PROTOCOL

Diabetic retinopathy screening and monitoring of early stage disease in general practice

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PROJECT OVERVIEW

Diabetic retinopathy (DR) is the leading cause of preventable blindness in Australians younger than 60 years, mainly from the development of diabetic macular oedema (DME) and the sequelae of advanced proliferative DR. However, the detection and treatment of DR with laser photocoagulation can prevent nearly all cases of severe vision loss and blindness.(1) Thus, the 2008 National Health and Medical Research Council (NHMRC) guidelines for DR management recommend regular ocular review of patients with diabetes.(2) However, many people with diabetes do not achieve this(3) demonstrating the need to develop systematic approaches to DR screening that will improve access and minimise preventable blindness by detecting early DR before any risk of visual loss from more advanced retinopathy signs, particularly early DME. Early detection will also permit optimal medical therapy of DR risk factors, glycaemia, blood pressure and lipids.

In partnership with Queensland Health (QH) and the Royal Australian College of Ophthalmologists (RANZCO), we have conducted a pilot project of general practice based DR screening using a non-mydriatic retinal camera. We showed that this approach is acceptable to general practitioners (GPs) and patients, can be readily incorporated into the existing annual cycle of diabetes care, and meets the NHMRC screening criteria.

The DR Screening and Monitoring in General Practice study extends our pilot work to more general practices and includes tele-ophthalmic consultations for diabetic patients with mild to moderate DR levels (but with no other sight threatening complications requiring intervention by an ophthalmologist as indicated in the 2008 NHMRC Guidelines).(2)

AIMS AND OBJECTIVES

This study aims to test the accuracy, acceptability and cost-effectiveness of general practice based DR screening integrated into the diabetes annual cycle of care compared to conventional methods of DR screening. Secondly, this project aims to test the accuracy, acceptability and cost-effectiveness of routine monitoring by the GP of mild to moderate DR levels with ophthalmic support and education through videoconferencing.

To achieve these aims, the specific objectives of the study are:

1. To recruit 8 GPs and their general practices to participate in the delivery of the projects intervention
2. To install non-mydriatic retinal cameras in these general practices, and to train the GPs and practice nurses (or other suitable general practice staff) in taking retinal photographs.
3. To train the 8 GPs in interpretation of retinal photographs
4. To recruit 8 comparable general practices to participate in the study as control practices
5. To work with all participating general practices to develop site specific patient recruitment process, and to document these processes.
6. To work with the intervention general practices to develop site specific processes for taking and reading the retinal photographs, and to document these processes.
7. To work with the intervention general practices to develop site specific processes for credentialing process, and to document these processes.
8. To determine the technical accuracy of the nurses (or other general practice) in taking the retinal photographs
9. To determine the diagnostic accuracy of the GPs through double reading of the retinal photographs from the 1st 50 patients participating in the project at each practice.
10. To work with the intervention practices and ophthalmologists to develop site specific processes for monitoring mild-to-moderate level DR, and coordinating the required bi-monthly teleconferences.
11. To determine the acceptability of the intervention with patients, GPs, general practice staff and ophthalmologists.
12. To conduct a retrospective chart audit to determine the proportion of patients with diabetes who have received appropriate and timely screening for DR over the 2 years prior to the commencement of this project and for the 2 years of the project. This will be calculated by referrals to ophthalmologists or optometrists and subsequent communication back to the general practice about the outcome of that referral.
13. To determine the cost effectiveness of this model of care compared to usual care.

**HYPOTHESES AND RESEARCH QUESTIONS**

Underpinning this research are two hypotheses:

1) General practice based DR screening and early stage disease monitoring will be feasible, accurate, acceptable and cost effective, compared with usual care.

2) General practice based DR screening, integrated into patients’ diabetes annual cycle of care visits, will improve access to, and compliance with, timely DR screening.

The specific research questions that will be addressed in this project are:

1. Can DR screening be conducted in mainstream general practice as part of the diabetes annual cycle of care?

2. Does integration of DR screening into the diabetes annual cycle of care increase the proportion of patients who receive DR screening as recommended in the 2008 NHMRC guidelines?

3. Can general practice nurses achieve an acceptable level of technical skill (i.e. low rate of ungradable images) in retinal photography using non-mydriatic cameras?

4. What is the diagnostic accuracy of GPs interpreting retinal photographs taken by a general practice nurse trained in non-mydriatic retinal photography?

5. Can patients with mild to moderate DR levels (but without sight threatening signs requiring ophthalmic intervention as per 2008 NHMRC Guidelines) be effectively monitored by distant ophthalmologists using video-conferencing?

6. Is general practice based DR screening and monitoring cost effective?

7. Is general practice based DR screening and monitoring acceptable to patients, GPs, general practice staff and ophthalmologists?
8. What potential adjustments to the MBS rebate for the Diabetes Annual Cycle of Care (Item number 2525) would be required to ensure the sustainability of general practice based DR screening?

Methods:

Study design
The DR Screening and Monitoring in General Practice study is an open controlled trial involving 16 general practices (8 in each arm), 4 ophthalmologist, at least 200 patients per practice.

In summary, DR screening in the control practices will be via their usual referral pathways. Patients attending intervention practices will have DR screening done “in-house”. Patients without DR re-screened in 12 months. Patients with mild-moderate DR are monitored by the GP with support from the “partner” ophthalmologist via bi-monthly teleconferences. Patients with severe DR or other pathologies referred immediately to the “partner” ophthalmologist.

![Graphical representation of the study design](image-url)
General practice recruitment:

General practices will be purposefully targeted to participate in this project. Intervention practices will be identified first, and then control practices matched on geographical region, hospital referral pathways, size, and characteristics of patients with diabetes. There will be an emphasis on rural towns, regional centres and areas with a high population of Indigenous Australians and DR screening access difficulty.

Inclusion criteria for the general practices:
- an established recall and reminder system for ensuring the maximum number of patients attend for their Diabetes Annual Cycle of Care visits.
- At least 200 patients with diabetes attending the practice

Additional inclusion criteria for the intervention practices:
- identification of an enthusiastic GP who will undertake the upskilling and accreditation assessment, read the retinal photographs, and will champion the project within the practice
- a sufficiently large practice with the physical space to accommodate the camera
- at least 1, preferably 2, practice nurses willing to be trained and to take the retinal photographs

Patient recruitment:

Participating patients with T2DM will be opportunistically recruited when they attend any of the participating practices for their diabetes annual cycle of care visits. Each practice will develop their own site specific methods for patient recruitment.

The study will be explained and informed consent will be obtained prior to any data collection or the retinal photographs being taken.

Inclusion criteria:
- aged 18 years and older
- sufficient cognition to provide to provide informed consent

Exclusion criteria:
- patients who have no perception of light in either eye
- patients who are terminally ill and are deemed too unwell to participate
- patients who have a physical or mental disability that prevents either screening or treatment
- patients who are currently under the care of an ophthalmologist for treatment and follow-up of DR

Consent

Written consent to participate in this study will be gained from patients, GPs, general practice staff taking the photographs, and the ophthalmologists.
### Intervention

#### Phase 1: Pre-patient recruitment
- Non-mydriatic retinal cameras and video-conferencing equipment installed
- Practice nurses trained in retinal photography and pupil dilation protocol
- GPs undergo upskilling and accreditation assessment

#### Phase 2: Primary care based DR screening
- Patients with diabetes attending general practice for Annual Cycle of Care visits recruited
- Practice nurse photographs retinas, assess visual acuity, and inserts digital image into patient record
- GP credentialled and technical quality of photos reviewed
- Trained GP views photograph, completes reporting sheet and inserts it into patient record
- Patient’s GP views report and discusses results with patient as part of overall diabetes management

#### Phase 3: Primary care based DR monitoring
- Patients with mild to moderate level DR (with no other sight threatening complications) will monitored in general practice with tele-ophthalmic support
- Management plan for patient developed and implemented
- Follow up of patient as required

#### Phase 4: Ongoing support
- Quarterly videoconference education sessions attended by GPs and ophthalmologists
- Ongoing support for practice nurses from Optimed (camera distributor) to ensure technical quality of photographs
- Training in camera use provided to any new practice nurses

**Figure 2: DR Screening and Monitoring Intervention**

### Phase 1: Pre-patient recruitment

**Camera installation and training**
Intervention practices will be supplied with non-mydriatic retinal digital camera. The participating GP and the practice nurses (or other practice staff) who will be taking the photographs will be trained in using the camera by a representative of Optimed (a partner in this project) on the day of camera installation. Optimed has committed to provide an additional 5 hours training and support in use of the retinal camera per site – this training could consist of a mixture of on-site training, a face-to-face group training session in Brisbane, and/or support via computer/phone link to Optimed.

**Pupil dilation**
Where possible, photographs will be taken on undilated eyes. However, patients who are 60 years of age or older, or patients who have had two sets of retinal photographs deemed
unreadable will require dilatation using tropicamide 0.5%. The practice nurse (or other staff member) will be trained in dilation, and will be provided a Standard Operating Procedure (SOP) for this.

GP upskilling and accreditation assessment

GPs participating in this project will complete competency based training and gain accreditation from the RANZCO (Qld Faculty) and UQ.

The training / accreditation program consists of the UQ Masters of Medicine (General Practice) web-based DR education segment coordinated by Dr Peter Cranston. It is estimated that this segment will take the GPs approximately 4 hours. The accreditation will be completed with a 90 minute examination involving the interpretation of 30 retinal photographs according to the NHMRC 5 staged classification system and determining the appropriate management/referrals. The photographs are marked by two independent RANZCO assessors.

The outcome of the training will be evaluated through a competency based examination to determine ability to:
1. accurately detect and grade retinopathy, according to the NHMRC diabetic retinopathy guidelines.
2. accurately detect the presence of diabetic maculopathy
3. develop an appropriate management/referral plan, according to the NHMRC diabetic guidelines.

75% or greater concordance over 30 images, compared with the results of 2 independent ophthalmologists (the gold standard) will need to be achieved in order to gain accreditation. This is classified as critical in terms of competence.

Phase 2: DR screening

Patients with diabetes attending general practice for Annual Cycle of Care visits recruited

Patients will be opportunistically recruited as they present at the practice for their annual cycle of care visit. Site specific processes will be developed to ensure that recruitment and consent processes have minimal impact on the practice’s normal routine.

Practice nurse photographs retinas and inserts digital copy into patient record

Prior to the patient’s appointment with the GP, the practice nurse (or other suitably trained staff member) will take single photographs of each retina using the non-mydriatric camera and insert a digital copy into the patient’s medical record. Patients who are ≥ 60 years of age or have had two sets of photographs deemed unreadable, will have their pupils dilated, according to the dilation SOP.

Visual acuity assessed

The practice nurse (or other suitably trained staff member) will also assess visual acuity using the following SOP:

GP credentialed and technical quality of photos reviewed
Practice staff will burn the retinal photographs of the 1st 50 patients (100 images) onto CD or DVD, and send to the Project Manager at UQ together with copies of the completed reporting sheets. The project manager will then ensure that all images have been reported on, and that all reporting sheets have corresponding images, and liaises with the practice if there are any omissions.

The project manager will forward to appropriate ophthalmologist copies of the images and reporting sheets. The reporting sheets will be blank, apart from date, patient name, gender, age, known duration of disease, latest HbA1c, blood pressure and visual acuity – the project manager will fill in these details prior to sending the reporting sheets to the ophthalmologist.

The ophthalmologist then reviews the retinal images, completes the corresponding reporting sheets which are returned to the project manager. The project manager checks that there are completed reporting sheets for all images forwarded to the ophthalmologist and liaises with the ophthalmologist if there are any omissions.

The project manager then enters the data into a spreadsheet and the individual and collective diagnostic sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) estimates of the GPs will be calculated, with 95% confidence intervals, using the ophthalmologist’s assessment as the reference standard. Diagnostic accuracy will only be determined for photographs deemed interpretable by both the GP and the ophthalmologist. If the GP’s diagnostic sensitivity is less than 90% and specificity less than 90-95%, images from increments of 10 patients (20 eyes) are to be submitted for independent review by the ophthalmologist until diagnostic accuracy is achieved.

Similarly, the project manager will also review the proportion of photos deemed uninterpretable by the GPs and the ophthalmologist. If more less than 90% of photographs are deemed interpretable, further education and training will be provided to the practice nurse (or whoever is taking the photographs) to improve technical skills. If there is discordance between GPs’ and ophthalmologist assessments of interpretability, further education and support will be provided to the GPs to increase their skills and confidence in differentiating between interpretable and uninterpretable retinal photographs.

*Trained GP views photographs, completes reporting sheets and inserts them into patient records*

GPs that have completed the RANZCO training read the photographs of all participating patients in their respective clinic, and complete the purposefully developed reporting sheets (Appendix 1). The diagnosis and recommended management/referral will be entered into the patients’ records. Patients with severe DR and / or other pathology will be provided with an urgent referral to the “partner” ophthalmologist (preferably) or to the nearest public ophthalmology outpatient clinic, if the patient prefers.

*Patient’s GP views report and discusses results with patient as part of overall diabetes management*

At the next convenient appointment, the patient’s own GP will review the photographs and the report, and discuss the results with the patient as part of the patient’s overall diabetes management.
care. Patients with no DR will be rescreened in 12 months time. Patients with mild to moderate DR levels and no sight threatening pathologies will be monitored by the GP, in consultation with the ophthalmologist.

**Phase 3: Primary care based DR monitoring**

*General Practice based DR monitoring*

Patients identified as having mild to moderate levels of DR, and no other sight threatening signs requiring ophthalmic intervention will remain in the care of their GP rather than being referred to an ophthalmologist. Practices will forward to the project manager the retinal photographs of these patients and accompanying completed reporting sheet. The practice manager will coordinate the forwarding of these images and reporting sheets to the appropriate ophthalmologist.

The GP and the ophthalmologist will have regular, scheduled bi-monthly video or teleconferences where they simultaneously review the retinal photographs of all patients who have consented to participate and develop patient-specific management plans that will detail the required regularity of GP review of the patient’s DR, and the timeframe for the next tele-ophthalmic consultation.

**Phase 4: Ongoing support**

*Quarterly videoconference education sessions attended by GPs and ophthalmologists*

Quarterly videoconference education sessions will be held and attended by GPs from the intervention practices, the ophthalmologists and project staff. These sessions will have 2 key purposes:

1) the provision of on-going education for the GPs in interpreting the retinal photographs; and
2) facilitating effective communication between the GPs, the ophthalmologists and the project staff.

QA&CPD recognition for these sessions will be sought from the Royal Australian College of General Practitioners (RACGP).

*Ongoing support for practice nurses from Optimed to ensure technical quality of photographs*

Practice nurses will be provided with up to 5 hours of support and additional training from Optimed (camera distributor). This support could be via telephone or face-to-face training, depending on the issues.

*Training in camera use provided to any new practice nurses*

It is important that all new practice nurses (or whichever practice staff are responsible for taking the retinal photographs) are adequately trained in using the camera and taking the photographs. This training will be provided by Optimed personnel.
**OUTCOME VARIABLES AND ANALYSIS**

The main outcomes measures for this study are:

1) the proportion of retinal photographs taken by practice nurses that are deemed acceptable and interpretable.
2) the diagnostic accuracy of the GPs reading the photos, using the ophthalmologist’s assessment as the reference standard, and compared against the 2008 NHMRC Guidelines.
3) the acceptability of general practice based DR screening and monitoring of mild to moderate levels of DR.
4) the proportion of patients with diabetes in the intervention practices who receive timely and appropriate DR screening, compared to the control practices and historical data from the intervention practices.
5) the proportion of patients with identified mild-to-moderate level DR who attend for review appointments in the intervention practices compared to the control practices and historical data from the intervention practices.
6) cost effectiveness of general practice based DR screening and monitoring of mild-to-moderate level DR, compared to the control practices.

**Outcome measure 1: interpretability of retinal photographs**

During the credentialing phase, both the GP and the ophthalmologist will assess the interpretability of the first 100 retinal photographs on a monthly basis and rates of 90 – 95% interpretable will be deemed acceptable, as per the 2008 NHMRC DR Guidelines (2). Remedial action, such as additional training and/or support for the nurses, will be taken if technical failure rates exceed this.

**Scenarios to consider:**

1) nurse takes photo and realise it is not interpretable and then take another – is this included in the denominator
2) nurse takes photo and GP decide it is uninterpretable, and request nurse to take another – is this included in denominator?
3) nurse takes photo, GP thinks it is ok, ophthalmologist deems it uninterpretable.

**Outcome measure 2: GPs’ diagnostic accuracy**

For each patient, the GP will assess the interpretability of the photograph, identify and grade the level of retinopathy if present (and record any of the clinical sign of DR), identify the presence of diabetic maculopathy and other pathology eg. Glaucoma, or macular degeneration, and specify the management / referral plan. For the 1st 100 patients, an ophthalmologist will independently review the same photos and make the same assessments. The GP’s diagnostic sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) estimates will be calculated, with 95% confidence intervals, using the ophthalmologist’s assessment as the reference standard. Diagnostic accuracy will only be assessed if the photograph is deemed interpretable by both GP and
ophthalmologist. Analysis of the aggregated GP diagnostic accuracy will be done, using weighted kappa statistics, with logistic regression to adjust for confounders like age, duration of diabetes, size of practice, GP training, etc. All statistical calculations will be undertaken using Stata version 10 (StataCorp, College Station, TX, USA) and α=5% will define statistical significance.

**Outcome measure 3: acceptability of general practice based DR screening and monitoring**

The acceptability of general practice DR screening and monitoring of mild to moderate level DR will be assessed using semi-structured interviews with participating GPs, practice nurses and other involved in the study, other staff of the general practices, ophthalmologists and patients (12). A purposeful sampling strategy will be used to recruit a range of patients from each practice: different age groups, genders, presence of absence of DR or other retinal pathology. Sampling of patients will cease when data analysis reveals that data saturation has been reached and no new themes, concepts or ideas are emerging. An interview schedule will be used to guide all interviews, interviews will be audiotaped, transcribed and thematic analysis will be used to identify and classify recurrent patterns and themes (13).

**Outcome measure 4: rates of DR screening**

The proportion of patients with T2DM that receive DR screening in the intervention practices will be calculated, using the total number of patients with diabetes on the practice diabetes registrar as the denominator. This will be compared with DR screening rates in the control practices during the time of the project, calculated by ophthalmic referrals and subsequent communication back from the ophthalmologist recorded in the records of the patients with diabetes in the control practices. DR screening rates from both the intervention and control practice for the 2 years prior to the project will also be calculated in the same way.

**Outcome measure 5: rates of monitoring of mild to moderate levels of DR**

The proportion of patients with mild to moderate levels of DR (and no sight threatening signs) that are monitored in the intervention general practice with distant ophthalmic support will be calculated, using the total number of patients with mild to moderate levels of DR as the denominator. This will be compared with rates of monitoring of patients with mild to moderate levels of DR in the control practices, and relevant data from both control and intervention practices for the 2 years prior to the project.

**Outcome measure 6: Cost effectiveness of general practice based DR screening and monitoring compared to usual care:**

The cost effectiveness of general practice based DR screening and monitoring of mild to moderate level DR will be measured in present-value terms using an incremental cost-effectiveness ratio (ICER): ie. the ratio of the change in costs to the change in effects eg increased screening rates for at risk individuals over the 2 years of the trial. This is a
conservative approach to valuing this intervention as it will not include analysis of future health benefits via disability adjusted life years. The analysis will take a ‘whole of health system’ approach including the costs of practice screening infrastructure, the screening process itself, remote consultation, and current state government costs in remote patient transfer and ophthalmology ‘fly in’ screening services.

Assessment of unit costs will include:

- costs of installing the intervention itself (camera and videoconferencing installation, training for doctors and nursing staff), with capital and training costs amortised over an appropriate time period.
- additional costs in time (eg. practice nurse time in taking photographs and GP time in interpreting the photographs and discussing the results with the patient) and disposables, including telecommunications costs, in intervention practices.
- costs in arranging referral for screening in control practices
- costs of remote consulting between GP and ophthalmologist in intervention practices
- costs (including MBS, QH and private costs) of DR screening for the control group via hospital OPDs, private ophthalmologists, optometrists, indigenous health services.
- state government costs in remote patient transfer (patient transport application processing and benefits paid) and ophthalmology ‘fly in’ screening services for control practices including opportunity costs of ophthalmologists performing routine DR screenings instead of sight saving surgery
- direct patient costs in both groups (travel, accommodation, loss of work time)
- historical data from the intervention and the control general practice records about patients’ previous access to DR screening and ophthalmic review

The economic evaluation will NOT include a direct assessment of the long-term key benefit of decreased rates of preventable blindness as a result of increased rates of screening is benefit as there is excellent established research evidence linking early detection and intervention for advancing diabetic retinopathy, with greatly improved ocular outcomes. Similarly, likely longer-term cost benefits of more appropriate use of existing ophthalmic services in sight-saving treatment rather than population screening will also not be included. Nevertheless, the analysis will seek to make inferences and extrapolations regarding the reduction in preventable blindness and the flow-on economic and social benefits, based on the existing literature.
TIMELINE

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Reporting Date | Milestones
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Year 1 | • Development and piloting of DR monitoring at the 2 pilot sites
• Recruitment of project manager
• Completion of a systematic review of general practice based DR screening and monitoring
• completion of accreditation assessments at newly identified practices and commencement of DR screening
• 1st 100 patients screened and GP diagnostic accuracy assessed at Bundaberg
• Implement DR monitoring protocols and procedures in Bundaberg
• Identification and recruitment of 3 additional intervention practices and
### Year 2
- Quarterly educational videoconferences with GPs, ophthalmologists and project team
- Meetings as per schedule of Steering, Evaluation and Operational Committees.
- Completion of accreditation assessments in three new general practices, and commencement of DR screening and monitoring
- Assessment of diagnostic accuracy of GPs in 3 new practices, and remedial attention given if issues identified
- Ongoing data entry and data quality monitoring

### Year 3
- Quarterly educational videoconferences with GPs, ophthalmologists and project team
- Meetings as per schedule of Steering, Evaluation and Operational Committees.
- Qualitative evaluation conducted and analysed
- Cost effectiveness analysis completed
- All reporting requirements fulfilled
- Results of project disseminated through papers in peer-reviewed journals and relevant conference presentations.
- Final Report