropathy.

A comparison of the study population against the UK diabetic population is presented in

Table 5. Data for the distribution of the UK diabetic population was obtained from the National Diabetes Audit (NDA) 2012-2013 (Health and Social Care Information Centre, 2014). Overall, apart from ethnicity, the composition of the study population is similar for age, gender, type of diabetes and duration of diabetes characteristics. The proportions of white and black ethnicities reported in the study sample differed considerably from the UK proportions. However the NDA had 23% missing data for ethnicity, therefore this disparity must be taken with caution.

Table 4. Characteristics of the study population

	Practice B n=100	Practice C n=126	Practice D n=99	Practice E n=124	All n=449
Gender (n=449)					
Female	40% (40)	37% (46)	33% (33)	43% (53)	38% (172)
Male	60% (60)	63% (80)	37% (66)	57% (71)	62% (277)
Mean age in years (n=449) [SD]	68 [11]	68 [14]	65 [14]	66 [12]	67 [13]
Type of diabetes (n=442)					
Type 1		7% (9)	4% (4)	6% (7)	5% (20)
Type 2	100% (100)	93% (115)	96% (92)	94% (115)	95% (422) 95% CI 93 to 97
Mean duration of diabetes in years (n=435) [SD]	6.9 [6.7]	9.0 [6.8]	8.8 [7.0]	8.6 [7.2]	8.4 [6.9] 95% CI 7.7 to 9.0
Ethnicity (n=448)					
White	92% (92)	95% (119)	23% (23)	98% (122)	80% (356) 95% CI 75 to 83
Black[a]	6% (6)	2% (2)	66% (65)	0% (0)	16% (73)
Asian[b]	2% (2)	1% (1)	9% (9)	2% (2)	3% (14)
Other[c]	0% (0)	2% (3)	2% (2)	0% (0)	1% (5)
History of retinopathy (n=441)	58% (58)	31% (37)	31% (31)	24% (30)	35% (156) 95% CI 31 to 40
History of DN (n=447)	13% (13)	5% (6)	2% (2)	6% (7)	6% (28) 95% CI 4 to 9

a Black includes: Black/ African/ Caribbean/ Black British Asian includes: Asian/ Asian British
b Asian includes: Asian/ Asian British
c Other includes: mixed/ multiple ethnic groups

Table 5. Characteristics of the study population compared against the UK population

Characteristic	Category	ENA study (n = 449)	UK diabetic population n = 1,979,929
Gender (n=449)	Females	38% (172) 95%CI 34 to 43	44%
	Males	62% (277)	56%
Age in years (n=449)	0 to 9	0% (0)	0%
	10 to 19	0% (1)	1%
	20 to 29	1% (6)	2%
	30 to 39	1% (5)	4%
	40 to 49	7% (31)	11%
	50 to 59	17% (75)	19%
	60 to 69	32% (144)	26%
	70 to79	27% (122)	24%
	80 to 89	14% (61)	12%
	90+	1% (4)	1%
Type of diabetes (n=442)	Type 1	5% (20) 95% CI 3 to 7	8%
	Type 2	95% (422)	92%
Duration of diabetes in years (n=435)	0 to 1	8% (34)	10%
	1 to 4	26% (111)	28%
	5 to 9	29% (125)	29%
	10 to 14	20% (89)	17%
	15 to 19	11% (46)	7%
	20 to 29	6% (24)	5%
	30 to 39	1% (4)	2%
	40 to 49	0% (1)	1%
	50+	0% (1)	0%
Ethnicity (n=448)	White	80% (356) 95% CI 75 to 83	61%
	Black [a]	16% (73)	4%
	Asian [b]	3% (14)	9%
	Mixed [c]	0% (0)	1%
	Other [c]	1% (5)	3%
	Unstated		23%

a Black includes: Black/ African/ Caribbean/ Black British
b Asian includes: Asian/ Asian British
c Other includes: mixed/ multiple ethnic groups/ other

3. Procedures

3.1 Training

Each participating optometrist completed the National Institute for Health Research (NIHR) Good Clinical Practice training (GCP) prior to the conduct of the study.

A two day in-house training workshop was held on 3rd and 4th March 2015 at the NIHR-Wellcome Trust Clinical Research Facility in Manchester. This was attended by the participating optometrists. Practice E, who joined the study after the initial workshop, attended a separate 2-day training course at the same venue and similar training and programme was provided. The course was designed specifically for this study and consisted of 5 hours of practical training in conducting CCM tests with healthy volunteers, as well as associated theoretical knowledge of corneal imaging and CCM, data collection procedures and group discussions (see Table 6). Competency of performing the test on

participants was determined at the end of the practical training, and was assessed by the Chief Investigator.

Table 6. Programme for 2 days training schedule (March 2015)

Day 1	
40 minutes	**Welcome. Introductions. The project aims and outline**
40 minutes	Introduction to Corneal Confocal Microscopy
60 minutes	HRT III and Rostock Cornea Module equipment
60 minutes	Practical demonstration and non-contact practice
120 minutes	Practice with 4 healthy volunteers and guidance from trainers
Day 2	
120 minutes	Practice with 10 healthy volunteers per examiner with guidance from trainers
30 minutes	How to export and transfer CCM images
60 minutes	Practice with a volunteer and guidance from trainers
60 minutes	**Data collection process and Good Clinical Practice revision**
30 minutes	**Evaluation of the training and optometrist interviews**

The majority of this training course would potentially be useful for future studies, or should CCM become part of routine care. However the sessions written in **bold text** indicate study-specific training that would not necessarily be required outside of the research setting.

A receptionist from each practice also attended for a half-day session during this course for study-specific training which covered: an overview of the project, data collection procedures and the patient recruitment process.

3.2 Ongoing support

Following the training course, there was delay of 4-5 weeks in each practice being set up to recruit patients into the study (primarily due to the delivery of the CCM equipment from Germany). Once set up, each optometrist was provided with additional expert support whilst performing their first four to eight CCM tests with patients in their practices until they were confident enough to perform CCM testing independently.

Ongoing support was provided as required through regular phone calls, emails and practice visits by the study team. Over the period of recruitment, submitted images were remotely checked by the Chief Investigator to identify if additional training was needed and to check if images were of sufficient quality to permit diagnosis.

3.3 CCM test procedure

Prior to the CCM test being performed, the optometrist entered basic patient data into the microscope's software. The procedure was explained to the patients and informed consent taken. In

preparation for the test, a drop of local anaesthetic (Benoxinate hydrocholoride 0.4%) was administered to the front of each eye to reduce blinking and numb the eye during the test. A gel tear substitute (Visco-tears) was applied to the front of each eye. A clean Tomocap cover (with Visco-tears applied inside) was then added to the microscope. The microscope was adjusted so that the Tomocap would touch the eye gel on the front of the eye. Images were then taken of the nerves at the front of the eye (cornea). Images were taken of both eyes. Detailed examination procedure and preparation of patient and camera is explained in the online video by Tavakoli and Malik (2011) using this link: http://www.jove.com/video/2194/corneal-confocal-microscopy-novel-non-invasive-technique-to-quantify?sectionid=4.

Following the test, a short self-reported questionnaire was completed by the patient ideally, when the patient had moved to the waiting room, which was sealed in an envelope to maintain confidentiality.

3.4 Image processing

Optometrists were trained to select a minimum of six images per patient from sub epithelial layer of the cornea, and export them via a secure server that specifically designed for this study to the Chief Investigator. The Chief Investigator then graded the quality of the images using ACCMetrics software. All the images transferred for each patient were graded an overall rating of *excellent, acceptable, poor or unacceptable*; where *acceptable* is the benchmark in order to make a successful diagnosis.

Neither patients nor their GPs received feedback on the study results, because CCM is mainly used as a research tool in clinical settings, and it is not known at present how accurate, specific or reliable the CCM test is as a surrogate marker for detecting diabetic neuropathy compared with other clinical methods.

3.5 Data collection

Table 7 describes the different methods of data collection for all of the information collected within this study.

Table 7. Summary of data collection

Data collected	Method
Training and support provided	A short evaluation questionnaire Optometrist interviews at the end of the study
Numbers of patients approached, eligible, consented and completed the test	Screening logs, consent forms and clinical record forms
Test duration and any difficulties encountered retinopathy results and optometrists grading of image quality	Short optometrist record form.
personal and demographic information, clinical history and symptoms	Short patient record form
CCM test tolerability (pain and discomfort), satisfaction with information on test provided	Anonymised short patient questionnaire
Quality of the images (on the scale of; 1=not acceptable, 2=poor, 3=acceptable, 4=excellent) acceptable is the benchmark in order to make a successful diagnosis	Chief Investigator grading of images for each patient

Training requirements, alignment with routine practice, and acceptability of the procedure from both the optometrist's perspective and perceived patient acceptance of the procedure.	Semi-structured interview with all optometrists at the end of the project.

3.6 Budget Impact Analysis

The budget impact was calculated over a 5 year period assuming that diabetic neuropathy screening using the CCM test would be combined with the current retinopathy screening test in the same appointment. There are over 182 retinopathy screening programmes in the UK, which use several models of delivery, therefore two separate models of annual screening were compared:

1) fixed equipment in community optometry practices (assuming all screening in England would be conducted in optometry practices)
2) mobile screening/equipment in roving vans (assuming all screening in England would be conducted in mobile units)

Costs calculated included staff time, equipment and training. The total cost of treating diabetic neuropathy was assumed to be unaffected by screening outcomes in the absence of such data. Further details of this analysis are available within the full report titled: Budget Impact Analysis of Introducing Diabetic Neuropathy Screening in England with Corneal Confocal Microscopy (Davidson et al, 2016)

4. Results

4.1 Feedback from the training workshop

The optometrists completed feedback forms specific designed for this study following the two day course in order to evaluate the training and so that the research team could tailor ongoing training and support in the areas most needed. Table 8 summarises the areas where optometrists felt most and least confident following the two day training course. This data was collected using a training evaluation questionnaire at the end of the course.

Table 8. Feedback from the optometrists on the training

Most confident	Least confident
• Preparing a patient for CCM scan • Preparing the equipment for a CCM scan • Inviting patient questions and knowing how to answer them or where to find the answers	• Assessing image quality • Selecting, uploading and transferring images • Carrying out a successful CCM scan

The majority of the training sessions were rated as very good or good, with the exception of the session on 'How to export and transfer CCM images' which was rated as satisfactory by two optometrists and good by the others (see Appendix 1). The exporting and transferring images session was delivered by demonstration; and further details, training and instructions were provided at each practice.

4.2 Evaluation of the training and support

At the end of the recruitment period, interviews were carried out with optometrists to explore their experience of the training and support they received during the course of the study. Qualitative research necessarily involves making use of respondents' subjective interpretations (Bryman, 1989), some of which are quoted below.

Positive aspects of the training

In interviews, the optometrists were asked whether the training had sufficiently equipped them to carry out the CCM test. In general they reported feeling prepared by the training to carry out the test on patients, with comments such as *"I felt prepared"* (01), *"I thought the training was fine, really thorough"* (03) and "*at no point did I struggle or at no point did I think, I don't need this, I don't need that. Everything was pretty straightforward*" (04). The optometrists generally thought that all of the elements of the training course had been relevant, useful and appropriate.

Two elements of the training that were mentioned as being particularly useful were the 'hands on' practice with volunteers during the initial training days: *"Oh yeah, that was very good. I mean, they had patients lined up and you could ask anything"* (02), and the subsequent supervised CCM tests with patients within the optometrist's practice, were described as *"definitely useful at the beginning*" (01).

Areas to develop within the training

Optometrists did express some feelings of apprehension when they were initially carrying out the screening with patients in their practice. One individual linked this to the length of time that there was between the end of the training and being ready to recruit patients within their practice: *"so by the time we actually started, the apprehension had increased! You weren't…you lacked confidence when you did…you know, how it was going to go and then there was a gap before you got started. So the first few were a bit nerve-racking"* (02). The average duration from the training course to optometrists being able to recruit patients independently was 5.5 weeks with a range of 4.5 to 8 weeks. Delays were due to CCM equipment delivery from Germany and set-up and arranging mutually convenient supervised sessions, which was out of the control of project team. Further in-house training was provided once the equipment arrived.

Two areas where it was considered that more training was needed were: 1) how to *produce* a good quality image (including why it might not always be possible to produce one), and 2) how to *recognise* a good quality image (which would improve diagnostic awareness). In relation to the second point, one optometrist commented *"I never felt confident about the quality of my work because we were not trained in interpreting the results…….. I knew what a good one was. I knew what was a completely unacceptable one. It's the grey area knowing whether they were good enough to be considered adequate*" (01). The view that not enough time was devoted to how to recognise a good quality image was contradicted by one optometrist who stated: *"We had a look at some sample images and [name of trainer] also showed us some software that actually counts the number of nerves and the size of the nerves, and things like that. So although we didn't need it for this study she told us that as well so we're aware of what a good quality image and what a poor quality image is as well"* (04). This individual did not attend the same two day training event as the other three optometrists, so it is possible that (04) did receive more advice about good quality images during their training. These comments support the usefulness of this knowledge.

One optometrist felt that there had been too much theory training: "*if I was in charge of it and running this for other optomotrists, I wouldn't teach them, I'd give them about an hour on theory"* (02). With reference to training on how to produce a good image, this optometrist commented: *"There are various tips that I taught myself as I went along. That I would say, do this, do this, do this, and I would spend longer on teaching them how to get confident to get a decent image"* (02). Another individual said that he would have found it useful to know more about why, on occasion, it seemed impossible to get a good image. He commented: *"There were times when we got lots of really good scans. There were times when it was impossible to get a scan but there were times where you expected a good scan and just couldn't get it and I wasn't quite sure why"* (01).

Ongoing in house training and support

The average number of in house supervised CCM tests per practice was five patients (minimum two, maximum eight). Receptionists also received further support at the practice with the recruitment process, completing the screening log, and organising data collection forms. Resolutions to queries or study issues were shared across all practices where relevant.

All optometrists expressed satisfaction with the ongoing support they received. The importance of receiving feedback about the quality of the images optometrists were producing was highlighted during the interviews by comments such as *"[trainer] did actually give us actual feedback after a certain number and said, yeah, I'm happy with this, this is fine, and quite encouraging really"* (02). Another optometrist explained how they had asked for some help with their technique, saying: *"I think part of the way through the study I was finding that I wasn't getting as good an image as I like and I did contact [trainer] for that and they told me, try to do this a little bit more, move the machine in a certain way, and that instantly made a difference as well"* (04).

4.3 Acceptability of the test for patients

4.3.1 Information provided about the test

97% of patients (95% CI 95 to 98) indicated they were neutral, satisfied or very satisfied with the information provided about the test (432 out of 446 patients who responded), 1% said they were unsatisfied (3 patients) and 2% said they were very unsatisfied (11 patients). See Figure 2.

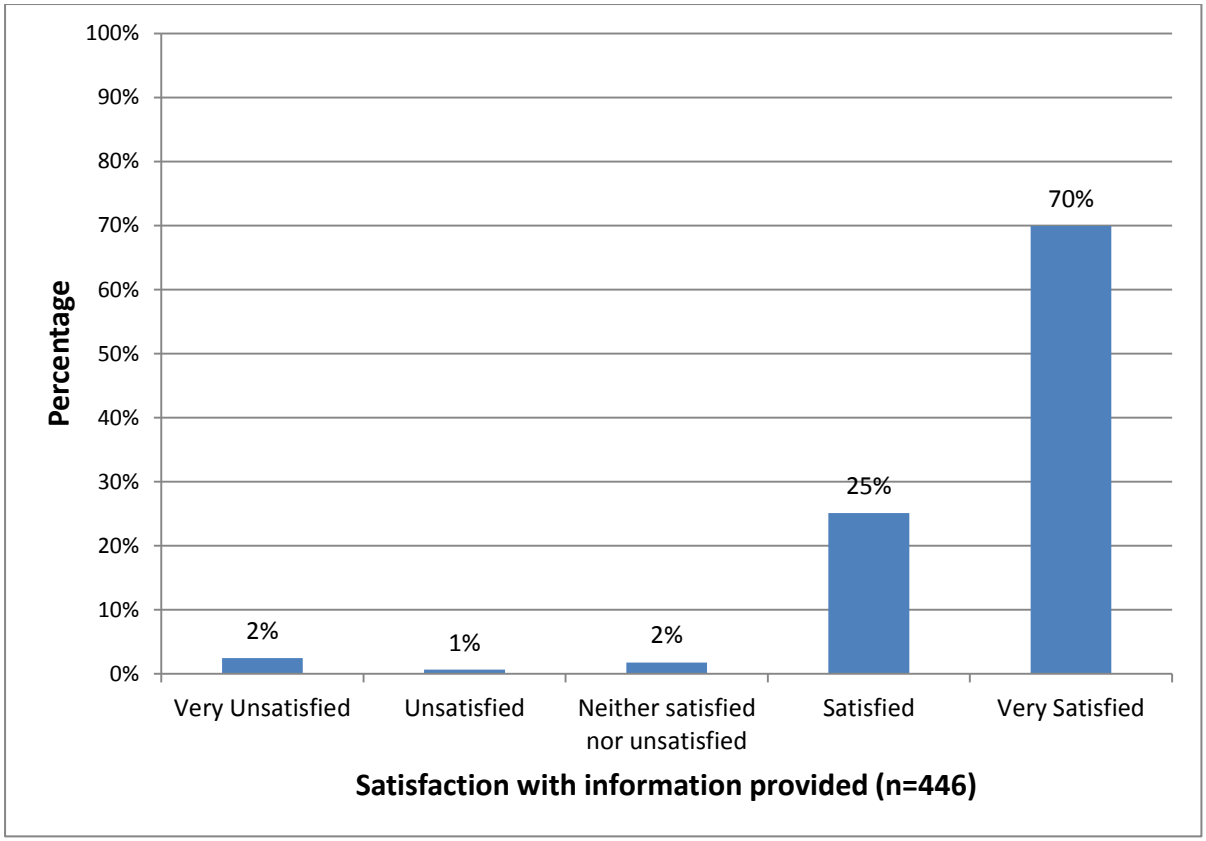

Figure 2. Patient reported level of satisfaction with information about the test

4.3.2 Level of comfort of the test

Figure 3 shows that 92% of patients (95% CI 89% to 94%) indicated the test was very comfortable, comfortable or neutral (411 out of 447 patients who responded), 6% said they found the test uncomfortable (25 patients) and 2% said it was very uncomfortable (11 patients).

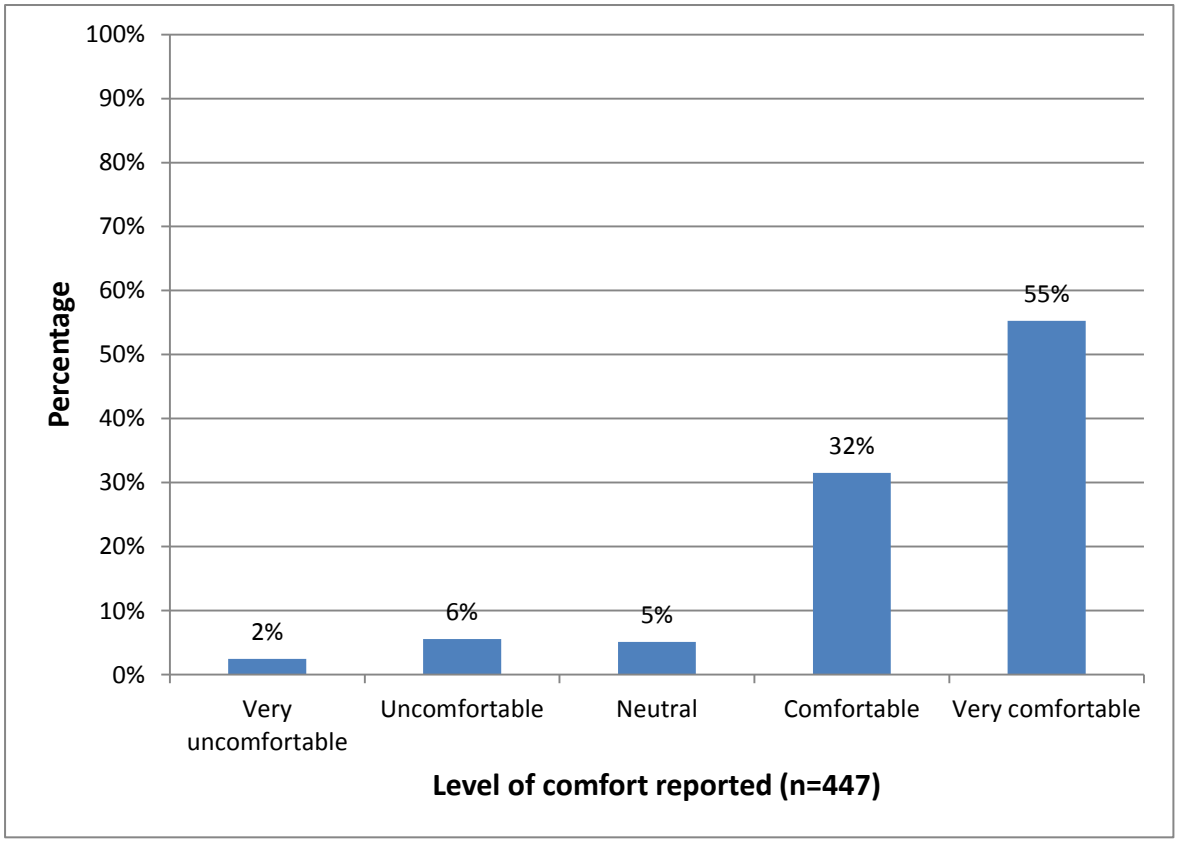

Figure 3. Level of comfort reported by patients.

The general consensus from the optometrists was that majority of patients did not find the procedure painful, but some patients found it uncomfortable. This was particularly noted in relation to the position that the patients had to maintain in order for the test to be carried out: *"they didn't seem very comfortable on the actual machine. Yeah, I think the actual equipment itself was not very comfortable for them"* (03). Another optometrist associated patient discomfort with the length of time they had to maintain their position: *"it takes longer to do it than most tests. So that's perhaps why it's a bit more uncomfortable"* (02). It was also commented that patients did not like something touching their eye: *"most of them just complain about the fact that they didn't like something touching their eye, even though they didn't actually feel anything"* (03), although it was acknowledged that this was the nature of the test, so could not be changed. Finally, one optometrist reported that he thought patients found the screening test to be better than they expected, making comments such *as "oh is that it?"* (04) once it had been carried out.

4.3.3 Level of reported pain during the examination

90% of patients (95% CI 87 to 93) indicated they had no pain at all (401 out of 446 patients who responded), 9% reported a little pain (39 patients) and 1% found it somewhat painful (6 patients). These numbers are presented at Figure 4. No patient found CCM very painful or extremely painful.

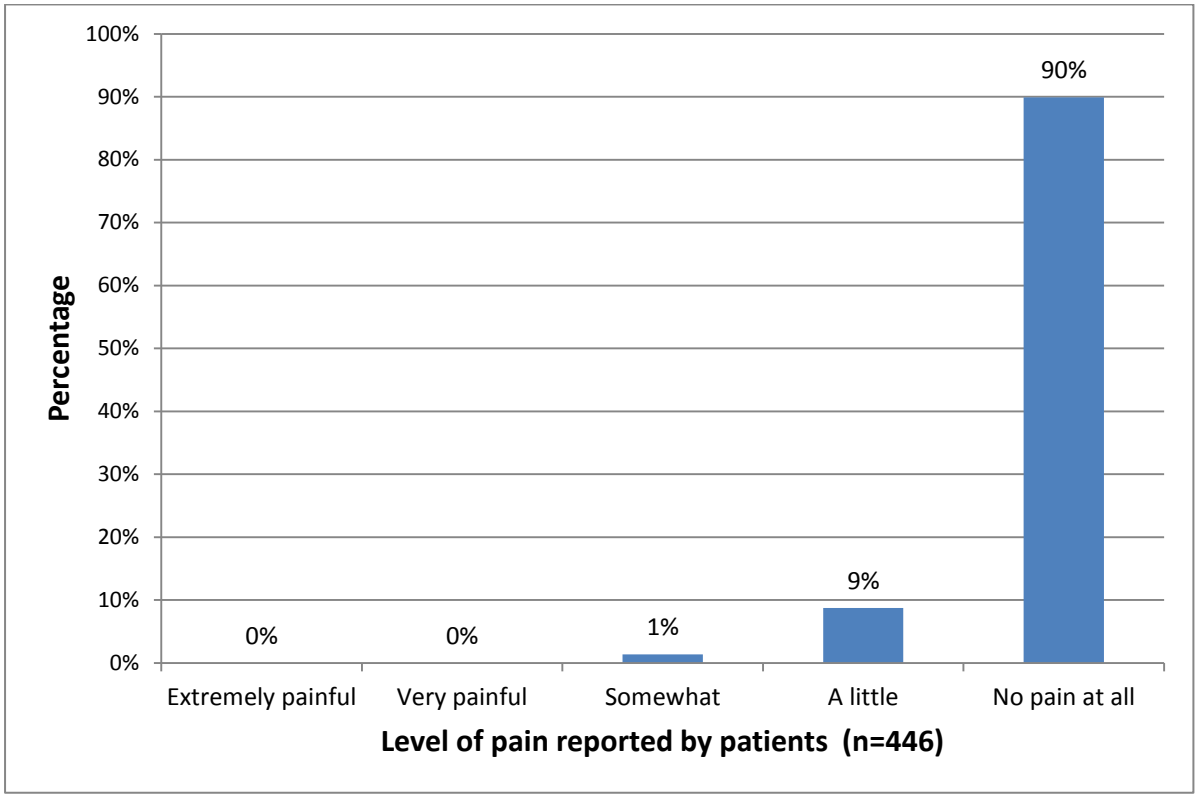

Figure 4. Patient reported level of pain.

4.3.4. Willingness to repeat the test in the future

97% of patients indicated they would be willing to do the CCM test again in the future (418 out of 432 patients who responded), and 3% (14 patients) indicated they would not want to do the test again. Of these 14 patients, 5 reported the test was a little painful and 1 patient found the test uncomfortable.

4.3.5. Further comments from patients

In total, 68 patients responded with additional comments on the patient satisfaction questionnaire. 81% of the comments were to express their satisfaction with the test, their optometrist or about taking part in the research study (55 comments out of 68 comments provided), 4% of comments indicated difficulties with the equipment (3 comments), 3% mentioned why they found the test uncomfortable (2 comments), 2% stated why they found the test painful (1 comment), and 10% made other miscellaneous comments (7 patients). These comments are valuable for the research team as they can affect the future direction of this as a potential screening programme.

4.4 Duration of the CCM scans

The average test duration (from inserting anaesthetic drops to finalising the test) was 13 minutes, although the time taken changed over time. When tests were grouped into quartiles, it shows the average duration decreased over time; from 16 minutes in the first quartile to 10 minutes in the fourth quartile (Figure 5).

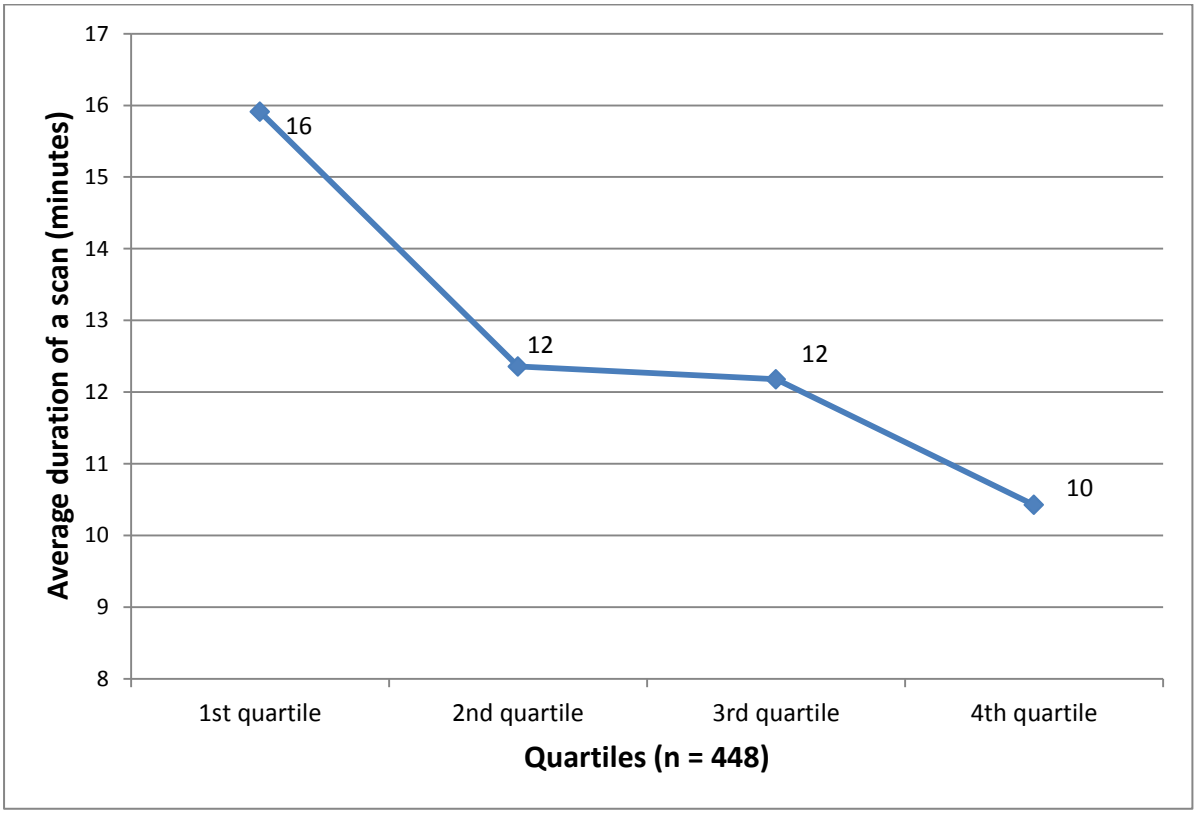

Figure 5. Average duration of a CCM scan by quartiles. The time taken to perform each test was captured, even for the tests that were considered difficult or impossible by the optometrist which would potentially increase the averages. Quartiles were defined so that the 1st quartile contains the first 25% of patients screened at each practice, 2nd quartile contains the next 25% and so on.

Although the average time to perform the procedure reduced over the duration of the study, there was a perception from three optometrists that the procedure was time consuming, but each optometrist reported different reasons for this as follows:

One optometrist commented: *"Without a doubt it was time consuming. It was highly variable. Sometimes, I mean, the data shows for itself on the sheet, sometimes you could get the job done in a very few minutes. Sometimes you would be there 15-20 minutes later still struggling... It was rather unpredictable whether it was going to be a four minute job or a 14 minute job or longer*" (01).

Two optometrists (02 and 03) stated that selecting and uploading the right images was time consuming. The research procedures such as the informed consent process and data collection forms were also deemed as time consuming. For (04) there were no issues with CCM being time consuming. "*So I allowed myself [time] for the patient to fill in the consent forms, and everything like that, half an hour but I found I was usually done within 15/20 minutes, so it was very quick, it wasn't difficult at all.*"

4.5 Performing CCM tests

Optometrists were able to complete the CCM test, providing six or more images, for 92% of patients (414 out of 449 patients). For two of the practices (D and E) often significantly more than six CCM images per patient were transferred. Successful completion of CCM tests improved over time; during the 1st quartile (containing the first 25% of scans from each practice) the proportion of completed scans was 80% whereas for the 2nd, 3rd and 4th quartiles this was 96%. The low average figure during the 1st quartile was due to a misunderstanding in one practice and when the issue was resolved the average improved. Figure 6 illustrates the proportion of completed CCM tests by practice across quartiles.

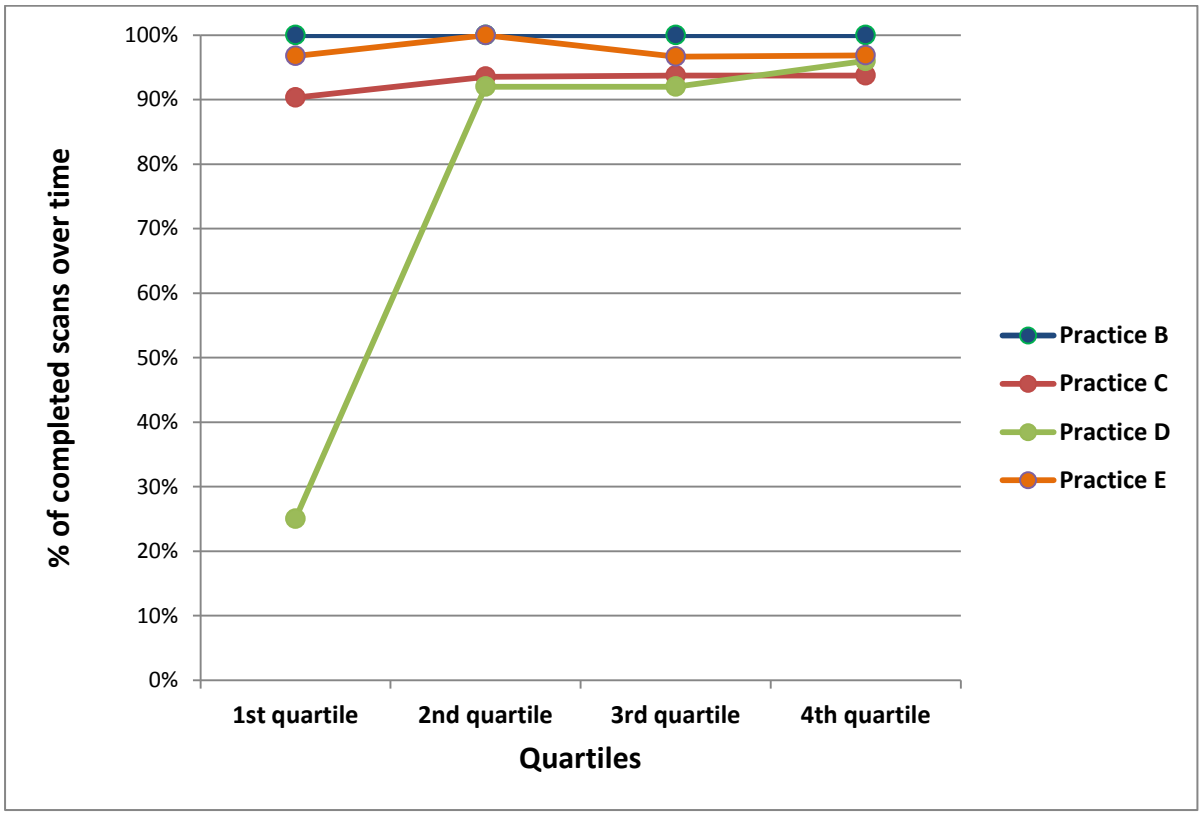

Figure 6. Proportion of completed scans by quartiles. A completed CCM test is defined as a test where six or more images were transferred for analysis to the Chief Investigator. Quartiles are defined so that the 1st quartile contains the first 25% of patients screened at each practice, 2nd quartile contains the next 25% and so on.

Optometrist-reported degree of difficulty in performing the CCM test

Optometrists were asked to rate the degree of difficulty in capturing the images. Over all the CCM tests (n=448), 60% (268) of the tests were said to be easy, 36% (162) were difficult and 4% (18) were impossible (see Figure 7).

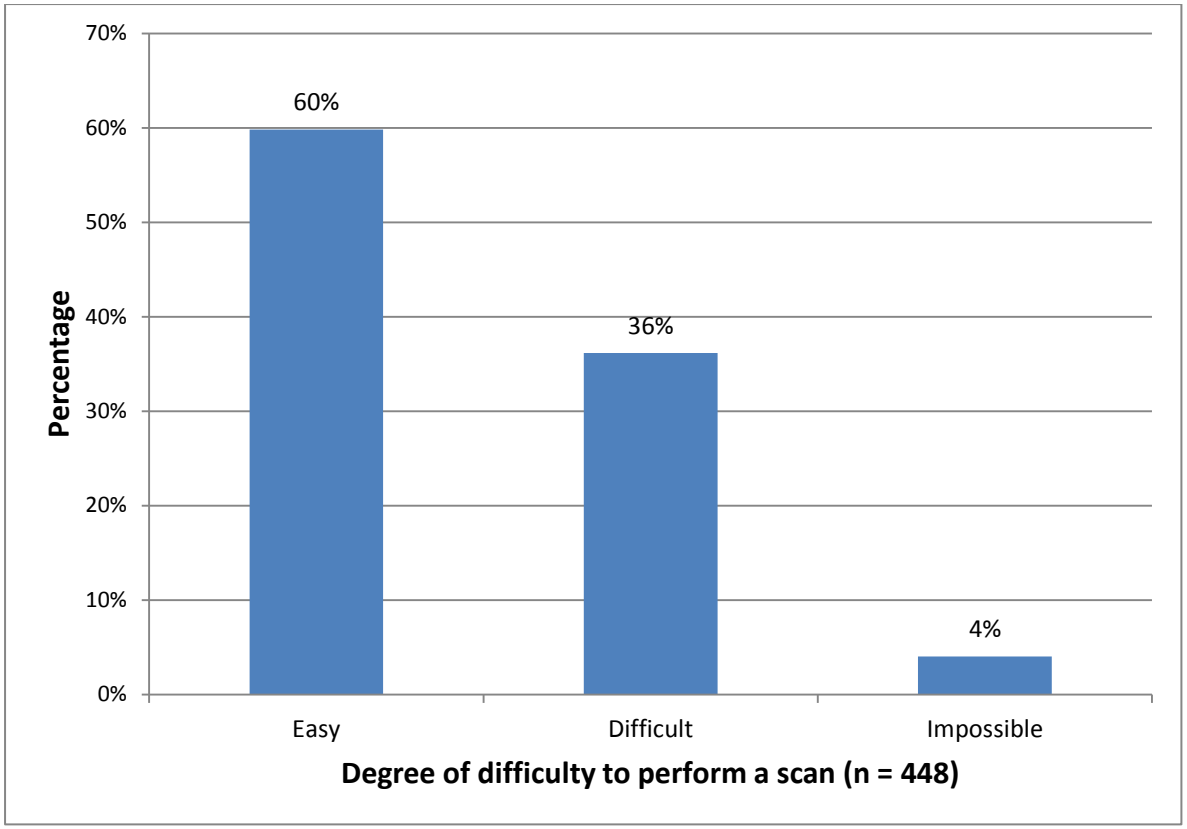

Figure 7. Optometrist reported degree of difficulty in performing the CCM test

Optometrists made a variety of comments about using the CCM equipment. One optometrist spoke of feeling wary of using the new equipment: *"I wouldn't say nervous or anxious, but I was a bit wary of what it would be like initially on a real patient because it was a new piece of equipment, something I'd never used before and it was quite clinical and quite invasive as well"* (04). There was a perception that this was normal, that with the use of a new technique it was to be expected that skills would take time to develop. One optometrist commented *"it was a learning curve for everybody and I think skills develop over a period of time"* (01) and another *"I think that…not that the training wasn't adequate, but it's just a difficult skill set to learn I think. You know, until you've done 30 or 40, you're just not going to be that good at it really"* (02).

There was a general perception that the CCM equipment was not 'user friendly'. This was mainly expressed in relation to the number of controls that there were, with one optometrist commenting: *"you are always a hand short even with a foot pedal"* (01). Another optometrist was not happy with the 'positioning' of the machine. He commented: *"with the CCM it was always looking down. For that reason the patient always had to be a little bit higher for them to be bowing down. So if I had a really tall patient it was quite difficult and there were some incidences where I was actually finding myself having to force the machine"* (04). Another optometrist commented about the positioning of the monitor in relation to the patient. He said: *"So when you're doing that [positioning the equipment], looking at the monitor, you don't get to look at the patient. So if the patient's slowly moving away, you're not going to realise until you look towards the patient again and, by now, they're already inching away from the headrest. So it's very impractical in that sense"* (03).

Whilst describing problems they experienced using the CCM equipment, optometrists commented that if CCM testing was to become part of routine clinical practice, the equipment design issues would need to be overcome.

If the optometrist indicated that a CCM test was difficult or impossible they were asked to provide a reason why. In total, 180 tests were rated as difficult or impossible, but reasons were only provided for 129 of these. One of the optometrists helped us to classify these reasons into whether or not the issue had the potential to be overcome fairly easily (Figure 8). This optometrist classified all of the reasons provided, even when they were provided by other optometrists, therefore there could be a risk of optometrist bias. However we attempted this as proxy to understand the challenges that would need to be overcome. The classification indicates that 38% of the cases could be overcome through additional training or by having an assistant to help perform the test, whereas 62% were due to reasons may be difficult to overcome (due to the patients characteristics or the equipment or the procedures required for the test).

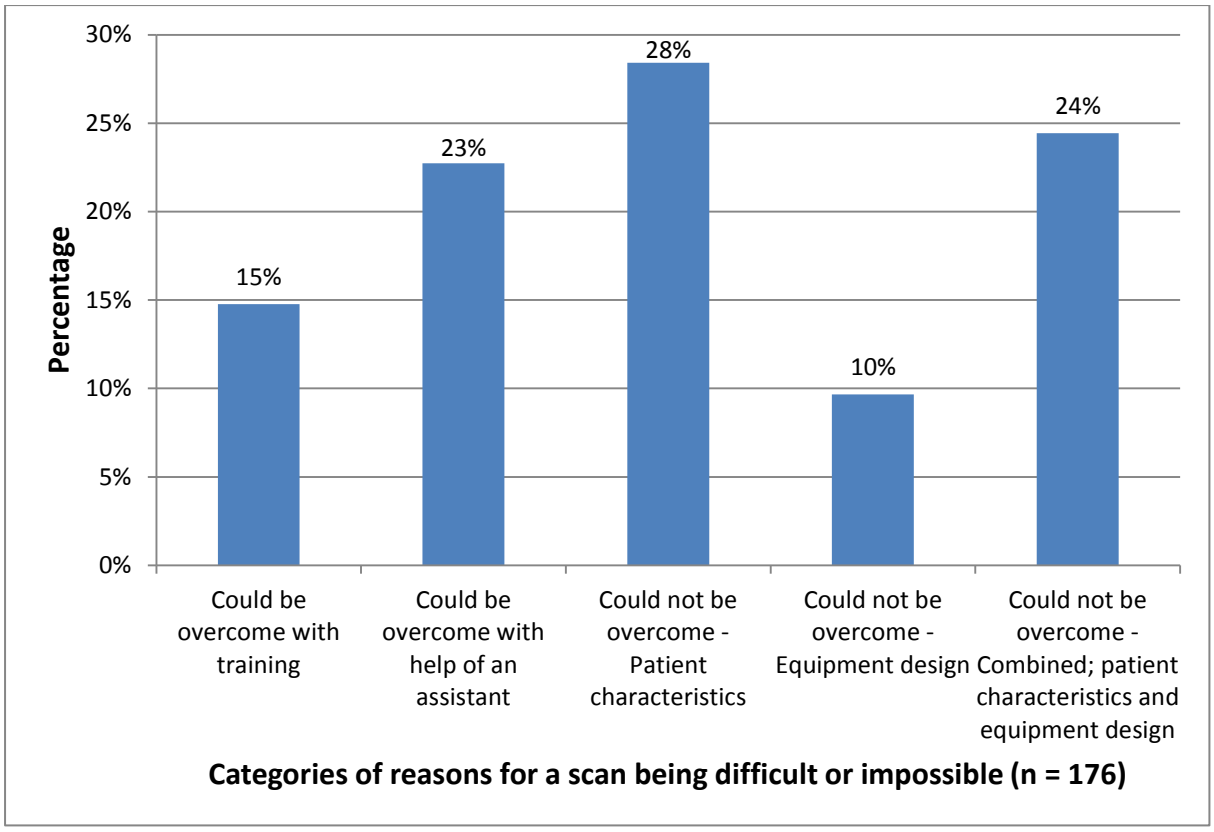

Figure 8. Optometrist perspective on which issues resulting in difficult or impossible scans could be overcome. Optometrists provided reasons as to why a scan was considered difficult or impossible in 129 tests, sometimes more than one reasons was provided for a given tests. The reasons were categorised depending on whether or not the issue could be overcome and the reason why.

A description of these is provided below.

- *Could be overcome with training*: Issues with CCM imaging for instance; limited experience with CCM images, struggled to get clear images or locating the nerves particularly where the patient had a poor quality nerve layer, potential dystrophy or even neuropathy.

- *Could be overcome with help of an assistant*: issues where optometrists could potentially capture images if they had an assistant present to hold the patient's eye open. Causes for this include patients' blink reflex, nervousness, poor patient co-operation, downturned or long lashes, ptosis, narrow palpebral aperture, or mild cases of blepharospasm.

- *Could not be overcome due to patient characteristics*: Issues including strong blepharospasm and fixation issues. Other patients had difficulties understanding what they needed to do in the test,

for instance patients with Alzheimer's disease. Some patients had a poor quality of vision and could not see/fix their gaze into the light. In some cases, where the issue only affected one eye, optometrists could get images from the other eye.

- *Could not be overcome due to CCM equipment design*: Some patients had difficulties positioning the head or chin correctly in the machine, particularly those with poor posture due to equipment restrictions, others struggled to keep their forehead resting steadily into the forehead rest. These difficulties tended to be reported for tall, obese or elderly patients.

- *Could not be overcome due to a combination of issues with patient characteristics and equipment design*: These were issues where patients had difficulties keeping a steady head in the forehead rest of the equipment for the required time, patients would have considerable head movement or heavy breathing, which made it difficult for the patients to fix the gaze into the target.

4.6 Processing captured CCM images

4.6.1 Selection of the images

Once the optometrist had completed the CCM tests they selected the best six images (good quality non-overlapping images from entire depth of Bowman layer; three per eye). Optometrists said that they routinely took more images than were needed to ensure that they had enough good quality images, which is more time consuming when selecting the images. One optometrist said that selecting the images presented *"absolutely no problems whatsoever"* (04), however, this optometrist also had training delivered differently to the other three optometrists who have mentioned some difficulties with image selection (see training section 4.2). For instance, one optometrist reported it took a long time to select the images, due to the extra time needed to ensure there were good enough images available however, over time this became quicker (02). Another described his experience thus: *"I thought the window was too small. I'd rather have been able to see all the pictures together rather than scrolling down because on a typical eye I would probably record 20 images because it just takes a lot of tries to get the right ones. Then you look at some of that and you think it's adequate and scroll further down and then you forget what the previous one looked like so you can't even make any comparison. Maybe a larger window so you can view all of them together*" (03).

4.6.2 Grading the quality of images

Of the images from 437 patients that were graded for quality by the optometrists, 26% (116) were rated as excellent, 52% (227) as acceptable, 17% as poor (73) and 5% as unacceptable (21). Of the 449 total patients, there were 12 patients that did not have a rating because 1) the optometrist had difficulty performing the test (1 test), or 2) struggled to provide an overall rating for both eyes, so instead provided a separate rating for both eyes (11 patients); these are not included in the percentages presented in Figure 9.

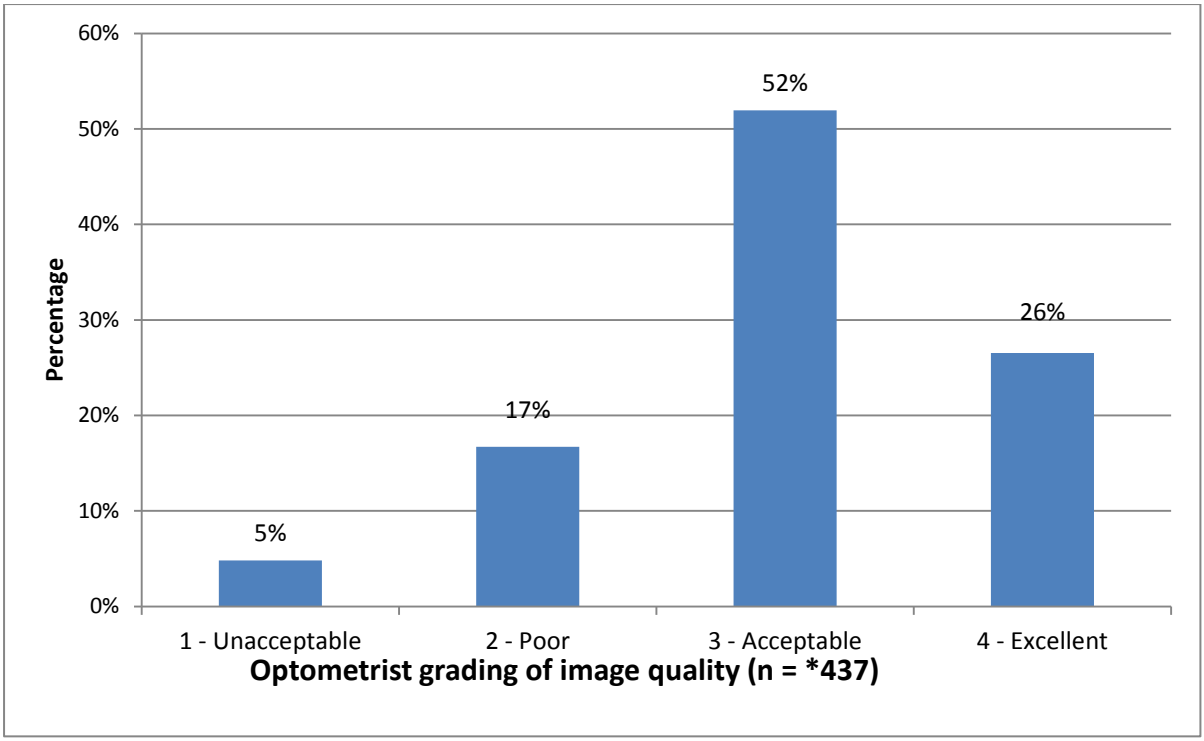

Figure 9. Optometrist grading of image quality. For each patient, the optometrists provided an overall quality rating of the images of both eyes.

Figure 10 shows the proportion of patients with average image rating of excellent increasing over time, as reported by the optometrists.

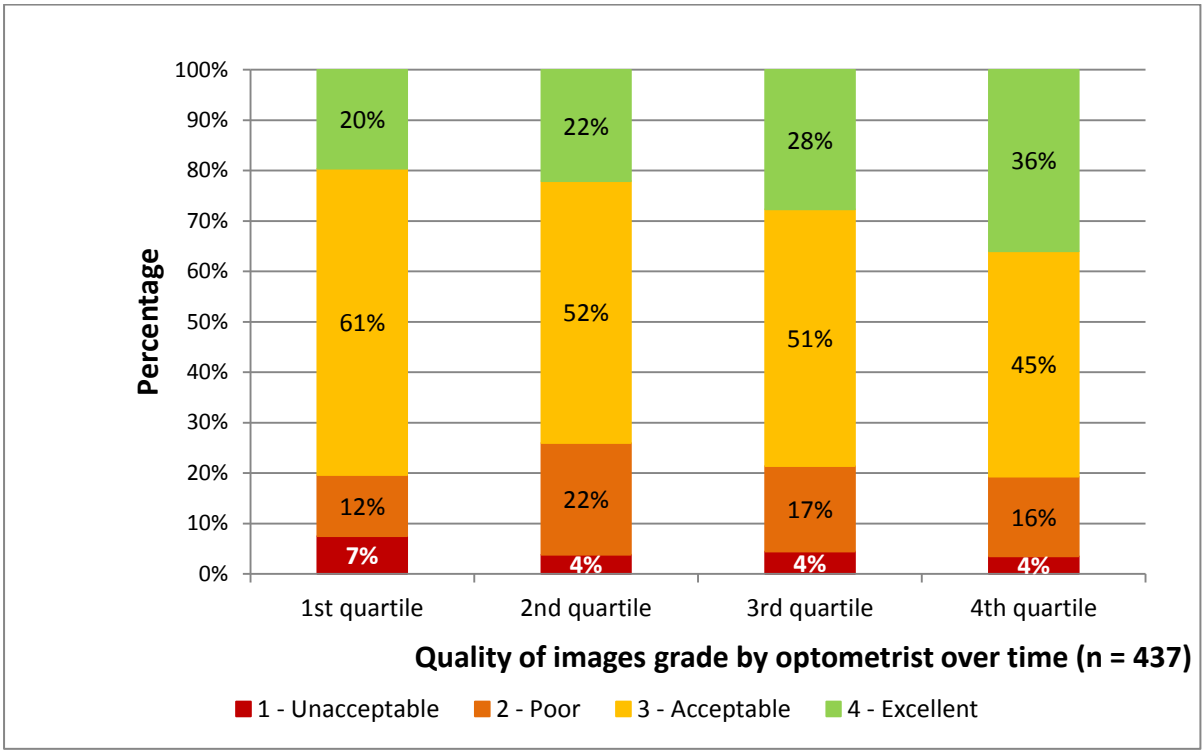

Figure 10. Quality of images graded by optometrists over time. Quartiles are defined so that the 1st quartile contains the first 25% of patients screened at each practice, 2nd quartile contains the next 25% and so on.

The Chief Investigator periodically reviewed and graded the images to provide feedback to the optometrists. By the end of the study, the Chief Investigator had rated 436 images, of which 33% (142) were rated as excellent, 63% (274) as acceptable, 2% (9) as poor and 2% (11) as unacceptable (Figure 11). Similarly to the optometrists, Figure 12 shows how the proportion of excellent images reported by the Chief Investigator increased over time.

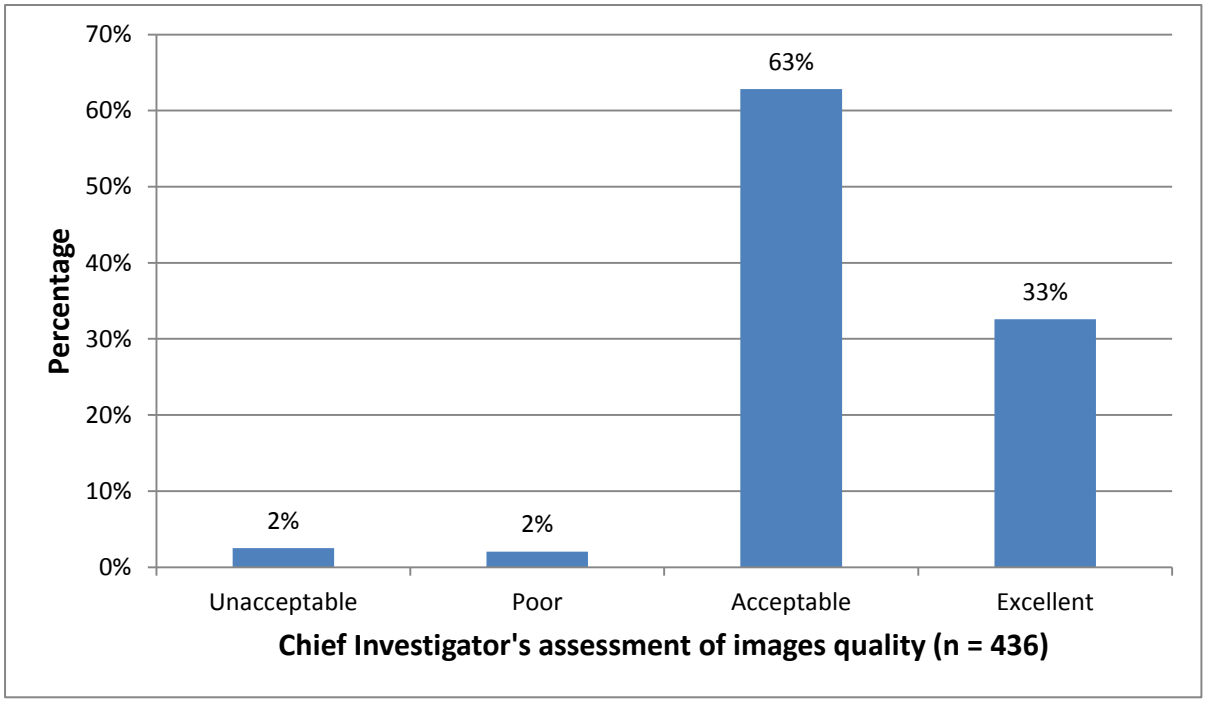

Figure 11. Grading of image quality by the chief investigator. For each test, the Chief Investigator provided an overall quality rating of the images of both eyes.

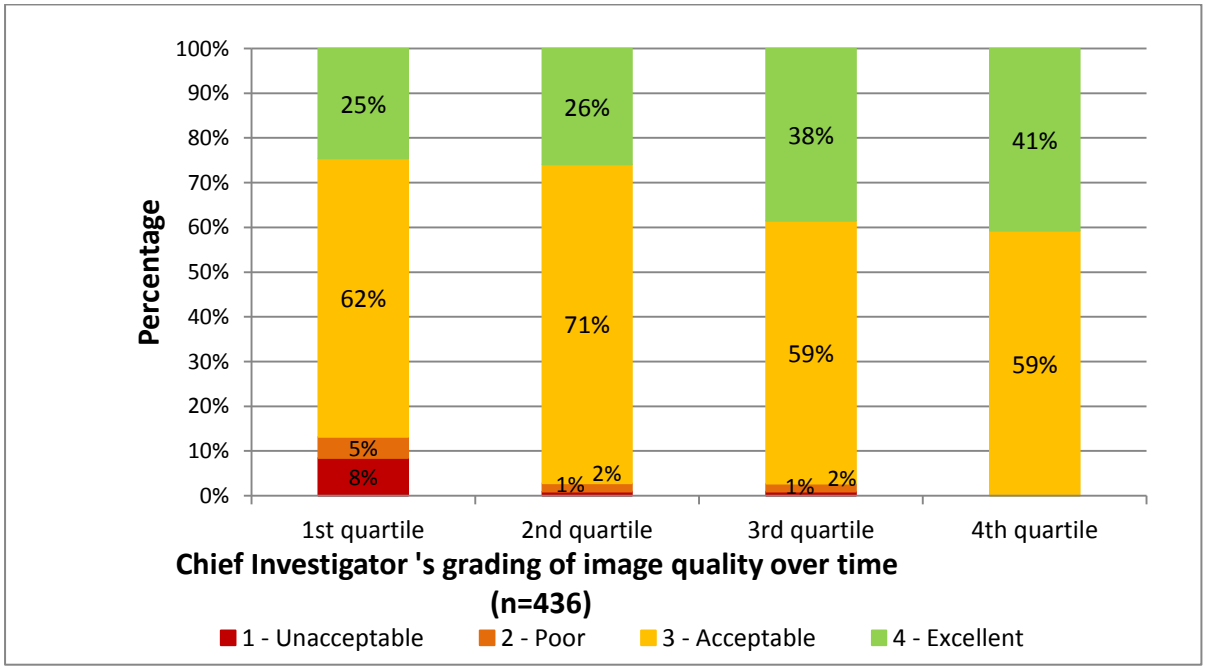

Figure 12. Chief Investigator's grading of image quality over time. Quartiles are defined so that the 1st quartile contains the first 25% of patients screened at each practice, 2nd quartile contains the next 25% and so on.

4.6.3 Level of agreement between grading the quality of images between additional graders

At the end of the study, images from a sample of 49 patients were re-assessed by the Chief Investigator and two additional graders, who received brief instruction from the Chief Investigator. Grader 2 received the same CCM training as the optometrists in this study had, plus additional two hours on image grading. Grader 3 had a PhD in the field of confocal microscopy but was not familiar with the CCM equipment, plus received one hour training to learn about image grading. They used the same grading scheme as the optometrists: 1-unacceptable, 2-poor, 3-acceptable and 4-excellent.

The Kappa statistic (Landis and Koch, 1977) was used to assess the levels of agreement between graders, including the optometrists. In this statistic, weightings are used to differentiate between a perfect match, a close match and no match. The Kappa Statistic is 0 when the amount of agreement is what would be expected by chance and 1 when there is perfect agreement. Kappa values are interpreted as follows:

- below 0.0 poor,
- 0.0 – 0.20 slight,
- 0.21 – 0.40 fair,
- 0.41 – 0.60 moderate,
- 0.61 – 0.80 substantial,
- 0.81 – 1.00 almost perfect

a) Comparison of image quality between the optometrists and the Chief Investigator
Figure 9 and Figure 11 show that that the Chief Investigator scored more of the images as acceptable (63%) and excellent (33%) than the optometrists (52% and 27%). Table 9 compares these gradings side by side. Table 9 only includes tests that were both rated by the optometrists and by the Chief Investigator (n=425). Missing tests were either: 1) not given an overall rating by the optometrist because they found it difficult to do so, 2) had a rating for each eye separately or 3) optometrists rated images as poor but no images were sent, therefore the Chief Investigator could not give a rating.

Table 9. Assessment of the quality of images by the optometrists and Chief Investigator

Grade	Optometrists overall assessment (n=425)	Chief Investigator overall assessment (n=425)
1 Unacceptable	3% (13)	2% (10)
2 Poor	17% (71)	2% (9)
3 Acceptable	53% (225)	62% (264)
4 Excellent	27% (116)	33% (142)

The strength of agreement was analysed and there was 82% agreement between the Chief Investigators and the optometrists ratings, which is classed as fair with a weighted Kappa statistic of 0.24, ($p<0.05$).

b) Comparison of image quality between the Chief Investigator at two time points
The Chief Investigator rated the sample of images for 49 patients at a second point in time. This is shown in Table 10.

Table 10. Assessment of the quality of images provided by the Chief Investigator at 2 time points

Grade	Chief Investigator time 1 (n=49)	Chief Investigator time 2 (n=49)
1 Unacceptable	2% (1)	0% (0)
2 Poor	4% (2)	4% (2)
3 Acceptable	71% (35)	73% (36)
4 Excellent	23% (11)	23% (11)

There was 92% agreement between the Chief Investigator grades at two different time points which is classed as moderate with a weighted kappa statistic of 0.47 ($p<0.05$).

c) Comparison of image quality between the Chief Investigator and two other graders
In addition to the Chief Investigator, a sample of 49 patients' images was independently assessed by two other graders, who are researchers in the field of optometry. They received 2 hours (Grader 2) and 1 hour (Grader 3) training on grading CCM images. Results are shown in Table 11.

Table 11. Assessment of the quality of images provided by three independent graders

Grade	Chief investigator Time 2 (n=49)	Grader 2 (n=49)	Grader 3 (n=49)
1 Unacceptable	0% (0)	6% (3)	0% (0)
2 Poor	4% (2)	27% (13)	35% (17)
3 Acceptable	73% (36)	43% (21)	49% (24)
4 Excellent	23% (11)	24% (12)	16% (8)

The strength of agreement between the graders is as follows:

- There was 80% agreement between the Chief Investigator and grader 2, with a weighted Kappa statistic of 0.19, indicating a slight level of agreement ($p<0.05$).
- There was 76% agreement between the Chief Investigator and grader 3, with a weighted Kappa statistic of 0.27, indicating a fair level of agreement ($p<0.05$).
- There was 85% agreement between grader 2 and grader 3, with a weighted Kappa statistic of 0.46, indicating a moderate level of agreement ($p<0.05$).

In summary, there was a fair agreement between the grades of the optometrists and the Chief Investigator, with the optometrist tending to be more cautious about the quality. This reflects the findings from the qualitative research. The highest level of agreement in this study was between the two scores of the Chief Investigator at different time points, indicating that an experienced person can grade the images with some consistency over time. Finally, the level of agreement between the Chief Investigator and the other two graders was lower than anticipated, indicating that further training on grading the quality of the images may be needed.

4.7 Optometrists' perspective on future implementation

Optometrists were asked for their views on continuing to use CCM testing as part of routine clinical practice after completion of the study. One was unequivocally supportive of this development. Others had some concerns, or identified areas which they thought would require clarification if the screening were to be rolled out. These included the purpose of screening, the costs involved, and improvements that would be necessary in relation to the process and the CCM equipment.

One optometrist was quite concerned that the purpose of the screening was not clear. He said*: "diabetic retinopathy screening, the purpose of the exercise is to reduce the risk, or eliminate if possible, the risk of blindness. My understanding is that there is nothing that can be done to prevent neuropathy, should neuropathy be starting and therefore the way to stop neuropathy is simply to educate the patient to look after their diabetes, which is something every diabetic patient should be doing anyway*" (01). He was concerned that, without what he considered a clear rationale, the CCM test would not be taken up by optometrists. This optometrist also said that he thought it needed to be made explicit whether all diabetic patients should be screened or only those within certain parameters, and that it was not clear whether diabetic retinopathy screening would continue to be carried out in primary care clinical practices, in which case it may not make sense to carry out CCM screening there.

The optometrists raised issues around the cost of the CCM equipment, and whether optometrists would receive adequate remuneration for carrying out testing. The cost of the equipment was articulated as a barrier by one optometrist. He commented: *"for an independent practitioner, or any high street chain, we don't get support from the NHS to buy anything. We buy all our equipment…… if they were say £50,000 and then the caps were £5 each or whatever, that would be a major barrier to most small practices like mine"* (02). Adequate remuneration for time per test was also important to optometrists.

In terms of the whole process, the length of time that the procedure took was also perceived as a barrier to the inclusion of CCM in routine clinical practice. One optometrist said: *"if it was to be a feature of regular practice then it would need to be quite a lot slicker*" (01). However, they did acknowledge that a good proportion of the time was due to research specific procedures rather than the CCM test. A number of suggestions were also made about how the CCM equipment could be improved to make uptake of CCM testing in clinical practice more likely. These are reproduced verbatim below in order to reflect their full meaning.

"I can't envisage a whole raft of optometrists rushing out to purchase HRT3 in order to do that process because they won't get a good feeling when they start doing it…… There may be a reluctance. Maybe they will fit a motor. I think somebody talked about there had been a motor fitted to the lens that whizzed it round one end and took it back again. That might improve it" (01).

"Maybe if they developed a, sort of, auto focus or something, they might be able to find some way of doing it in quarter of the time, you know…If they could get it to auto focus and then some software to select the best images, the whole thing could be done in seconds" (02).

4.8 Budget Impact Analysis

Our economic calculations based on this research study estimate that current retinopathy screening costs £12 per person screened per year. Introducing diabetic neuropathy screening within optometry practices using CCM would cost an additional £20 per person per year which is based on estimates of £212,041,014 over five years (2016-2020). The budget impact of using mobile units would cost an additional £15 per person per year which is based on estimates of £153,191,099 over

five years (2016-2020). Mobile units are a cheaper option primarily because they employ designated screeners rather than optometrists to deliver the service.

A sensitivity analysis was conducted which involves changing values with some uncertainty to other feasible values to test their overall impact on the outcome. For example, changing the amount of time spent on selecting images, the salary costs of the optometrists and the training venue costs. Overall, costs remained stable to the changes used in the analysis. The full report titled: Budget Impact Analysis of Introducing Diabetic Neuropathy Screening in England with Corneal Confocal Microscopy (Davidson et al, 2016) is available as a separate document.

5. Future work

In this section, key elements that would need to be considered or addressed in any future development of the CCM test are summarised, which may also be pertinent for similar techniques. This includes identifying the *key enablers* and *key barriers* to successful studies or implementation of the test. In addition, we have highlighted areas for future research and limitations of this research, to highlight unanswered questions.

Successful implementation of CCM testing

- Sufficient time for practical CCM training with volunteers to master the technique, ask questions and build confidence in this procedure. During the current study, approximately five hours practice with volunteers was provided during the workshop, plus supervision of first few recruited patients (five hours); feedback suggests most optometrists would have welcomed longer period of training and practice.
- Additional training on useful hints and tips on how to perform a successful CCM test in more difficult scenarios (see figure 8).
- Timely feedback to optometrists on the quality of the images they have submitted for analysis.
- Access to ongoing clinical, technical and procedural support to resolve issues quickly.
- In this study, CCM testing was conducted after the retinopathy test as an additional appointment, so that the research did not impact on the patient's standard care within their retinopathy screening. However, there is a 30 minute wait during the retinopathy appointment whilst waiting for the pupils to dilate and since there were no observed issues with CCM, the CCM test could potentially be delivered in the middle of the patient's retinopathy test to save time. This is not a finding of this study, but a speculative finding by the research team based on the analysis of the process of conducting retinopathy assessment and CCM.

Potential barriers to successful implementation of CCM testing

- Delay between training and start of the study in the practice resulted in a greater need for in-house retraining.
- There were a disproportionate number of images rated as acceptable by the expert that were classified as poor or unacceptable by the optometrists. Additional training for optometrists may be needed on how to assess quality of images. Suboptimal ability to assess image quality resulted in difficulty in selecting appropriate images and excessive numbers of images being uploaded, both of which slowed the process.
- Appointment time needed to conduct CCM test varied from patient to patient, and was difficult to predict, impacting on scheduling of appointments in optometry practices.
- The CCM equipment design and test procedures presented issues for certain patients, in 36% of cases it was difficult and in 4% of cases the CCM test impossible to perform. Currently 90% of adults with type II diabetes are either overweight or obese (Public Health England 2014).

However, the design of the CCM equipment made it difficult for obese patients to get into the required position, therefore this is an important issue to consider with any machine redesign.

Future research opportunities

- Further work is required to determine the accuracy of the CCM test, compared to other available techniques and clinical information.
- The benefit of earlier diagnosis on the impact of improved diabetic management (as no treatment for neuropathy is currently available) warrants further investigation.
- Inclusion of lessons learned from the development of the national retinopathy-screening programme.
- There are over 182 retinopathy screening programmes across the country, with several different models of delivery; the nuances of these need to be explored and evaluated in relation to how CCM testing could be incorporated alongside the existing programmes.
- A larger sample size (in terms of patient recruitment), and/or the experiences of a greater number of optometrists, may be illuminating.
- Feedback from patients and/or general practitioners on CCM diagnostic findings may also be beneficial.

Limitations of the present study

To our knowledge, this is the first study that assessed implementation of CCM testing for diabetic neuropathy in clinical practice, outside of research environment. The following are some of the limitations of the current study.

- Relatively small sample size of the current study
- The observer effect: optometrists knew that each CCM test performed was rated by patients and this would be analysed by the research team. Optometrist may have modified or improved their behaviour as a response to this.
- All four participating practices were independent and (two of the practices were part of small chains) the optometrists were highly experienced and motivated optometrists. It would be useful to see the success of implementing this test in other type of practices e.g. hospital optometrists, large chain practices (e.g. Specsavers, Boots Opticians, etc.) and also with more junior optometrists.
- Currently based on the guidelines from College of Optometrists and General Optical Council, only optometrists and medically trained individuals are permitted to perform these types of eye examinations. The possible options to train ophthalmic technicians would need to be explored.
- One of the major challenges is lack of standard definition for diabetic neuropathy and lack of reference point and defining the cut-off points. In this study, we used normative value ranges from a large cohort of healthy control subjects (Tavakoli, et al. 2015)
- All CCM images have been analysed by automated software that was developed by a research team in Manchester (ACCMetrics), however the accuracy of the performance of this method of analysing is low compare to using semi-automated (CCMetrics) software. In the coming months, all images will be analysed by semi-automated software and we will then be in position to confirm the accuracy of clinical findings based on these 2 systems.

6. Conclusions

The patient population of this study purposefully included a wide ethnic and socio-economic mix, as a result of prudent practice recruitment. This was broadly comparable to the adult diabetic national population, with the exception of notably a greater proportion of white participants represented in this study. Patient recruitment was very successful, with target numbers overachieved, ahead of schedule.

Most patients reported that the CCM test was pain-free, comfortable, and the vast majority would agree to do the test again. Optometrists noted that some patients seemed uncomfortable because the test involved touching the eye, whereas others found it difficult to maintain the required position for the length of time required.

The average duration of the test decreased over the course of the study. Selecting images for uploading was deemed time consuming, but appeared to be primarily related to the lack of confidence in determining image quality.

Optometrists were able to successfully complete the test on most patients, and the success rate improved over time. However, optometrists rated a significant proportion of images as difficult or impossible to take, due to patient characteristics, equipment design or a combination of these issues. Assessment of the submitted images by the Chief Investigator showed that 95% of images were deemed to be of sufficient quality to permit grading. This was higher than anticipated by the optometrists, based on their self-assessment of image quality, which was backed up by the qualitative data. There was good agreement when a subset of images was regraded for quality by the Chief Investigator, whereas reproducibility was less consistent when compared with two other graders.

Introducing diabetic neuropathy screening using CCM tests in tandem with retinopathy testing within optometry practices would cost an additional £20 per person per year, or an additional £15 per person per year to deliver in mobile units.

To be implemented in routine practice, the following would need further consideration: clinical rationale in practice, cost and remuneration and technological improvements.

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Appendix 1.

Table. 12. Training sessions and the rating by optometrists

Training sessions	Respondent 1	Respondent 2	Respondent 3	Respondent 4	Respondent 5
Background: The role of CLAHRC project aims and outline	Very Good	Very Good	Very Good	Very Good	Very Good
Background: A new way of detecting diabetes	Very Good	Very Good	Very Good	Very Good	Very Good
Background: Heidelberg Engineering HRT III and Rostock Corneal Module	Very Good	Very Good	Very Good	Very Good	Very Good
Practical non-contact demonstration and practice	Very Good	Good	Very Good	Very Good	Very Good
Background: A new window for understanding the cornea	Very Good	Very Good	Very Good	Very Good	N/A
Practice with a volunteer and guidance from trainers	Very Good	Good	Very Good	Very Good	Very Good
How to export and transfer CCM images and demonstration	Satisfactory	Satisfactory	Very Good	Very Good	Very Good
Practice with volunteer and competency assessment	Very Good	Very Good	Very Good	Very Good	Very Good
Data collection process	Good	Good	Very Good	Very Good	Very Good