Enhanced Scheme Evaluation Project - IRAS ID 128578 (GR01873)

Study Protocol ESEP V2.0

An evaluation of the clinical effectiveness of the Manchester Glaucoma Referral Refinement Scheme

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**Background:**
Community optometrists identify ~95% of suspect glaucoma and ocular hypertension (OHT) cases in the UK through the routine GOS sight test. Unfortunately the false positive rate for referrals for suspect glaucoma is high, running at ~40% for many decades. Glaucoma referral refinement schemes (GRRS) have been in operation in the UK for more than a decade and Manchester’s scheme was the first (Henson et al, 2003). The reduction in false positives through GRR as opposed to the normal sight test has been documented (a reduction from 40% to 10% is typical) but the false negative (FN) rate has not yet been evaluated systematically. One study, in Carmarthenshire, did undertake an analysis of 100 sets of notes and optic nerve images of patients not referred through the GRRS and ‘indicated no compromise on patient safety’ (Devarajan et al, 2010). In this study, the optic disc photographs of these non-referred patients were also shown to three hospital consultants, devoid of any accompanying information, who were also asked to note whether the discs appeared normal, suspicious, or obviously pathological. These three opinions were ‘averaged’ and compared with those of the referring optometrist. Consultant ophthalmologists were in agreement with the referring optometrist 50% of the time, suggested overestimation of CDR 35% of the time, with the remaining 15% of images displaying underestimation. Of these 15 patients, 2 showed changes that merited recall to the HES for further investigation. Neither of these was started on ocular anti-hypertensives. The authors went on to state that ‘this translates as a false-negative rate of between 3 and 10%’. There are, however, a number of difficulties with estimating the FN rate from this retrospective case review of optic disc photos, including: the possibility that other ocular parameters may have been abnormal (e.g. status of the anterior chamber angle, retinal nerve fibre layer, IOP) and furthermore the sample of 98 optic disc images reviewed provides limited precision for the estimated FN rate. Clearly a narrative is needed in dealing with what a FN case actually is, hence the range quoted in the Carmarthenshire study.

As part of this evaluation, we propose to estimate the FN rate by routine examination in secondary care of a systematic sample of non-referred GRRS patients using the same clinical assessment for cases as used for new glaucoma suspect referrals through the GRR scheme to MREH’s clinic, assessment which is in accordance with the NICE guideline on the diagnosis and management of OHT and glaucoma.

**Primary objective:**

- To estimate the false negative rate within the new Manchester GRR scheme.

**Secondary objectives:**

- To simultaneously estimate the false positive rate in the same cohort
- To estimate the proportion of non-glaucomatous ocular co-morbidities within this glaucoma suspect population.
Method of recruitment:
The community scheme will function as it does currently from the patients' perspective, there will be no change to the patients care. If an optometrist identifies possible glaucoma following a routine sight test, they will, as they do now, refer their patient to a GRR accredited community optometrist for evaluation of their suspect glaucoma patient. This GRR accredited optometrist will, post GRR examination, either make a referral for their patient to MREH for specialist hospital assessment or not.

All glaucoma suspects deemed to not require referral following examination by the GRRS optometrist will be provided with the patient information sheet informing them of the study, introducing the study team and explaining that although their examination is clear (and that in the opinion of the examining optometrist the patient had no need for referral to the hospital), the hospital may invite them to participate in a study being conducted at the eye hospital. If any patient at that stage expresses an unwillingness to be contacted their details will not be passed on to the research team. Contact details for all other non-referred patients will be passed on to the research team. We will subsequently invite a sample of non-referred patients (by systematically sampling across the non-referred patients examined by the 18 GRR participants- see below) to attend MREH for a specialist reference standard assessment. Patients will be telephoned by the research team to provide this invitation. If patients are willing to participate, and provide informed consent, study participants will be invited to attend one of the bi-monthly hospital-based GRR clinics established for the purpose undertaking a ‘reference standard’ examination.

The patients will be given contact details in the event of any questions and written consent will be taken at the clinic prior to the examination, after allowing the opportunity for further questions.

Inclusion and exclusion criteria:
Adult patients >18 years of age who consent to participate and who have been assessed within the Manchester GRR scheme and deemed to not require referral to MREH for specialist assessment will be included. We will exclude children, those unable to communicate in English or other patients who are unable to provide fully informed consent.

Sampling methodology and sample size requirements:
We will systematically sample a proportion of the non-referred patients attending all 14 different optometric practices for GRR assessment to include patients assessed by all 18 GRR clinicians (i.e. 17 optometrists and 1 ophthalmologist) participating in the new Manchester GRR scheme. The timeline for recruitment will be for an 15 month period, commencing in ~October 2014. Initially one patient will be selected at random from those screened negative in the previous month (at the date of invitation letters going out) at each optometry practice, and invited to the MREH clinic. This gives a maximum of 18 invitees per month and we would anticipate 10-15 will attend. If there are fewer than 15 such patients (as centres will not always have
seen patients in the time frame) further patients will be randomly sampled from all centres. The attendance rates will be monitored and if they are low then larger numbers of patients will be sampled in later months. The numbers screened at each centre will be recorded and the FN rates weighted to match the total attendance. This process will allow us to retest 200 patients in the period.

A final sample of 200 non-referred cases which contained zero false negatives would have an upper 95% confidence limit of 2% - that is we would have demonstrated with reasonable confidence that the FN rate was<2%. More generally we will be able to estimate the rate with a ±4% error (based on the 95% CI) if the FN rate was as high as 5%. We propose therefore that this proportion is both reasonable in terms of precision of FN rate and realistic in terms of sample size feasibility.

**Hospital based ‘reference standard’ examination:**

To be able to define a FN referral we require a reference standard assessment and this assessment will comprise the standard tests and examinations undertaken for glaucoma suspect investigation in referred patients.

Reference examinations will take place at weekly (or as required) hospital GRRS research clinics run by RH with support from two other DipGlauc optometrists. The research study will not impose upon usual NHS clinic activity. A comprehensive new patient referral examination to include all elements of assessment as required for glaucoma/OHT diagnosis (NICE guideline, 2009) will be undertaken. These tests will include: evaluation of referral data, symptoms and history, general health and medications, previous eye history, family history, evaluation of glaucoma risk factors, visual acuities, anterior segment assessment, van Herick assessment, gonioscopy, Goldmann applanation tonometry, pachymetry, dilated fundus examination incorporating a clinical optic disc assessment using slit-lamp BIO (the latter with either a 78D, 60D or 66D lens). In addition to undertaking HFA 24-2 in each eye, a technician will undertake colour stereo-optic disc photographs and OCT imaging of the RNFL.

It is anticipated that a patient who agrees to attend the hospital for this reference standard examination will not require any further visits and this single visit will suffice; however, we do not know what the FN rate is from the enhanced scheme and there are natural variations in the clinical parameters underpinning a diagnosis of glaucoma and it is therefore possible that a proportion of people who participate (expected to be <10%) will be required to attend for hospital follow-ups (for example, if they have glaucoma or a higher risk of glaucoma). The care pathway for these patients will fall within the remit of usual NHS care and will follow review timelines as recommended by the NICE guideline. More specifically, if we detect glaucoma or OHT or glaucoma suspect status (or any co-morbidity) necessitating hospital review, we will inform the patient direct, the participant’s GP and make a referral to the relevant hospital clinic for ongoing hospital review as required.
Post reference standard categorisation of patients:
The HES optometrist will review their clinical assessment data and classify the patient into a number of diagnostic groups as well as noting any non-glaucomatous ocular co morbidities. In essence, a FN case will be deemed to be a case of missed glaucoma, glaucoma suspect or OHT where the GRRS criteria for referral would have been ‘triggered’ upon reference standard examination. Specifically, we will use intraocular pressures, visual fields, the status upon examination of the optic nerve head and the anterior chamber angle status. Parameters will be assessed for adherence to the single and combined criteria for GRRS referral (as specified in Appendix 1). Visual field loss consistent with glaucoma will be defined by the Early Manifest Glaucoma Trial (EMGT) criteria.

The definition of a FN will therefore be one of addressing the question, should the patient have been referred? Cases of missed glaucoma, missed OHT or glaucoma suspect status necessitating review (in accordance with the NICE guideline), as well as noting the rate of (and significance of) any co morbidities not noted by the referring optometrist.

Discrepancy between clinical examination in the community and within the hospital is expected in a number of cases, not all of which will reflect true FN cases, for example, where natural fluctuation within clinical parameters, such as intraocular pressure, may cause the decision for a patient to tip from non-referral to referral based upon measurement variation. A narrative for the categories of FN will allow any discrepancies to be placed in an appropriate wider context such that a distinction can be made between a ‘barn-door’ FN rate of cases who ought to have been referred versus more subtle discrepancies that might arise through test-retest variation/glaucoma assessment difficulties (i.e. the clinical importance of any ‘misses’ will be described in an appropriate context). One key area in glaucoma assessment where inter-observer variation is well documented is in the assessment of optic disc status. Our reference standard is the clinical assessment on slit-lamp BIO by a DipGlauc optometrist but in every case where the disc is judged by them to be abnormal we will obtain independent verification of this decision by seeking review by one of our reference panel ophthalmologists (glaucoma specialist consultant ophthalmologists, AFS and CHF). Here, data from the OCT imaging of the retinal nerve fibre layer imaging and conventional optic disc photos will be made available. In the event that this glaucoma specialist decision differs from that of the HES optometrist, the case will be reviewed by the second glaucoma specialist consultant to reach a consensus decision. Decision status will be masked from our reference panel ophthalmologists by asking them to review a random sample of optic disc and RNFL images not deemed to be abnormal.

A final FN classification will be assigned to each participant as follows:

Unlikely: No evidence from any element of the reference standard assessment of any suspicion of glaucoma or ocular hypertension necessitating hospital review. Patients falling into this group will, upon reference standard assessment, not meet the referral criteria within the GRRS.
**Possible:** In this categorisation, some element of assessment (e.g. IOP, visual fields, optic disc status etc) provides evidence of possible requirement for review, but potentially a requirement that may not have been met upon community GRRS examination (e.g. due to variation in IOP). This category of ‘FN’ will be grouped into clinical parameter categories, permitting the FN rate to be differentially determined, dependent upon inclusion or exclusion of such cases, allowing us to add a narrative to the FN outcomes when disseminating findings that reflects the realities of glaucoma suspect case finding and subsequent diagnosis.

**Likely:** In this categorisation there will be much clearer evidence of a requirement at GRRS examination for the participant to have needed to be referred (e.g. consensus of optic disc examination shows abnormality, confirmed visual field loss consistent with glaucoma). The consensus optic disc status will be formed on the basis of 2 of our co-applicant consultant ophthalmologists reviewing independently every case of disagreement between the GRRS referring optometrist and the reference standard DipGlauc optometrist examination (i.e. on the basis of optic disc stereo-photos). We will also intersperse this independent evaluation of optic disc status with an equivalent proportion (50% of optic discs where both the community optometrist undertaking the GRRS examination and the DipGlauc optometrist undertaking the reference standard assessment agree that the disc is normal, with the consultant ophthalmologists being blind to this judgement).

**Ethical approval:**
Ethical approval is being sought via the Integrated Research Application System (IRAS Project ID 128578). A patient information sheet has been developed that encompasses the expected information needs of patients who will be invited to participate to include, for example, the background to the project, how the GRRS works, why the patient has been approached and invited to participate, why the study is necessary, the voluntary nature of the invitation, what will happen if they decide to take part or decide not to take part, who will examine the patient and/or see their data, who will be informed about the visit after attendance, what will happen to the patient if further review is needed in the hospital, and relevant contact information at the hospital.

**Data analysis:**
False negative and positive rates based on agreed definitions will be estimated with their associated 95% CI. Exploratory analyses will examine differences over time and between centres and their association with practice and patient characteristics. However individual practices will not be identified in any reports.

We will compare false positive rates in 6-monthly cohorts, with those in the year prior to the study commencement in order to determine whether referral practice has changed as a result of the trial.
References:


Appendix 1: GRRS referral criteria

Modifications to the original criteria to reflect joint Colleges’ recommendations and the over-arching NICE treatment guidance mean that referral for IOPs <30mmHg will be based on specific age and CCT levels as follows:

Single referral criteria
- IOP >30*mmHg confirmed at a second visit. If IOP >35mmHg then no confirmatory measurement is necessary.
- Unequivocal pathological cupping at the optic nerve head. Abnormal neuroretinal rim configuration. Large cup, taking into account the overall size of the disc. Notched neuroretinal rim. A >0.2 asymmetry of cup to disc ratio. The existence of a disc haemorrhage merits closer inspection for early nerve fibre loss. Refer for an optic disc haemorrhage through GRRS only where there are additional optic disc and/or other indicators of glaucoma.
- Visual field loss consistent with a diagnosis of glaucoma, confirmed at a second visit. If explained by other disc or retinal pathology to be referred as such and not through scheme.

Combined referral criteria
- IOP, age and CCT criteria aligned with the NICE treatment algorithm Table 1 below.
- Raised IOP (age related criteria) plus an optic disc appearance suspicious of glaucoma or optic disc asymmetry
- Glaucomatous optic disc and corresponding visual field defect (IOP not raised) (no need for confirmatory measures).

Additional referral criteria
- Optic disc change over time e.g. increase in cup size, change in the rim appearance, or the occurrence of a new haemorrhage (documented within the scheme.) Refer for an optic disc haemorrhage through GRRS only where there are additional optic disc and/or other indicators of glaucoma.
- Anterior segment signs of secondary glaucoma (e.g. pseudoexfoliation) with raised IOP (age-related criteria) on two occasions
- Suspected narrow-angle glaucoma (symptoms of sub-acute attacks or occludable angle and raised IOP
- Emergency referral for suspected angle closure glaucoma should be made directly to emergency secondary care services such as MREH Acute Referral Centre or Emergency Eye Centre.
- In the event of an unusual clinical presentation or for those patients <40 years of age suspected of having developmental glaucoma, GRR optometrists should ring the hospital for advice on referral.
Table 1

<table>
<thead>
<tr>
<th>CCT</th>
<th>&gt;590 micrometres</th>
<th>555–590 micrometres</th>
<th>&lt;555 micrometres</th>
<th>Any</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP (mmHg)</td>
<td>&gt;21-25</td>
<td>&gt;21-25</td>
<td>&gt;21-25</td>
<td>&gt;25-29</td>
</tr>
<tr>
<td>Referral</td>
<td>No</td>
<td>No</td>
<td>Refer if ≤60</td>
<td>Refer if ≤60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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*Note:
Although the NICE treatment recommendation (not a referral recommendation but for ease of alignment to risk profiles structured in the same way) sees treatment commenced at >32 for any age/CCT, it is ‘safer’ to allow for a margin of error of 2mmHg in respect of ‘higher end’ IOP referrals by adopting a catch all referral criterion of >30mmHg. This approach permits commissioners to regain the value added of the original scheme from 2000 by permitting optometrists to retain patients who have a very low likelihood of treatment needing to be commenced (up to 29mmHg in contrast to 27mmHg in the original scheme, but with the added age/CCT risks being reflected in the IOPs below 26mmHg in the original scheme).