Multimodal imaging interpreted by graders to detect re-activation of diabetic eye disease in previously treated patients: the EMERALD diagnostic accuracy study

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Scientific summary

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Background

Diabetic retinopathy is a leading cause of sight loss in people of working age. Patients with diabetic retinopathy may lose sight from diabetic macular oedema and/or proliferative diabetic retinopathy. In diabetic macular oedema fluid accumulates at the macula, the retinal area responsible for central sight, with subsequent central visual loss (e.g. that required for reading). In proliferative diabetic retinopathy abnormal ‘new vessels’ grow in the retina and may rupture causing a vitreous haemorrhage or scarring that could lead to a tractional retinal detachment. Vitreous haemorrhage and tractional retinal detachment cause loss of central and peripheral vision. Owing to increasing numbers of people with diabetes, it is expected that the burden of diabetic retinopathy will continue to rise, despite improvements in glycaemic control and screening for retinopathy having reduced the risk of advanced retinopathy.

The estimated prevalence of diabetic macular oedema and proliferative diabetic retinopathy is similar, at ≈ 7%. Considering the prevalence of diabetes in UK (≈ 3.9 million in 2019), a minimum of 273,000 people have diabetic macular oedema and proliferative diabetic retinopathy in the UK.

Diabetic macular oedema is treated with macular laser photocoagulation (when the central retinal thickness, measured by spectral domain optical coherence tomography, is < 400 µm) or intravitreal injections of antivascular endothelial growth factor therapies (when the central retinal thickness is ≥ 400 µm). Patients should be followed up every 3–4 months after laser treatment. After antivascular endothelial growth factors, patients should usually be followed up monthly during the first year of treatment and every 1–3 months thereafter, as diabetic macular oedema can recur.

Proliferative diabetic retinopathy is currently treated with laser panretinal photocoagulation. After treatment, patients are followed up at 4- to 6-month intervals for life, as proliferative diabetic retinopathy can recur and vitreous haemorrhage/tractional retinal detachment could still occur. A high proportion of patients followed up in Hospital Eye Services have treated and inactive proliferative diabetic retinopathy.

Currently in the NHS, ophthalmologists assess patients during follow-up visits. At each visit, patients with diabetic macular oedema/proliferative diabetic retinopathy receive a visual acuity test, often undertaken by a nurse; Spectral Domain Optical Coherence Tomography obtained by a photographer/imaging technician; and fundus examination by slit-lamp biomicroscopy by an ophthalmologist. Based on slit-lamp biomicroscopy and Spectral Domain Optical Coherence Tomography, the ophthalmologist determines whether or not diabetic macular oedema is present; based on slit-lamp biomicroscopy the ophthalmologist determines if there is active proliferative diabetic retinopathy. Spectral Domain Optical Coherence Tomography is non-invasive, safe and fast, obtaining scans of the macula. Fundus (retinal) photographs or fundus fluorescein angiography are not routinely carried out to determine the activity of proliferative diabetic retinopathy, but they are used in selected patients. Fundus fluorescein angiography requires injection of a dye into a peripheral vein. Images are taken as the dye circulates in the retina. Standard cameras used to obtain fundus photographs and fundus fluorescein angiography cannot image the retinal periphery, but newer ultra-wide field imaging captures nearly the entire retina in a single image.

The large number of people with diabetic macular oedema/proliferative diabetic retinopathy and the need for patients to be followed up at short intervals is making it difficult for the NHS to cope, especially because of a shortage of ophthalmologists. Difficulties will increase given the increasing prevalence of diabetes. Identifying new ways to increase NHS capacity/efficiency without compromising quality of care is essential. EMERALD (Effectiveness of Multimodal imaging for the Evaluation of Retinal oedema And new vesselS in Diabetic retinopathy) was planned with this in mind.
Objective

The objective was to determine whether or not patients with successfully treated diabetic macular oedema/proliferative diabetic retinopathy could be followed through a new care pathway involving multimodal retinal imaging and image assessment by trained ophthalmic graders. Diagnostic accuracy, cost-effectiveness and acceptability of this new pathway to patients and health-care professionals were evaluated against the current standard of care.

Methods

Design
This was a prospective, case-referent, cross-sectional diagnostic study.

Setting
This was carried out in specialist Hospital Eye Services.

Participants
Adults with diabetes, with previously successfully treated diabetic macular oedema/proliferative diabetic retinopathy in one/both eyes; at the time of enrolment, diabetic macular oedema/proliferative diabetic retinopathy could be active or inactive.

Clinical pathways assessed
New pathway: multimodal imaging (Spectral Domain Optical Coherence Tomography to detect diabetic macular oedema; seven-field Early Treatment Diabetic Retinopathy Study and ultra-wide field fundus images to detect proliferative diabetic retinopathy) with subsequent review by trained, tested and certified ophthalmic graders.

Standard care pathway: ophthalmologist examining patients in clinic as per current standard practice (for diabetic macular oedema slit-lamp biomicroscopy examination and Spectral Domain Optical Coherence Tomography; for proliferative diabetic retinopathy slit-lamp biomicroscopy examination).

Outcomes
The primary outcome was sensitivity of the new pathway to detect active diabetic macular oedema/proliferative diabetic retinopathy.

The secondary outcomes were specificity, concordance, cost-effectiveness, acceptability of the new pathway to patients and health-care professionals, proportions of patients requiring subsequent assessment by ophthalmologist, unable to undergo imaging and with images of inadequate quality for interpretation.

EMERALD patient flow
Patients with previously treated diabetic macular oedema/proliferative diabetic retinopathy were identified from clinical records, electronic databases or in clinic. At their review appointment, an ophthalmologist confirmed patient eligibility, obtained informed consent and determined whether or not active/inactive diabetic macular oedema/proliferative diabetic retinopathy was present (reference standard). Visual acuity, Spectral Domain Optical Coherence Tomography and fundus examination were carried out as per routine standard practice. In some participating sites patients were evaluated in ‘research’ clinics, and in others they were evaluated in usual NHS clinics.

Non-stereoscopic seven-field Early Treatment Diabetic Retinopathy Study and ultra-wide angle fundus images were obtained, anonymised, uploaded to a central facility and allocated randomly to ophthalmic graders. Graders did not grade images from their own centre (to ensure masking to the reference standard).
Graders did not grade both seven-field Early Treatment Diabetic Retinopathy Study and ultra-wide fundus images from the same patient (to prevent the grading of one technology influencing the grading of the other). Graders judged whether there was active/inactive diabetic macular oedema/proliferative diabetic retinopathy or if they were uncertain.

Given the possibility of new vessels not being seen by the ophthalmologist on slit-lamp biomicroscopy but detected on photographs, EMERALD also evaluated an ‘enhanced’ reference standard for proliferative diabetic retinopathy consisting of the reference standard supplemented by evaluation of seven-field Early Treatment Diabetic Retinopathy Study and ultra-wide field fundus images reviewed by an ophthalmologist expert in diabetic retinopathy. If active proliferative diabetic retinopathy was detected by one of these three methods, it was considered that the enhanced reference standard identified active proliferative diabetic retinopathy. Seven-field Early Treatment Diabetic Retinopathy Study and ultra-wide field images of the same participant were reviewed by different ophthalmologists, who did not grade images from their own centre.

Focus groups
To determine acceptability of the new pathway to patients and health professionals, focus group discussions were undertaken.

Sample size and statistical analysis
The sample size was based on the number of patients with reactivated (active) diabetic macular oedema and proliferative diabetic retinopathy which would enable sensitivity to be tested against a pre-specified target level of 80%, considered the minimum acceptable level for the ophthalmic grader’s pathway. A lower specificity was thought acceptable; a target of 65% was used to confirm sufficiency of the sample size for assessing specificity. To detect sensitivity of the new pathway with 80% and 90% power (10% and 12% higher than the 80% minimal target set) required 89 participants with each diabetic macular oedema and PDR that had reactivated, with two-sided 5% significance level. Ninety-three participants whose disease had not reactivated would enable a specificity of 80% to be detected with 90% power. A 95% confidence interval for photographer sensitivity and specificity would have a confidence interval (Wilson method) with a width of 10–20%, depending on the observed level. Allowing for 10% missing/indeterminate results, 104 individuals with each active and inactive diabetic macular oedema and active and inactive proliferative diabetic retinopathy were required.

Separate analyses were planned for diabetic macular oedema and proliferative diabetic retinopathy. Participants were categorised as having active or inactive diabetic macular oedema/proliferative diabetic retinopathy according to the reference standard, at the person level. Those with previously successfully treated diabetic macular oedema/proliferative diabetic retinopathy constitute ‘eligible’ participants for each analysis (diabetic macular oedema/proliferative diabetic retinopathy) for the new pathway. This person-based assessment reflects the consequences of the clinical decision. The diagnostic performance of the new pathway was quantified against the reference standard. Reflecting how the new pathway would function in practice, ‘unsure’, ‘ungradable’ and ‘active’ classifications required ‘referral’ and examination by an ophthalmologist under the main analyses.

Planned sensitivity analyses included (1) assessment of the impact of ‘unsure’ and ‘ungradable’ on the diagnostic performance of the ophthalmic grader; (2) using the ophthalmologist’s decision to do further treatment, rather than presence of active disease; (3) detection of more severe disease (central-involving diabetic macular oedema, pre-retinal or vitreous haemorrhage in proliferative diabetic retinopathy); (4) diagnostic performance within routine NHS clinics (vs. ‘research’ clinics); and (5) for proliferative diabetic retinopathy only, diagnostic performance of the ophthalmic grader against the ‘enhanced’ reference standard. The impact of using ultra-wide field versus seven-field Early Treatment Diabetic Retinopathy Study images on the diagnostic performance of the new pathway was assessed under the principal analyses for proliferative diabetic retinopathy using both reference standard and enhanced reference standard. Additional analyses were carried out in the proliferative
diabetic retinopathy group to aid understanding findings from pre-planned analyses. Agreement between proliferative diabetic retinopathy assessment methods was quantified.

Secondary analyses included evaluation of eye level data; analysis including all patients (with or without diabetic macular oedema/proliferative diabetic retinopathy); assessment of the overall referral (diabetic macular oedema and proliferative diabetic retinopathy); and use of visual acuity as a proxy to detect active disease.

Analyses were carried out using Stata® version 15 (StataCorp LP, College Station, TX, USA). A statistical analysis plan was agreed and made accessible on the EMERALD website and the EMERALD protocol published prior to data analysis.

Health economic evaluation

Costs of ophthalmic grader and standard pathways were prospectively obtained, including collection of time costs for each procedure. It was hypothesised that the new pathway would have the same sensitivity as the standard care pathway but at lower cost, making the analysis a cost–consequences one, including assessment of ophthalmologist time released by the new pathway. Diabetic macular oedema and proliferative diabetic retinopathy were assessed separately. If there was marginal loss in sensitivity in the new pathway, a cost-effectiveness analysis was planned in which the disutility of the visual impact of the marginal loss would be assessed against costs saved. If there was an unacceptably low sensitivity for proliferative diabetic retinopathy, no modelling would be done.

Results

Three-hundred and ninety-seven participants, 272 eligible with diabetic macular oedema (152 active diabetic macular oedema and 120 inactive diabetic macular oedema) and 281 eligible with proliferative diabetic retinopathy (111 active proliferative diabetic retinopathy and 170 inactive proliferative diabetic retinopathy) were recruited. Most eligible participants with diabetic macular oedema were white (n = 240, 88%), male (n = 175, 64%) and over half were aged ≥ 60 years (n = 159, 58%). Most eligible participants with proliferative diabetic retinopathy were white (n = 234, 83%), male (n = 185, 66%) and slightly less than half (n = 133, 47%) were aged ≥ 60 years.

Under the main analysis of diabetic macular oedema (grader referring patient to ophthalmologists due to presence of active diabetic macular oedema or unsure or ungradable), graders had a sensitivity of 97% (142/147; 95% confidence interval 92% to 99%) with a specificity of 31% (35/113; 95% confidence interval 23% to 40%) when compared with the reference standard. Similar results were obtained for analysis evaluating people with diabetic macular oedema requiring further treatment (sensitivity 95%; 81/85, 95% confidence interval 89% to 98%; specificity 21%; 36/175, 95% confidence interval 15% to 27%) and those with central-involving diabetic macular oedema (sensitivity 94%; 121/129, 95% confidence interval 88% to 97%; specificity 56%; 72/128, 95% confidence interval 48% to 65%). Results were similar to those of the main analysis when only referral for active diabetic macular oedema was considered (i.e. excluding the ‘unsure’ and ‘ungradable’) and when patients were assessed in NHS clinics (vs. ‘research’ clinics).

Under the main analysis of proliferative diabetic retinopathy (grader referring patients to ophthalmologists due to presence of active proliferative diabetic retinopathy or unsure or ungradable), graders had similar sensitivity and specificity whether they used seven-field Early Treatment Diabetic Retinopathy Study (sensitivity 85%; 87/102, 95% confidence interval 77% to 91%; specificity 48%; 77/160, 95% CI 41% to 56%) or ultra-wide field (sensitivity 83%; 87/105, 95% confidence interval 75% to 89%; specificity 54%; 86/160, 95% CI 46% to 61%) images. Sensitivity and specificity were similar when grading patients
requiring further treatment (for seven-field Early Treatment Diabetic Retinopathy Study images: sensitivity of 88%; 74/84, 95% confidence interval 79% to 93%; specificity 46%; 82/178, 95% confidence interval 39% to 53%; for ultra-wide field images sensitivity of 86%; 77/90, 95% confidence interval 77% to 91%; specificity 52%; 91/175, 95% confidence interval 45% to 59%). Sensitivity and specificity of the graders to detect more severe disease (proliferative diabetic retinopathy with pre-retinal or vitreous haemorrhage) were slightly higher when using ultra-wide field imaging (sensitivity 87%; 62/71, 95% confidence interval 78% to 93%; specificity 49%; 95/193, 95% confidence interval 42% to 56%; for seven-field Early Treatment Diabetic Retinopathy Study sensitivity 80%; 53/66, 95% confidence interval 69% to 88%; specificity 40%; 79/196, 95% confidence interval 34% to 47%). Results against the enhanced reference standard were similar to those against the reference standard (for seven-field Early Treatment Diabetic Retinopathy Study images, sensitivity of 82%; 111/135, 95% confidence interval 75% to 88%; specificity 54%; 68/127, 95% confidence interval 45% to 62%; for ultra-wide field images sensitivity 80%; 110/138, 95% confidence interval 72% to 86%; specificity 60%; 76/127, 95% confidence interval 51% to 68%). Findings were similar whether patients were assessed in NHS or ‘research’ clinics. Sensitivity and specificity, however, were lower when considering referrals due to active proliferative diabetic retinopathy only (i.e. excluding ‘unsure’ and ‘ungradable’).

Thirty-six participants attended ten focus groups in Northern Ireland (n = 4), Scotland (n = 2) and England (n = 4). Participants preferred face-to-face evaluations by ophthalmologists, where information about their eye condition could be received and anxieties assuaged. In the absence of ophthalmologists, participants voiced the need for immediate results from the grader’s reading of images. Patients wanted periodic evaluation by ophthalmologists, even if at longer intervals. Patients are uncertain of the professional identity, training and performance of graders. Graders and ophthalmologists were supportive of the new pathway, but graders expressed caution about their ability to answer potential questions from patients unrelated to the activity of their disease.

The cost–consequences analysis, in monetary terms, showed that for diabetic macular oedema, where sensitivity was very good, the cost-difference (savings) for the grader’s pathway would be £1390 per 100 patients. For proliferative diabetic retinopathy, if sensitivity was considered acceptable, the cost would be reduced by £461 for seven-field Early Treatment Diabetic Retinopathy Study images and by £1889 for ultra-wide field images, per 100 patients. The difference arises because ultra-wide images require less time to be obtained and read than seven-field Early Treatment Diabetic Retinopathy Study.

Conclusions

The sensitivity of the new grader’s pathway to determine diabetic macular oedema was 94% or above in all analyses suggesting that, for diabetic macular oedema, the new ophthalmic grader pathway would be safe. The sensitivity to determine proliferative diabetic retinopathy was 80% or above in all planned analyses with one exception (referrals for active proliferative diabetic retinopathy only, excluding ‘unsure’ and ‘ungradable’). This level of sensitivity, although potentially less than ideal, may be acceptable for patients previously treated with laser panretinal photocoagulation, for whom this new pathway is being proposed. Where waiting targets are not achieved and people with serious eye conditions are waiting longer than acceptable, this new pathway would be reasonable and justified. Ultra-wide field imaging had slightly higher sensitivity to detect proliferative diabetic retinopathy with pre-retinal/vitreous haemorrhage (i.e. high-risk) and was less costly than seven-field Early Treatment Diabetic Retinopathy Study, thus, would be the preferred option. Despite the relatively low specificity of the new ophthalmic grader pathway, this pathway would save ophthalmologists’ time that could then be redirected to a more timely evaluation and treatment of patients requiring urgent care, which would likely be sight-saving for many patients. Recommendations from the focus groups should be followed if the new pathway is to be introduced to ensure acceptability to users.
Recommendations for future research

For proliferative diabetic retinopathy, a pilot study could be run prior to its widespread implementation in the NHS, to further ensure its safety. Measures to further improve the sensitivity of this pathway (e.g. providing continuous feedback to graders, selecting patients entering the pathway, enhancing resolution of screens used to view images) could be introduced and evaluated.

Could artificial intelligence be used for automated reading of images in this previously treated population?

Trial registration

This trial is registered as ISRCTN10856638 and ClinicalTrials.gov NCT03490318.

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