PRIORITY BRIEFING

The purpose of this briefing paper is to aid Stakeholders in prioritising topics to be taken further by PenCLAHRC as the basis for a specific evaluation or implementation research project. They were compiled in 2-3 days.

Can screening intervals for diabetic digital retinal photography be individualised to enhance screening performance and cost-effectiveness, on the basis of individual clinical risk?

Question ID: 26
Question type: Intervention
Question: Can screening intervals for diabetic digital retinal photography be individualised, to enhance screening performance and cost-effectiveness, on the basis of individual clinical risk?
Population: Patients with type 2 diabetes enrolled in diabetic retinal screening programmes in Cornwall and Devon, and who have stable background retinopathy without macular involvement, over at least two successive annual screening visits, and controlled risk factors for retinopathy progression (ie non-smokers, normotensive or treated hypertension, good glycaemic control, no nephropathy). This group represents the group at relatively low risk of rapid progression, but who require substantial resource use in view of their large and increasing numbers. Patients excluded from this algorithm would include all patients with type 1 diabetes or with nephropathy (higher risk) or those with other concomitant eye disease (at the discretion of the ophthalmologist.
Intervention: In patients who meet these criteria, and who have stable, non sight-threatening retinopathy, to increase the screening interval up to 2 years. This is subject to specific stringent safeguards including that good metabolic control is maintained, the patient is non-pregnant, and no other risk factors for retinopathy develop, and the decision is also at the discretion of the retinal photography reporter.
Control: Eligible (low risk) patients who meet criteria for increased interval screening (say 2 years or could be more flexible) could be randomised to this or to continued annual screening. The two groups can be evaluated for progression of retinopathy after a minimum of 2 years, to determine whether increased interval screening is any less effective.
Outcome: The aim is to improve the cost-effectiveness of screening by reducing surveillance of those with stable eyes and at low risk. A method to quantify cost-effectiveness of eye screening dependent on interval could also be developed. To reduce the numbers of eye screens that result in no action other than annual follow-up, in low risk patients, and to enable services to offer increased screening to individuals at higher risk of sight-threatening retinopathy.

Diabetes: Diabetes is a common life-long condition where the amount of glucose in the blood is too high as the body cannot use it properly. There are two types of diabetes: Type 1 diabetes which develops when the insulin-producing cells have been destroyed and the body is unable to produce any insulin. Usually it appears

before the age of 40, and especially in childhood. It is treated with insulin either by injection or pump, a healthy diet and regular physical activity; Type 2 diabetes which develops when the body doesn't produce enough insulin or the insulin that is produced doesn't work properly. Usually it appears in people aged over 40. It is becoming more common in children and young people of all ethnicities. It is treated with a healthy diet and regular physical activity, but medication and/or insulin is often required.

Diabetic retinopathy: Retinopathy is damage to the retina which in this case is caused by the impact of diabetes on the vascular system around the eyes. This leads to blurred vision and can lead to blindness although symptoms may not appear for some time. The progression of retinopathy can be slowed or stopped if detected early enough, but it cannot be cured. Blindness can be prevented in 90% of those at risk.

Diabetic Digital Retinal Photography: This involves digital photography of the retina followed by a two- or three- stage image grading process to identify the changes of sight-threatening diabetic retinopathy in the retina. Currently, patients with diabetes are screened at least once per year – this is not an invasive process.

The Health Problem:

Diabetes affects about 24,000 individuals in Cornwall (5.3% of adult population), and figures are similar elsewhere in the south west. In 2007 prevalence of diabetes in Devon and Cornwall was 3.59% and 3.80% respectively. Recent figures for the prevalence of retinopathy within people with diabetes in the UK is unclear. A recent study conducted in Sweden suggests a 41% prevalence in people with Type 1 diabetes and 28% prevalence in those with Type 2 diabetes[1], of these sight-threatening retinopathy was detected in 12% of Type 1 and 5% of Type 2.

Every person > 12 years old with diabetes is invited for annual digital retinal photography. However, only a small proportion of these require laser treatment or other ophthalmological intervention. With increasing numbers of patients with diabetes, retinal services across the country are under increased strain to maintain the standards required of an effective screening programme. The DoH reported that in the period 2008-2009, 21% of diabetics in the south west did not receive retinal screening, and over a third of PCTs in the south west are not meeting national standards of screening 80% of diabetics using a digital camera; it is a similar picture across the UK[2] (this is partly due to lack of resources). There is potential therefore, to improve the cost effectiveness of the retinal screening programme by reducing the proportion of tests that lead to no action there by increasing capacity for follow-up appointments for those already diagnosed with retinopathy.

The numbers of people with diabetes are rising rapidly. Most of these patients

are older, and have type 2 diabetes, and most are well controlled in terms of blood glucose and blood pressure. Therefore, many – although not all – are at a lower risk of progression to diabetic retinopathy. Since many of these patients exhibit no change in the retinal photos from one year to the next, there maybe a case for a flexible screening interval, rather than annual intervals. For example, if most people with type 2 diabetes and stable retinopathy, and satisfactory control of risk factors for progressive retinopathy could reduce their screening interval, increased surveillance might be offered to the higher risk individuals who more often develop blindness. Blindness remains a devastating complication, both medically and economically, for young adults with type 1 diabetes. The approach proposed here might be a more effective use of resources, and allow some savings on the costs of screening everyone with diabetes every year irrespective of need.

It may be hypothesised that the number of eye screening tests amongst those with type 2 diabetes (92% of all diabetes) could potentially be reduced by at least 25%, without any detrimental impact on the detection of progression of retinopathy (though this should be considered alongside the proportion who do not receive screening). Diabetes UK report that the lifetime cost of dealing with diabetic retinopathy is £237,000 per person, 50% of these costs are due to productivity losses as a result of the condition.

Guidelines:

A 2008 update to the NICE guidelines on Type 2 Diabetes (2002) recommend that eye screening should be repeated annually, and that quality assured digital retinal photography should be used.

The DoH National Service Framework (2002) recommended that by 2006, a minimum of 80% of people with diabetes should be offered screening for the early detection (and treatment if needed) of diabetic retinopathy as part of a systematic
programme that meets national standards, rising to 100% coverage of those at risk of retinopathy by the end of 2007.

NHS Priority:

Regional

SW SHA Priorities framework 2008-11

- Fully implement the standards set out in the National Service Framework for Diabetes
- Improve the productivity of clinical activity by at least £700million per annum by 2014 (achieve 50% of this by March 2011)

QIPP - long term conditions groups are set up to show savings and performance efficiencies in areas of long term conditions management. Whilst diabetes prevalence will continue to increase, there will be an increased need for extra resources to be found unless efficiency can be improved. QIPP also has an aim to reduce procedures of limited clinical benefit.

Local
- Cornwall & IOS PCT- Minimum Guarantee 'Achieve financial balance (productivity & efficiency)

Existing Research:

Published research
One systematic review on the economic evidence of diabetic retinopathy screening was identified[8]. This review suggests that systematic screening for diabetic retinopathy is cost-effective in terms of sight years preserved compared with no screening and that there are cost-effective ways to make screening accessible for hard to reach populations. However, it also suggests that further research is needed to address the issue of optimal screening interval as variation in compliance rates, age of onset of diabetes, glycaemic control and screening sensitivities are important sources of uncertainty in relation to this issue and influence the cost-effectiveness of the screening programmes. As well as this review there have been three recent studies in this area in the last two years[3,7,9] (as well as at least three previously[4-6]). Of the three most recent studies two are primary research studies and one used modelling methodology. Results from each of the studies suggest that there is potential to extend the diabetic retinal screening interval for those patients who currently exhibit no form of retinopathy and who are at low risk of developing retinopathy quickly. However, screening interval decisions may need to take into account individual variance and confounders[9].

Ongoing research
One relevant ongoing study was identified which investigates the question 'Can the annual screening interval for diabetic retinopathy be extended in patients with no retinopathy?'. This study is being conducted in Wales and began in 2009 and they hope to involve 20,600 participants (author was contact for details but contact has not been forthcoming).

Feasibility:
HTA have just identified screening intervals in diabetic retinopathy as a subject for outline research applications. The question appears clinically pertinent in the field of diabetes, given the huge and rising numbers of people now requiring screening, and could be researchable by PCMD and its clinical partners. The diabetic retinal screening manager (Stephen Matthews) and the clinical Lead (opthalmologist, Mr Nicholas Wilson-Holt) in Cornwall have both expressed an interest in this research proposal and may therefore be interested in acting as a potential site if the question gets taken forward.

References:
1) Heintz et al (2010) Diabetologia 'Prevalence and healthcare costs of diabetic retinopathy: a population based register study in Sweden'

AIMS/HYPOTHESIS: The aim of the present study was to estimate the prevalence and healthcare costs of diabetic retinopathy (DR). METHODS: This population-based study included all residents (n = 251,386) in the catchment area of the eye clinic of Linkoping University Hospital, Sweden. Among patients with diabetes (n = 12,026), those with and without DR were identified through register data from both the Care Data Warehouse in Ostergotland, an administrative healthcare register, and the Swedish National Diabetes Register. Healthcare cost data were elicited by record linkage of these two registers to data for the year 2008 in the Cost Per Patient Database developed by Ostergotland County Council. RESULTS: The prevalence of any DR was 41.8% (95% CI 38.9-44.6) for patients with type 1 diabetes and 27.9% (27.1-28.7) for patients with type 2 diabetes. Sight-threatening DR was present in 12.1% (10.2-14.0) and 5.0% (4.6-5.4) of the type 1 and type 2 diabetes populations respectively. The annual average healthcare cost of any DR was euro72 (euro53-91). Stratified into background retinopathy, proliferative DR, maculopathy, and the last two conditions combined, the costs were euro26 (euro10-42), euro257 (euro155-359), euro216 (euro113-318) and euro433 (euro232-635) respectively. The annual cost for DR was euro106,000 per 100,000 inhabitants. CONCLUSIONS: This study presents new information on the prevalence and costs of DR. Approximately one-third of patients with diabetes have some form of DR. Average healthcare costs increase considerably with the severity of DR, which suggests that preventing progression of DR may lower healthcare costs.

2) Nagi, D. K., C. Gosden, et al. (2009). "A national survey of the current state of screening services for diabetic retinopathy: ABCD-diabetes UK survey of specialist diabetes services 2006." Diabet Med **26**(12): 1301-5.
The main aims were to ascertain the progress made in the implementation of retinal screening services and to explore any barriers or difficulties faced by the programmes. The survey focused on all the essential elements for retinal screening, including assessment and treatment of screen-positive cases. Eighty-five per cent of screening programmes have a coordinated screening service and 73% of these felt that they have made significant progress. Eighty-five per cent of screening units use 'call and recall' for appointments and 73.5% of programmes follow the National Screening Committee (NSC) guidance. Although many units worked closely with ophthalmology, further assessment and management of screen-positive patients was a cause for concern. The fast-track referral system, to ensure timely and appropriate care, has been difficult to engineer by several programmes. This is demonstrated by 48% of programmes having waiting lists for patients identified as needing further assessment and treatment for retinopathy. Ophthalmology service for people with diabetic retinopathy was provided by a dedicated ophthalmologist in 89.4% of the programmes. Sixty-six per cent of the programmes reported inadequate resources to sustain a high-quality service, while 26% highlighted the lack of infrastructure and 49% lacked information technology (IT) support. In conclusion, progress has been made towards establishing a national screening programme for diabetic retinopathy by

individual screening units, with a number of programmes providing a structured retinal screening service. However, programmes face difficulties with resource allocation and compliance with Quality Assurance (QA) standards, especially those which apply to ophthalmology and IT support. Screening programmes need to be resourced adequately to ensure comprehensive coverage and compliance with QA.

3) Soto-Pedre, E., M. C. Hernaez-Ortega, et al. (2009). "Six-year retrospective follow-up study of safe screening intervals for sight-threatening retinopathy in patients with diabetes mellitus." J Diabetes Sci Technol **3**(4): 812-8.
BACKGROUND: We estimate safe screening intervals for sight-threatening diabetic retinopathy (STDR). METHODS: A 6-year retrospective follow-up study to review screening results of two cohorts of patients with diabetes mellitus (DM) was conducted; a cohort free of diabetic retinopathy (DR) and a cohort with mild nonproliferative diabetic retinopathy (NPDR) at baseline. Patients had been screened by means of a nonmydriatic retinal camera. Baseline age, sex, and diabetes characteristics were also collected. Statistical analysis was based on life-table method of risk estimation. RESULTS: A total of 286 patients with DM free of DR and 144 patients with mild NPDR at baseline were included in the study. For patients free of DR, the probability of remaining free of STDR was 97% (95% confidence interval [CI] 94-99%) at the end of the fourth year. In this cohort of patients, those with type 2 DM were more likely to progress to STDR than those who had type 1 DM ($p < .01$). For patients with mild NPDR, the probability of remaining free of STDR dropped to 94% (95% CI 88-97%) at the end of the second year, and it was still 100% at the end of the second year for those with a glycated hemoglobin level < or =7.5% at baseline ($p < .05$). CONCLUSIONS: Screening at a 3-4 year interval for diabetes patients free of DR is safe because of their low risk of developing STDR. Patients with mild NPDR require screening at a 1 year interval, or at a 2 year interval with good metabolic control.

4) Vijan, S., T. P. Hofer, et al. (2000). "Cost-utility analysis of screening intervals for diabetic retinopathy in patients with type 2 diabetes mellitus." JAMA **283**(7): 889-96.
CONTEXT: Annual eye screening for patients with diabetes mellitus is frequently proposed as a measure of quality of care. However, the benefit of annual vs less frequent screening intervals has not been well evaluated, especially for low-risk patients. OBJECTIVE: To examine the marginal cost-effectiveness of various screening intervals for eye disease in patients with type 2 diabetes, stratified by age and level of glycemic control. DESIGN: Markov cost-effectiveness model. SETTING AND PARTICIPANTS: Hypothetical patients based on the US population of diabetic patients older than 40 years from the Third National Health and Nutrition Examination Survey. MAIN OUTCOME MEASURES: Patient time spent blind, quality-adjusted life-years (QALYs), and costs of annual vs less frequent screening compared by age and level of hemoglobin A1c. RESULTS: Retinal screening in patients with type 2 diabetes is an effective intervention;

however, the risk reduction varies dramatically by age and level of glycemic control. On average, a high-risk patient who is aged 45 years and has a hemoglobin A1c level of 11% gains 21 days of sight when screened annually as opposed to every third year, while a low-risk patient who is aged 65 years and has a hemoglobin A1c level of 7% gains an average of 3 days of sight. The marginal cost-effectiveness of screening annually vs every other year also varies; patients in the high-risk group cost an additional $40530 per QALY gained, while those in the low-risk group cost an additional $211570 per QALY gained. In the US population, retinal screening annually vs every other year for patients with type 2 diabetes costs $107510 per QALY gained, while screening every other year vs every third year costs $49760 per QALY gained. CONCLUSIONS: Annual retinal screening for all patients with type 2 diabetes without previously detected retinopathy may not be warranted on the basis of cost-effectiveness, and tailoring recommendations to individual circumstances may be preferable. Organizations evaluating quality of care should consider costs and benefits carefully before setting universal standards.

5) Davies, R., P. Roderick, et al. (2002). "The evaluation of screening policies for diabetic retinopathy using simulation." Diabet Med **19**(9): 762-70.
AIMS: To develop a model for evaluating screening strategies and to use it to determine the cost effectiveness of varying the screening method and the screening interval. METHODS: A discrete event simulation was designed, validated and run for a population of 500000. Most parameters were derived from peer-reviewed publications. RESULTS: Standard methods of screening save up to 50% of the potential sight years lost. They give up to 85% of the sight years saved by an idealized gold standard programme using mydriatic seven-field photography reported by an ophthalmologist. The mobile camera, used for annual screening and 6-month follow-up after the detection of background retinopathy, had an estimated cost of pound 449200 per year with pound 2842 per sight year saved. It is less efficient to screen Type 2, rather than Type 1 diabetes mellitus patients, but they contributed to almost three-quarters of the sight years saved. CONCLUSIONS: The model can evaluate screening intervals and methods on a national or health authority basis. Results indicate that it appears more cost effective to continue to screen outside an ophthalmology clinic, until treatment is needed. Programmes with annual screening, and more frequent screening for those with background retinopathy, are robust to realistic fluctuations in compliance and screening sensitivity.

6) Younis, N., D. M. Broadbent, et al. (2003). "Incidence of sight-threatening retinopathy in patients with type 2 diabetes in the Liverpool Diabetic Eye Study: a cohort study." Lancet **361**(9353): 195-200.
BACKGROUND: Incidence data on which to base targets and protocols for screening for sight-threatening diabetic retinopathy are few. We aimed to investigate yearly and cumulative incidence of any retinopathy, maculopathy, and sight-threatening diabetic retinopathy in patients with type 2 diabetes in an established systematic programme and to calculate optimum screening intervals

according to retinopathy grade at baseline. METHODS: We investigated all patients with type 2 diabetes registered with enrolled general practices (except those who were attending an ophthalmologist) who had retinopathy data available at baseline and at least one further screening event. To screen patients, we used non-stereoscopic three-field mydriatic photography and modified Wisconsin grading. Sight-threatening diabetic retinopathy was defined as moderate preproliferative retinopathy or worse, or clinically significant maculopathy in either or both eyes. FINDINGS: Results were obtained from 20 570 screening events. Yearly incidence of sight-threatening diabetic retinopathy in patients without retinopathy at baseline was 0.3% (95% CI 0.1-0.5) in the first year, rising to 1.8% (1.2-2.5) in the fifth year; cumulative incidence at 5 years was 3.9% (2.8-5.0). Rates of progression to sight-threatening diabetic retinopathy in year 1 by baseline status were: background 5.0% (3.5-6.5), and mild preproliferative 15% (10.2-19.8). For a 95% probability of remaining free of sight-threatening diabetic retinopathy, mean screening intervals by baseline status were: no retinopathy 5.4 years (95% CI 4.7-6.3), background 1.0 years (0.7-1.3), and mild preproliferative 0.3 years (0.2-0.5). INTERPRETATION: A 3-year screening interval could be safely adopted for patients with no retinopathy, but yearly or more frequent screening is needed for patients with higher grades of retinopathy.

7) Misra, A., M. O. Bachmann, et al. (2009). "Trends in yield and effects of screening intervals during 17 years of a large UK community-based diabetic retinopathy screening programme." Diabet Med **26**(10): 1040-7.
AIMS: To describe changes in risk profiles and yield in a screening programme and to investigate relationships between retinopathy prevalence, screening interval and risk factors. METHODS: We analysed a population of predominantly Type 2 diabetic patients, managed in general practice, and screened between 1990 and 2006, with up to 17 years' follow-up and up to 14 screening episodes each. We investigated associations between referable or sight-threatening diabetic retinopathy (STDR), screening interval and frequency of repeated screening, whilst adjusting for age, duration and treatment of diabetes, hypertension treatment and period. RESULTS: Of 63 622 screening episodes among 20 788 people, 16 094 (25%) identified any retinopathy, 3136 (4.9%) identified referable retinopathy and 384 (0.60%) identified STDR. The prevalence of screening-detected STDR decreased by 91%, from 1.7% in 1991-1993 to 0.16% in 2006. The prevalence of referable retinopathy increased from 2.0% in 1991-1993 to 6.7% in 1998-2001, then decreased to 4.7% in 2006. Compared with screening intervals of 12-18 months, screening intervals of 19-24 months were not associated with increased risk of referable retinopathy [adjusted odds ratio 0.93, 94% confidence interval (CI) 0.82-1.05], but screening intervals of more than 24 months were associated with increased risk (odds ratio 1.56, 95% CI 1.41-1.75). Screening intervals of < 12 months were associated with high risks of referable retinopathy and STDR. CONCLUSIONS: Over time the risk of late diagnosis of STDR decreased, possibly attributable to earlier diagnosis of less

severe retinopathy, decreasing risk factors and systematic screening. Screening intervals of up to 24 months should be considered for lower risk patients.

8) Jones, S. and R. T. Edwards (2010). "Diabetic retinopathy screening: a systematic review of the economic evidence." Diabet Med **27**(3): 249-56.
This paper systematically reviews the published literature on the economic evidence of diabetic retinopathy screening. Twenty-nine electronic databases were searched for studies published between 1998 and 2008. Internet searches were carried out and reference lists of key studies were hand searched for relevant articles. The key search terms used were 'diabetic retinopathy', 'screening', 'economic' and 'cost'. The search identified 416 papers of which 21 fulfilled the inclusion criteria, comprising nine cost-effectiveness studies, one cost analysis, one cost-minimization analysis, four cost-utility analyses and six reviews. Eleven of the included studies used economic modelling techniques and/or computer simulation to assess screening strategies. To date, the economic evaluation literature on diabetic retinopathy screening has focused on four key questions: the overall cost-effectiveness of ophthalmic care; the cost-effectiveness of systematic vs. opportunistic screening; how screening should be organized and delivered; and how often people should be screened. Systematic screening for diabetic retinopathy is cost-effective in terms of sight years preserved compared with no screening. Digital photography with telemedicine links has the potential to deliver cost-effective, accessible screening to rural, remote and hard-to-reach populations. Variation in compliance rates, age of onset of diabetes, glycaemic control and screening sensitivities influence the cost-effectiveness of screening programmes and are important sources of uncertainty in relation to the issue of optimal screening intervals. There is controversy in relation to the economic evidence on optimal screening intervals. Further research is needed to address the issue of optimal screening interval, the opportunities for targeted screening to reflect relative risk and the effect of different screening intervals on attendance or compliance by patients.

9) Mehlsen, J., M. Erlandsen, et al. (2010). "Individualized optimization of the screening interval for diabetic retinopathy: a new model." Acta Ophthalmol.
Abstract. Introduction: Screening programmes for diabetic retinopathy follow guidelines that ensure that vision-threatening complications are detected even when the disease progression is fast. This implies that patients with slow disease progression will be recommended examinations more often than needed. Method: On the basis of previously defined individual risk factors, multiple logistic regression was used to develop a model for individualized determination of the screening interval in diabetic retinopathy, while adjusting for the fact that in the data set used to construct the model, the screening interval acted as a time-dependent confounder. The model was tested on 1372 patients screened during year 2000. Results: It was possible to construct a model for calculating the optimal screening interval in low-risk patients in whom the recommended screening interval was longer than 12 months. When the probability of reaching a treatment requiring event was set to 0.5%, none of the patients reached a

treatment end-point in a validation of the model, and the screening interval was prolonged on average 2.9 times in patients with type 1 diabetes and 1.2 times in those with type 2 diabetes. The predictive strength of the model depended on the number of variables included. Conclusions: It is possible to construct a model for optimizing the examination interval during screening for diabetic retinopathy in low-risk patients. The model can potentially be improved by identifying unknown or unmeasured confounders and by including knowledge of risk factors before and after the examination on the basis of which the prediction is made.