Institution: University of Liverpool		
Unit of Assessment: UoA1 Clinical Medicine		
Title of case study: Global implementation of diabetic retinopathy screening		
Period when the underpinning research was undertaken: 2000 - 2019		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): Professor Simon Harding	**Role(s) (e.g. job title):** Chair in Clinical Ophthalmology and Head, Department of Eye and Vision Science (DEVS), Institute of Life Course and Medical Sciences	**Period(s) employed by submitting HEI:** Since 1986
Period when the claimed impact occurred: August 2013 to present		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

The Liverpool-devised method of diabetic retinopathy (DR) eye screening, as used in England's national programme, has been adopted internationally. It has been introduced and implemented as national programmes in Australia, Hong Kong, Singapore and Northern Ireland. In these countries, all diabetic patients are now eligible for eye screening, and sight-correcting/-saving treatment as needed. Bangladesh trialled the approach recently, and recommended implementation. In Europe, guided by the Liverpool Declaration, most countries have improved DR screening provision.

Liverpool's work on switching from annual to longer intervals, for more affordable DR screening, has widely informed programmes. In the UK, our research was pivotal to a UK National Screening Committee recommendation (2016) to the national programme to lengthen DR screening to 2-yearly for low risk people. Liverpool's unique evidence on personalised variable-interval risk-based screening (2019, 2020), is guiding NHS implementation in England. Scotland adopted the recommendation for extended screening, which is planned in other countries.

2. Underpinning research

Diabetic retinopathy (DR) is a disease in which the retina is damaged by high and abnormally varying levels of blood sugar associated with diabetes. It is present in 40% of diabetes mellitus (DM) patients and is associated with significant morbidity. Worldwide it is the leading cause of blindness among working age people. When identified in its early- to mid- stages, DR can be treated effectively by laser and other interventions.

The Liverpool Diabetic Eye Study is a long-running collaborative research programme led by Liverpool's Departments of Eye and Vision Science (Harding, Broadbent) and Diabetes and Endocrinology (Vora), working to promote early DR detection. Tackling the issue among the local Liverpool population (initial work through to 2001), the group developed and tested a model of systematic screening for DR comprising two-field mydriatic digital photography using fundus cameras, captured and graded by purpose-trained technicians. This Liverpool approach showed superior performance to the previous standard, and cost-effectiveness was demonstrated (Younis et al, 2003; James et al, 2000 (3.1, 3.2)).

Between 2000 and 2003, our preliminary research was furthered and refined, with a view to UK-wide implementation. Key contributions included: a grading method for severity of DR as captured by retinal photography; technician-training resources; planning advice and work on screening intervals (Harding et al, 2003 (3.2)). This work defined the DR screening approach that was introduced for the UK from 2003, with full implementation by 2008. Since

2011, UoL research has continued to refine elements of the programme, through input into the English National Diabetic Eye Screening Programme (ENDESP) grading, training and research committees, and the national association of retinal screeners.

Our work on screening intervals has demonstrated increasing importance in recent years. This addresses how frequently patients should be screened, for optimal balancing of health gains, programme costs and patient experience. The Group's work showed that a 3-year screening interval should be considered in patients with no DR (Younis et al, 2003 (3.1)). From 2011, Liverpool has extended work on this theme, to explore a personalised approach. The Group's RCT evidence has shown that an "individualised variable-interval risk-based" approach, calculated through complex mathematical modelling, is safe, effective and offers substantial improvements in cost-effectiveness (Harding et al, 2017, 2020 (3.4, 3.5).

A unique and complementary strand of this work, completed through interdisciplinary collaboration with Liverpool social scientists (led by Prof. M. Gabbay), has examined DM patient acceptability/behaviour of changes to screening intervals (Byrne et al, 2020, (3.6)). This research is filling a significant evidence gap, crucial to policy decisions about implementing more cost-effective screening for large groups of the DM population.

3. References to the research

3.1. **Younis N**, Broadbent DM, Vora JP, Harding SP. Incidence of sight threatening retinopathy in type 2 diabetes in a systematic screening programme. ***Lancet* 2003**;361:195-200. https://doi.org/10.1016/S0140-6736(03)12267-2

3.2. **James M**, Turner DA, Broadbent DM, Vora J, Harding SP. Cost-effectiveness analysis of screening for sight threatening diabetic eye disease. ***British Medical Journal*, 2000**;320:1627-31. https://doi.org/10.1136/bmj.320.7250.1627

3.3. **Harding S**., Greenwood R., Aldington, S., Gibson, J., Owens, D., Taylor, R., . . . Dis, D. R. G.. Grading and disease management in national screening for diabetic retinopathy in England and Wales. ***Diabetic Medicine***, 2003;20(12), 965-971. https://doi.org/10.1111/j.1464-5491.2003.01077.x

3.4. **Harding, S. P.**, Eleuteri, A., Fisher, A. C., **Broadbent, D. M**., **Garcia-Finana, M**., Cheyne, C. P., . . . Seddon, D. Individualised variable interval risk-based screening for sight threatening diabetic retinopathy – the Liverpool Risk Calculation Engine. ***Diabetologia***, **2017**;60(11), 2174-2182. https://doi.org/10.1007/s00125-017-4386-0

3.5. **Broadbent DM,** Wang A, Cheyne CP, James M, Lathe J, Stratton IM, Roberts J, Moitt T, **Vora JP**, **Gabbay M**, **Garcia-Finana M**, **Harding SP** and the ISDR Study Group. Safety and cost-effectiveness of individualised screening for diabetic retinopathy: the ISDR open-label, equivalence RCT. ***Diabetologia*** 64, 56–69 (2021) (first published 4 November 2020). https://doi.org/10.1007/s00125-020-05313-2

3.6. **Byrne P,** Thetford C, **Gabbay M**, Clarke P, Doncaster E, Harding SP and the ISDR Study Group. Personalising screening of sight-threatening diabetic retinopathy - qualitative evidence to inform effective implementation. ***BMC Public Health* 2020**;20:881. https://doi.org/10.1186/s12889-020-08974-1

4. Details of the impact

Diabetic retinopathy (DR) is the leading cause of vision loss among working age people. It is a key complication of diabetes, affecting 1 in 3 persons with diabetes mellitus (DM). With DM increasing globally (WHO estimates 463,000,000 in 2019 rising to 578,000,000 by 2030), DR is a global medical issue; vision loss is of enormous consequence for the individual, family and society, with significant economic costs. WHO estimate that 64,000,000 people in the European Region have diabetes of whom 950,000 have vision impairment or blindness due to diabetes.

Liverpool is at the forefront of addressing this challenge, through its efforts towards advancement of early detection of DR. Early detection halves the risk of blindness. The

ENDESP was an early outcome of our work (REF2014 impact case). How that programme has rewritten the story of DR in England has now received international recognition, being highlighted in the WHO World Vision Report 2019 (5.1). Since that ground-breaking work the impact of our research has expanded importantly as follows:

Implementation of national DR screening programmes internationally, following the England model

The England model has now been fully implemented in a further three countries, with the success of the England case highlighted in the rationales for their implementation. Australia announced its national screening programme in July 2018, with coverage of 1,200,000 people (5.2). Only half that number were covered by previous provisions. Initial government investment of AUD1,000,000 (07-2018) for year one, was matched by Specsavers, who also pledged a further AUD4,000,000 (07-2018). Hong Kong and Singapore progressed to full implementation of their respective national, systematic photographic screening programmes, by expanding to further polyclinics and GPs (5.3, 5.4). The Singapore Integrated Diabetic Retinopathy Programme (SiDRP) covers 600,000 people, and achieves a saving of USD173 (12-2016) per patient compared to the previous approach; 92% of patients found SiDRP more convenient than the previous model (5.4). Harding worked directly with policymakers and clinicians to inform implementation.

Beyond these countries, trialling of systematic DR screening was undertaken in Bangladesh, as a feasibility study, inspired by the England programme and followed the England model, e.g. using Harding's grading system. In total, 49,264 patients were screened (5.5). Sight-saving surgery (vitrectomy) was performed in 309 patients; a further 3077 treatments for correction of visual impairment were undertaken. A recommendation for urgent upscaling of the service was made.

In Europe, countries have made significant progress with DR screening implementation, working towards the Liverpool Declaration 2005 (a target of 80% DM population eye screening). The latest meeting (Manchester 2016 (5.6)) of the group of European policymakers and clinicians that Harding established and convenes (www.drscreening.eu, 2005), for sharing best practice and disseminating latest research findings, gathered 40 national representatives. The progress report highlights include: a) Hungary's introduction in 2013 of a Diabetic Retinopathy Screening Programme, covering 13 areas of the country and involving 4 universities. Negotiations with the Ministry of Health for a fully-funded national programme are in progress; b) in Republic of Moldova results of a rapid review of DR reported in 2014, in which 3877 people were examined, using Harding's grading system (5.6). Harding, and other members of the Liverpool Group support such efforts through international conferences (EASDec, EASD, DUK), personal contact, visits, meetings and workshops.

WHO Europe, in 2020, commissioned Harding and Broadbent to the writing group of 'Diabetes Eye Screening – A Guide for Europe', and a situational analysis on screening (5.7). These provide key information for policymakers in 56 countries in the WHO European Region. Liverpool publications are cited in national DR guidelines in Finland (2014), Netherlands (2017), Sweden (2018) and Spain (2019). The Liverpool work on cost-effectiveness is cited in guidelines for Portugal (2015).

Further impact in the UK: the Northern Ireland 'internal control'

Whereas systematic DR screening was taken-up by the other three home nations in the 2000s, Northern Ireland did not implement the approach. By 2010, DR in England and Wales had fallen to the 4th most common cause of blindness in working age people, and since then the rate of sight loss caused by DR has continued to fall from 3.5 per 100,000 to 3.1 in England. In Northern Ireland, DR remains the most common cause of vision loss.

Observing this trend and contrast, Northern Ireland is quickly moving to closer compliance with the recommended UK approach, following Liverpool's underpinning research. Full adoption of national, systematic screening for DR began in 2016. The 2016/17 programme report (5.8) points to the large amount of previously undetected DR, now being identified through alignment with the England model: of 45,845 people attending in the first year of systematic screening, 946 (2.06%) were referred urgently for treatment of advanced disease. That rate is 5 times higher than in same period in Liverpool. This has continued in the last 2 years.

Extending screening intervals for affordable delivery of DR systematic screening

Liverpool's research also played an important role in guiding a UK National Screening Committee recommendation (19 January 2016) that extended intervals from annual to 2-yearly for low-risk patients should be implemented (5.9). Scotland adopted the recommendation (5.10), as has NHS England (23 September 2020) (5.10). Liverpool's robust data from 2020 (3.5) adds to this, showing that individualised variable-interval risk-based screening, as developed by us (the next step beyond simple 2-yearly screening for low risk patients), would release GBP23,900,000 from screening if implemented in England alone.

This very substantial improvement in cost-effectiveness will allow repurposing of funds to low income and hard to reach groups and help to mitigate against the increasing prevalence of diabetes. For society as a whole this is an even higher impact at GBP31,900,000.

Liverpool's unique work on patients' behaviour within an extended interval scenario is part of the evidence base that the UK National Screening Committee notes will prove decisive to the England decision (5.9). Extended intervals or variable intervals, with support of Liverpool research on that theme, have been introduced in Armenia, Austria, Denmark, Finland, Germany, Israel, Netherlands, Norway, Scotland, Spain, Sweden (5.7*).*

5. Sources to corroborate the impact

5.1. WHO, World Report on Vision, October **2019**, Box 3.2 p.56. Available at: https://www.who.int/publications/i/item/world-report-on-vision

5.2. Australia introduce national diabetes eye screening programme after England model and noting UK success: https://www.vision2020australia.org.au/news/2018-07-13/peak-health-groups-welcome-government-funding-for-new-national-diabetes-eye-screening-program-to-prevent-blindness/ *(see yellow highlight p.2).*

5.3. Hong Kong programme:
Lian JX, Gangwani RA, McGhee SM, et al. Systematic screening for diabetic retinopathy (DR) in Hong Kong: prevalence of DR and visual impairment among diabetic population British Journal of Ophthalmology **2016**;100:151-155. *(see e.g. references to England National Screening Programme in 'Introduction' and 'Methods' sections).*

5.4. Singapore programme: The Singapore Integrated Diabetic Retinopathy Programme: Achievements and Future Challenges. Available at: https://www.nmrc.gov.sg/docs/default-source/events-library/diabetes-and-metabolic---ecosse-lamoureux.pdf2019 *(re. reference to the England NHS Programme (UoL-derived) see p.17/36, for USD173 figure p.31/36).*

5.5. Bangladesh: Trial of England approach
Muqit, M. M. K., Kourgialis, N., Jackson-de Graffenried, M., Talukder, Z., Khetran, E. R., Rahman, A., Chan, W. O., Chowdury, F. A., Nag, D., Ahmad, J., & Friedman, D. S. Trends in Diabetic Retinopathy, Visual Acuity, and Treatment Outcomes for Patients Living With

Diabetes in a Fundus Photograph-Based Diabetic Retinopathy Screening Program in Bangladesh. **2019**. *JAMA Network Open*, *2*(11), e1916285. https://doi.org/10.1001/jamanetworkopen.2019.16285 *(re. following after England approach see e.g. p.3 'Training of Graders' section and 'Methods' noting use of and referencing the England classification system (derived from Harding 3.3).*

5.6. www.drscreening.eu (**2017**). Screening for Diabetic Retinopathy in Europe - Progress Since 2011. National Representatives Meeting. Manchester. Report of Meeting. Available from www.drscreening2005.org.uk/manchester_2016.html *(see respective country summaries).*

5.7. WHO Regional Office for Europe. Diabetic retinopathy screening – a short guide. Copenhagen: WHO Regional Office for Europe, 2020 *(key Liverpool research outputs are cited 2000 (3.1), 2003 (3.2), 2020 (3.5), and elements of the Liverpool work are showcased, for example, the mobile van DR screening approach, Figure 8);* Diabetic retinopathy screening in the WHO European Region: current situation. Copenhagen: WHO Regional Office for Europe, 2021 *(evidence of extended and variable intervals, subsection "Frequency of screening", page 6).*

5.8. Northern Ireland Diabetic Eye Screening Programme, 2016/17 Annual Report. Available at: https://www.publichealth.hscni.net/publications/diabetic-eye-screening-programme-annual-report-2016-2017. 45,845 figure is from p.16.
and Northern Ireland RQIA Review of the Diabetic Retinopathy Screening Programme 2015 https://www.eyescreening.org.uk/userFiles/File/DiabeticEyeJournal/DEJ13part1.pdf (*cites at page 4 England classification system (derived from Harding 3.3).* 2017 adoption of UK National Standards).

5.9. UK National Screening Committee (2016) The UK NSC recommendation on Diabetic Retinopathy screening in adults. Available from: https://legacyscreening.phe.org.uk/diabeticretinopathy
UK NSC DES Review (Appendices 1-4*) (Appendix 3, p.5 - cites Harding's work as support for extending intervals for low-risk groups (reference '4' is the Lancet paper, Younis et al, 2003); Appendix 4, p.41 - notes the University of Liverpool research into the impact of changing intervals on uptake, and, by implication, how this will clarify their assessment of cost-effectiveness under different uptake scenarios).*

5.10. NHS adoption of 2-year interval screening for lowest risk:
Scotland, Diabetic Retinopathy Screening Service, Annual Report 2018/19 *(extending intervals cited in Executive Summary and Appendix H p.42).* Available at: https://www.ndrs.scot.nhs.uk/wp-content/uploads/2019/11/DRS-Annual-Report-2018.pdf

England, 'Diabetic eye screening intervals extended for people at lowest risk' (23 September 2020), states "the gap between routine diabetic eye screening (DES) tests has been extended for those at lowest risk". Available at: https://www.gov.uk/government/publications/diabetic-eye-screening-longer-intervals-for-people-at-lowest-risk.