Standard threshold laser versus subthreshold micropulse laser for adults with diabetic macular oedema: the DIAMONDS non-inferiority RCT

Noemi Lois,[1*] Christina Campbell,[2] Norman Waugh,[3] Augusto Azuara-Blanco,[4] Mandy Maredza,[3] Hema Mistry,[5] Danny McAuley,[1,6] Nachiketa Acharya,[7] Tariq M Aslam,[8,9] Clare Bailey,[10] Victor Chong,[11] Louise Downey,[12] Haralabos Eleftheriadis,[13] Samia Fatum,[14] Sheena George,[15] Faruque Ghanchi,[16] Markus Groppe,[17] Robin Hamilton,[18] Geeta Menon,[19] Ahmed Saad,[20,21] Sobha Sivaprasad,[18] Marianne Shiew,[22] David H Steel,[23,24] James Stephen Talks,[25] Paul Doherty,[2] Clíona McDowell[2] and Mike Clarke[2,4] on behalf of the DIAMONDS study group

[1]The Wellcome-Wolfson Institute for Experimental Medicine, Queen's University Belfast, Belfast, UK
[2]Northern Ireland Clinical Trials Unit (NICTU), Belfast, UK
[3]Division of Health Sciences, University of Warwick, Coventry, UK
[4]Centre for Public Health, Queens University, Belfast, UK
[5]Warwick Clinical Trials Unit, University of Warwick, Coventry, UK
[6]The Regional Intensive Care Unit, Royal Victoria Hospital, Belfast, UK
[7]Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK
[8]The Manchester Academic Health Science Centre, Manchester Royal Eye Hospital, Manchester, UK
[9]Division of Pharmacy and Optometry, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK
[10]Bristol Eye Hospital, Bristol, UK
[11]Royal Free Hospital NHS Foundation Trust, London, UK
[12]Hull and East Yorkshire Hospital, Hull and East Yorkshire NHS Trust, Hull, UK
[13]King's College Hospital NHS Foundation Trust, London, UK
[14]John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[15]Hillingdon Hospitals NHS Foundation Trust, London, UK
[16]Bradford Teaching Hospitals NHS Trust, Bradford, UK

[17]Stoke Mandeville Hospital, Buckinghamshire NHS Trust, Aylesbury, UK
[18]National Institute for Health and Care Research Moorfields Biomedical Research Centre, Moorfields Eye Hospital NHS Foundation Trust, London, UK
[19]Frimley Park Hospital NHS Foundation Trust, Camberley, UK
[20]James Cook University Hospital, South Tees Hospitals NHS Foundation Trust, Middlesbrough, UK
[21]Zagazig University, Zagazig, Egypt
[22]Hinchingbrooke Hospital North West Anglia NHS Trust, Huntingdon, UK
[23]Sunderland Eye Infirmary, Sunderland, UK
[24]Bioscience Institute, Newcastle University, Newcastle upon Tyne, UK
[25]Newcastle Eye Centre, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK

*Corresponding author n.lois@qub.ac.uk

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/SZKI2484.

Primary conflicts of interest: Augusto Azuara-Blanco is a member of the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Prioritisation Committee B (2020 to present). Danny McAuley is the NIHR/Medical Research Council Efficacy and Mechanism Evaluation (EME) Programme Director and member of the EME Strategy Advisory Committee, EME Funding Committee member and EME Funding Committee Remit and Competitiveness Sub-Group (2019–present). Danny McAuley is also a former member of the NIHR/UK Research and Innovation COVID-19 reviewing committee (2020–20) and the HTA General Committee (2016–18) and Commissioning Committees (2013–16). Clare Bailey has been an ad-hoc advisor for Bayer AG (Leverkusen, Germany), Novartis AG (Basel, Switzerland), Alimera Sciences (Alpharetta, GA, USA), Roche (F. Hoffmann-La Roche Ltd, Basel, Switzerland), Boehringer Ingelheim (Boehringer Ingelheim International GmbH, Ingelheim am rhein, Germany) and Janssen (Janssen Global Services, LLC, Beerse, Belgium). Victor Chong is an employee of Janssen but his role in this study is unrelated to his employment with Janssen and, thus, the content of this manuscript is not endorsed by Janssen. He has also received speaker fees from Quantel Medical (Cournon-d'Auvergne, France). Louise Downey has performed advisory board work for Bayer, Novartis, Allergan (now part of AbbVie Inc., North Chicago, IL, USA), Alimera Sciences and Alcon (Geneva, Switzerland). She has also received travel grants from Bayer, Novartis and Allergan, and research studies sponsored by Bayer, Novartis, AbbVie, Roche and Alimera Sciences. Haralabos Eleftheriadis has been an ad hoc advisor for Novartis and Bayer, received educational travel grants from Novartis, Bayer and Allergan and has given a remunerated talk for IRIDEX (IRIDEX Corporation, Mountain View, CA, USA). Faruque Ghanchi has had advisory roles for Alimera Sciences, Allergan, Apellis (Apellis Pharmaceuticals Inc., Watham, MA, USA), Bayer, Boehringer Ingleheim, Novartis and Roche, and received travel grants from Allergan, Novartis and Roche. Robin Hamilton has received research grants from Novartis and Bayer, and received travel expenses from and attended advisory board meetings of Novartis, Bayer, Roche, Allergan and Ellex (Mawson Lakes, SA, Australia). Sobha Sivaprasad has received research grants and travel fees from and attended advisory board meetings of Novartis, Allergan, Bayer, Optos (Optos Inc. Marlborough, MA, USA), Boehringer Ingleheim, Heidelberg Engineering (Heidelberg Engineering GmbH, Heidelberg, Germany), Roche, Oxurion (Oxurion NV, Leuven, Belgium), Oculis (Oculis SA, Lausanne, Switzerland) and Biogen (Biogen Inc., Cambridge, MA, USA). Sobha Sivaprasad was a former NIHR HTA Commissioning Board member (2017–2021), Chair of the Scientific Advisory Committee of Sight UK (May 2018–present), Scientific Advisory Committee Member of Retina UK (August 2019–present), Trustee of the Macular Society (August 2019–present), as well as Chair

of the Scientific Committee of the UK Royal College of Ophthalmologists (May 2020–present). David H Steel acted as a consultant to Alcon, Gyroscope (Gyroscope Therapeutics Limited, London, UK) BVI® (Waltham, MA, USA) and Roche, and received research funding from Bayer, Alcon, Gyroscope, DORC (Dutch Ophthalmic Research Center B.V., Zuidland, the Netherlands) and Boehringer Ingelheim. James S Talks has received travel grants from Bayer and research support from Novartis. Mike Clarke is a member of the HTA Prioritisation Committee B Methods Group (2019 to present) and a former member of the HTA General Committee (2016–19). None of the authors has any commercial interest in any of the diagnostic or treatment devices used in this trial, including the lasers.

Published December 2022
DOI: 10.3310/SZKI2484

Scientific summary

DIAMONDS non-inferiority RCT

Health Technology Assessment 2022; Vol. 26: No. 50
DOI: 10.3310/SZKI2484

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Diabetic macular oedema (DMO) is a leading cause of central visual loss in people with diabetes. In DMO fluid, and at times lipid (fat) and blood, leak from blood vessels and build up in the macula, the central area of the retina responsible for giving central sight. As a result, damage to the macula occurs and loss of vision ensues.

The Early Treatment Diabetic Retinopathy Study (ETDRS) was a landmark randomised clinical trial (RCT) conducted in the 1980s that demonstrated the benefit of standard threshold macular laser (SL) for preventing sight loss in people with clinically significant diabetic macular oedema (CSMO). In the past decade, anti-vascular endothelial growth factor (anti-VEGF) therapy has been introduced to treat DMO. However, the National Institute for Health and Care Excellence (NICE) recommends macular laser to treat centre-involving DMO with a central retinal subfield thickness (CRT) of < 400 µm on optical coherence tomography (OCT), as for this group macular laser is as clinically effective as anti-VEGF therapy but more cost-effective.

When SL is applied to the retina it produces a burn, killing retinal cells, including those of the pigmented layer of the retina, called retinal pigment epithelium (RPE). It is believed that the effect of the SL is at least partly related to the stimulation of RPE cells around the laser burn. Laser burns to the retina may be associated with adverse events. In more recent years, subthreshold micropulse laser (SML) has been introduced to treat a variety of macular diseases, including DMO. In contrast to SL, SML does not 'burn' the retina. After its application there is no anatomical change observed; because of this, there were uncertainties about its potential effectiveness.

Objectives

To determine the clinical effectiveness, safety and cost-effectiveness of SML compared with SL for the treatment of DMO suitable for macular laser treatment.

Methods

Design

A pragmatic, allocation-concealed, double-masked (participants and outcome assessors), multicentre, randomised, non-inferiority clinical trial.

Participants

Adults (aged ≥ 18 years), with type 1 or 2 diabetes and centre-involving DMO suitable for laser and with a CRT of < 400 µm, as determined with spectral domain optical coherence tomography (SD-OCT), and a visual acuity of > 24 ETDRS letters (Snellen equivalent $> 20/320$) in one or both eyes. If both eyes were eligible then both received the same type of laser but one was designated as the 'study eye', which was the eye with the better best-corrected visual acuity (BCVA) at randomisation or, if BCVA was the same in both eyes, the eye with the lesser CRT.

Setting

Hospital eye services ($n = 16$) in the UK.

Interventions

Participants were randomised 1:1 to receive SML (577 nm) or SL [e.g. using an argon, frequency-doubled neodymium-doped yttrium aluminium garnet (Nd:YAG) 532 nm laser]. Laser treatment could be repeated as needed using the laser allocated at randomisation. Rescue treatment with anti-VEGF therapy/steroids was allowed if vision dropped by 10 ETDRS letters and/or CRT increased to > 400 µm.

Outcomes

The primary outcome was the mean change in BCVA in the study eye from baseline to month 24. The non-inferiority margin was set at 5 ETDRS letters. This margin was chosen as it is accepted that a visual change of this size is not clinically relevant.

Secondary outcomes included the mean change from baseline to month 24 in binocular BCVA; CRT; mean deviation (MD) of the Humphrey 10–2 visual field in the study eye; percentage of people meeting driving standards; and EuroQol-5 Dimensions, five-level version (EQ-5D-5L), National Eye Institute Visual Function Questionnaire – 25 (NEI-VFQ-25) and Vision and Quality of life Index (VisQoL) scores. Other secondary outcomes were the cost per quality-adjusted life-years (QALYs) gained, adverse effects, number of laser treatments done and additional treatments used.

Statistical analysis

Although the DIAMONDS (DIAbetic Macular Oedema aNd Diode Subthreshold micropulse laser) trial was a non-inferiority trial, it was also powered to demonstrate equivalence and superiority (if this were to exist) of SML when compared with SL. With a maximal permitted difference of $\pm$ 5 ETDRS letters, it was estimated that 113 participants per group would be required at month 24 to determine statistically significant differences in the primary outcome between laser groups. This sample size would also detect differences between groups on important secondary outcomes, including changes in CRT and vision-related quality of life. Considering a 15% attrition rate, 266 participants were planned to be recruited.

The primary statistical analysis was per protocol, as this is preferred for non-inferiority and equivalence trials given that intention to treat (ITT) increases the risk of a type I error, although ITT analysis was also undertaken. ITT analyses were used for all secondary outcomes because the aim was to assess superiority for these. The change in BCVA from baseline to month 24 was compared between laser groups using an independent two-sample *t*-test. The primary outcome was adjusted for baseline BCVA score, baseline CRT and minimisation factors/covariates including centre, BCVA at presentation and previous use of macula laser or anti-VEGF therapy in the study eye using an analysis of covariance (ANCOVA) model. The primary analysis was based on available data (with no imputation of missing values) from the study eye only, and statistical significance on two-sided tests and a p -value of < 0.05 with no adjustment for multiple testing. A secondary analysis was performed on the subset of participants with both eyes included in the trial, including study eye as a random effect within the mixed model. Sensitivity analyses were undertaken to assess the impact of missing data by imputing extreme values (i.e. lowest and highest) and the last observation carried forward; the impact of including patients who were not treatment naive (i.e. excluding those who had had previous laser for DMO or previous anti-VEGF therapy for DMO or proliferative diabetic retinopathy in the study eye); the impact of including patients who had previously undergone cataract surgery (i.e. pseudophakic at baseline) in the study eye; and the impact of using month-24 data collected outside $\pm$ 14 days of the due date. The primary outcome was analysed according to the pre-specified subgroups of centre; distance BCVA at baseline of $\geq$ 69 ETDRS letters [Snellen equivalent of $\geq$ 20/40; logarithm of the minimum angle of resolution (log-MAR) $\geq$ 0.3] or 24–68 ETDRS letters (Snellen equivalent of $\leq$ 20/50; log-MAR 0.4–1.2); and previous use of macular laser or anti-VEGF therapy in the study eye. The analysis was performed by including the corresponding interaction terms in the regression model using stricter criteria for statistical significance ($p \leq 0.01$).

Copyright © 2022 Lois *et al.* This work was produced by Lois *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health and Social Care. This is an Open Access publication distributed under the terms of the Creative Commons Attribution CC BY 4.0 licence, which permits unrestricted use, distribution, reproduction and adaption in any medium and for any purpose provided that it is properly attributed. See: https://creativecommons.org/licenses/by/4.0/. For attribution the title, original author(s), the publication source – NIHR Journals Library, and the DOI of the publication must be cited.

Side effects and use of additional treatments were analysed using logistic regression models, adjusted for minimisation covariates. Secondary measures of visual function, anatomical outcomes and number of treatments required were analysed using linear regression models adjusted for baseline BCVA score and minimisation variables. 'Driving ability' (i.e. meeting standards for driving) was analysed using a logistic regression model adjusted for baseline BCVA and minimisation variables.

For the health economic evaluation, data on resource use from the perspective of the NHS and Personal Social Services were collected. Outcomes included health-related (EQ-5D-5L scores) and vision-related quality of life (NEI-VFQ-25 and VisQoL scores). The economic evaluation took the form of a cost–utility analysis, expressed in terms of cost per QALY gained.

Results

A total of 266 participants, 133 allocated to each laser group, were recruited. One patient in the SL group withdrew consent for their data to be used; thus 265 participants were included in the analysis. There were 231 participants (87%), 116 (87%) and 115 (86%) in the SML and SL groups, respectively, with primary outcome data at month 24.

The mean age of participants was 62.2 [standard deviation (SD) 10.3] years. Most were male (70%), with a mean known duration of DMO of 2.5 (SD 4.5) years. Most participants were white (77%), had type 2 diabetes (85%) and were overweight, obese or morbidly obese (88%), with a mean glycated haemoglobin type A1c (HbA_{1c}) value of 69.5 mmol/mol (SD 18.4 mmol/mol) [8.5% (SD 3.8%)]. Some (24%) had received previous laser treatment [median number of sessions 1 (interquartile range 1–2); with a mean length of time since last session of 4.2 years (SD 4.8 years)]. The mean CRT was 329.2 µm (SD 37.3 µm) and the mean BCVA was 80.2 ETDRS letters (SD 8.4 ETDRS letters). Both treatment groups were comparable regarding baseline characteristics.

Clinical and cost-effectiveness results

Primary outcome

Subthreshold micropulse laser was deemed not only non-inferior but also equivalent to SL as the difference between treatment groups in the primary outcome [−1.98 ETDRS letters, 95% confidence interval (CI) −3.9 to −0.04 ETDRS letters] was within both the upper and lower margins of the permitted maximum difference (−5.0 to 5.0 ETDRS letters). The difference in the primary outcome between treatment groups of −1.98 ETDRS letters favouring SL was statistically significant ($p = 0.046$) but not clinically relevant. A further analysis adjusted for BCVA, CRT and minimisation covariates showed no statistically significant difference between treatment groups with a mean change in BCVA in the study eye from baseline to month 24 of −2.36 ETDRS letters [standard error (SE) 0.67 ETDRS letters] in the SML group and −0.53 ETDRS letters (SE 0.67 ETDRS letters) in the SL group (mean difference −1.84 ETDRS letters, 95% CI −3.72 to 0.047 ETDRS letters; $p = 0.056$). Results from the ITT analysis followed those of the per protocol analysis.

Secondary outcomes

There were no statistically significant differences in most secondary outcomes measured, including mean change in binocular BCVA (mean difference 0.32 ETDRS letters, 95% CI −0.99 to 1.64 ETDRS letters; $p = 0.63$), CRT (mean difference −0.64 µm, 95% CI −14.25 µm to 12.98 µm; $p = 0.93$), MD of the 10–2 Humphrey visual field (0.39 dB, 95% CI −0.23 dB to 1.02 dB; $p = 0.21$), percentage of people meeting driving standards (percentage point difference 1.6%, 95% CI −25.3% to 28.5%, $p = 0.91$), side effects (risk ratio 0.28, 95% CI 0.06 to 1.34, $p = 0.11$), and number of people requiring additional treatments (percentage point difference −2.8%, 95% CI −13.1% to 7.5%, $p = 0.59$). The VisQoL analysis

showed no statistically significant differences in utility scores between treatment groups for each of the VisQoL dimensions and at each of the follow-up time points. The NEI-VFQ-25 subscales showed similar results.

The number of laser treatments performed was slightly higher in the SML group (mean difference 0.48 treatments, 95% CI 0.18 to 0.79 treatments; $p = 0.002$). This difference was driven by a small number of participants who required a larger number of laser treatments in the SML group. Specifically, 13 participants required six or seven laser treatments in the SML group, compared with only two needing this number of treatments in the SL group. Anti-VEGF therapy was more common in the SL group, but the difference was not statistically significant.

No statistically significant differences were observed in EQ-5D-5L scores between treatment groups with a non-significant difference of 0.008 QALYs gained. The mean total costs of care between baseline to month 24 month post-randomisation were slightly lower in the SML group than the SL group, but with overlapping 95% CIs (£897.83 vs. £1125.66, respectively, bootstrap 95% CI −£848.02 to £392.35). Costs of laser treatment and outpatient visits were similar, but the SL group had higher costs for anti-VEGF therapy, mainly because five patients received more than 10 injections. Therefore, average costs for SML were lower and the average benefits were marginally higher, but neither costs nor benefits were statistically significantly different from those for SL.

Conclusions

Subthreshold micropulse laser was deemed non-inferior and clinically equivalent to SL for the treatment of DMO with CRT of < 400 µm. A higher number of laser sessions (by 0.48 sessions, on average) was required when SML was used.

Implications for health care

The DIAMONDS trial, a methodologically robust and adequately powered RCT, showed that SL and SML have equivalent efficacy for the treatment of people with DMO with a CRT of < 400 µm and, thus, either can be used to treat those affected by this complication of diabetic retinopathy.

In the DIAMONDS trial, the great majority of participants were overweight, obese or morbidly obese, with poor metabolic control. Tackling these major risk factors is essential to prevent DMO and other complications of diabetes. Despite this, undergoing macular laser, an inexpensive form of therapy, enabled most participants to maintain good vision for at least two years. Thus, macular laser treatment should continue to be offered to people with DMO with a CRT of < 400 µm, as recommended by NICE.

Recommendations for research

Given that SML does not burn the retina, and, thus, carries no risk of burning the fovea, and considering the increasing demand for DMO treatments in the NHS, it may be possible to instruct allied non-medical staff to undertake this therapy. Hospital optometrists and nurses are already administering anti-VEGF therapy to people with DMO in the NHS. Proof-of-concept studies evaluating the feasibility of training non-medical professionals, and the efficacy and safety of macular laser performed by non-medical professionals, would seem advisable.

The DIAMONDS trial showed that macular laser achieved good outcomes in a very metabolically uncontrolled patient cohort of people with a CRT ≤ 400 µm and reduced vision.

Copyright © 2022 Lois *et al.* This work was produced by Lois *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health and Social Care. This is an Open Access publication distributed under the terms of the Creative Commons Attribution CC BY 4.0 licence, which permits unrestricted use, distribution, reproduction and adaption in any medium and for any purpose provided that it is properly attributed. See: https://creativecommons.org/licenses/by/4.0/. For attribution the title, original author(s), the publication source – NIHR Journals Library, and the DOI of the publication must be cited.

A trial in people with DMO with a CRT of ≥ 400 µm, comparing anti-VEGF therapy alone with anti-VEGF therapy and macular laser applied only when the CRT has decreased to < 400 µm following anti-VEGF injections, would be of value. It could reduce the number of anti-VEGF injections required and, subsequently, the cost of the treatment and the risk and inconvenience of eye injections to patients. This trial has not yet been conducted.

A trial comparing the clinical effectiveness, safety, and cost-effectiveness of SML compared with anti-VEGF therapy could also be considered.

Trial registration

This trial is registered as EudraCT 2015-001940-12, ISRCTN17742985 and NCT03690050.

Funding

This project was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 26, No. 50. See the NIHR Journals Library website for further project information.

Health Technology Assessment

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.014

Launched in 1997, *Health Technology Assessment* (HTA) has an impact factor of 4.014 and is ranked 27th (out of 108 titles) in the 'Health Care Sciences & Services' category of the Clarivate 2021 Journal Citation Reports (Science Edition). It is also indexed by MEDLINE, CINAHL (EBSCO Information Services, Ipswich, MA, USA), Embase (Elsevier, Amsterdam, the Netherlands), NCBI Bookshelf, DOAJ, Europe PMC, the Cochrane Library (John Wiley & Sons, Inc., Hoboken, NJ, USA), INAHTA, the British Nursing Index (ProQuest LLC, Ann Arbor, MI, USA), Ulrichsweb™ (ProQuest LLC, Ann Arbor, MI, USA) and the Science Citation Index Expanded™ (Clarivate™, Philadelphia, PA, USA).

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta.

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

Health Technology Assessment (HTA) research is undertaken where some evidence already exists to show that a technology can be effective and this needs to be compared to the current standard intervention to see which works best. Research can evaluate any intervention used in the treatment, prevention or diagnosis of disease, provided the study outcomes lead to findings that have the potential to be of direct benefit to NHS patients. Technologies in this context mean any method used to promote health; prevent and treat disease; and improve rehabilitation or long-term care. They are not confined to new drugs and include any intervention used in the treatment, prevention or diagnosis of disease.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 13/142/04. The contractual start date was in April 2016. The draft report began editorial review in January 2022 and was accepted for publication in May 2022. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health and Care Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, the HTA programme or the Department of Health and Social Care.

Copyright © 2022 Lois *et al.* This work was produced by Lois *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health and Social Care. This is an Open Access publication distributed under the terms of the Creative Commons Attribution CC BY 4.0 licence, which permits unrestricted use, distribution, reproduction and adaption in any medium and for any purpose provided that it is properly attributed. See: https://creativecommons.org/licenses/by/4.0/. For attribution the title, original author(s), the publication source – NIHR Journals Library, and the DOI of the publication must be cited.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).

NIHR Journals Library Editor-in-Chief

Dr Cat Chatfield Director of Health Services Research UK

NIHR Journals Library Editors

Professor John Powell Consultant Clinical Adviser, National Institute for Health and Care Excellence (NICE), UK, and Professor of Digital Health Care, Nuffield Department of Primary Care Health Sciences, University of Oxford, UK

Professor Andrée Le May Chair of NIHR Journals Library Editorial Group (HSDR, PGfAR, PHR journals) and Editor-in-Chief of HSDR, PGfAR, PHR journals

Professor Matthias Beck Professor of Management, Cork University Business School, Department of Management and Marketing, University College Cork, Ireland

Dr Tessa Crilly Director, Crystal Blue Consulting Ltd, UK

Dr Eugenia Cronin Consultant in Public Health, Delta Public Health Consulting Ltd, UK

Dr Peter Davidson Interim Chair of HTA and EME Editorial Board. Consultant Advisor, School of Healthcare Enterprise and Innovation, University of Southampton, UK

Ms Tara Lamont Senior Adviser, School of Healthcare Enterprise and Innovation, University of Southampton, UK

Dr Catriona McDaid Reader in Trials, Department of Health Sciences, University of York, UK

Professor William McGuire Professor of Child Health, Hull York Medical School, University of York, UK

Professor Geoffrey Meads Emeritus Professor of Wellbeing Research, University of Winchester, UK

Professor James Raftery Professor of Health Technology Assessment, School of Healthcare Enterprise and Innovation, University of Southampton, UK

Dr Rob Riemsma Consultant Advisor, School of Healthcare Enterprise and Innovation, University of Southampton, UK

Professor Helen Roberts Professor of Child Health Research, Child and Adolescent Mental Health, Palliative Care and Paediatrics Unit, Population Policy and Practice Programme, UCL Great Ormond Street Institute of Child Health, London, UK

Professor Jonathan Ross Professor of Sexual Health and HIV, University Hospital Birmingham, UK

Professor Helen Snooks Professor of Health Services Research, Institute of Life Science, College of Medicine, Swansea University, UK

Professor Ken Stein Professor of Public Health, University of Exeter Medical School, UK

Professor Jim Thornton Professor of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, University of Nottingham, UK

Please visit the website for a list of editors: www.journalslibrary.nihr.ac.uk/about/editors

Editorial contact: journals.library@nihr.ac.uk