

Placebo comparator group selection and use in surgical trials: the ASPIRE project including expert workshop

David J Beard,^{1*} Marion K Campbell,²
Jane M Blazeby,³ Andrew J Carr,¹ Charles Weijer,⁴
Brian H Cuthbertson,⁵ Rachelle Buchbinder,⁶
Thomas Pinkney,⁷ Felicity L Bishop,⁸
Jonathan Pugh,⁹ Sian Cousins,³ Ian Harris,¹⁰
L Stefan Lohmander,¹¹ Natalie Blencowe,³
Katie Gillies,² Pascal Probst,¹² Carol Brennan,¹³
Andrew Cook,¹⁴ Dair Farrar-Hockley,¹³
Julian Savulescu,⁹ Richard Huxtable,³
Amar Rangan,^{1,15} Irene Tracey,¹⁶
Peter Brocklehurst,¹⁷ Manuela L Ferreira,¹⁸
Jon Nicholl,¹⁹ Barnaby C Reeves,²⁰
Freddie Hamdy,²¹ Samuel CS Rowley,²²
Naomi Lee²³ and Jonathan A Cook¹

¹Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK

²Health Services Research Unit, University of Aberdeen, Aberdeen, UK

³Centre for Surgical Research, NIHR Bristol and Weston Biomedical Research Centre, Population Health Sciences, University of Bristol, Bristol, UK

⁴Departments of Medicine, Epidemiology and Biostatistics, and Philosophy, Western University, London, ON, Canada

⁵Department of Critical Care Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada

⁶Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia

⁷Academic Department of Surgery, University of Birmingham, Queen Elizabeth Hospital Birmingham, Birmingham, UK

⁸Faculty of Environmental and Life Sciences, University of Southampton, Southampton, UK

⁹The Oxford Uehiro Centre for Practical Ethics, University of Oxford, Oxford, UK

¹⁰Faculty of Medicine, South Western Sydney Clinical School, University of New South Wales, Sydney, NSW, Australia

¹¹Department of Clinical Sciences Lund, Orthopedics, Clinical Epidemiology Unit, Lund University, Lund, Sweden

- ¹²Department of General, Visceral and Transplantation Surgery, University of Heidelberg, Heidelberg, Germany
- ¹³Patient representative, Oxford, UK
- ¹⁴Wessex Institute, University of Southampton, University Hospital Southampton NHS Foundation Trust, Southampton, UK
- ¹⁵Department of Health Sciences, University of York, York, UK
- ¹⁶Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford, UK
- ¹⁷Birmingham Clinical Trials Unit, Institute of Applied Health Research, University of Birmingham, Birmingham, UK
- ¹⁸Faculty of Medicine and Health, Institute of Bone and Joint Research, Northern Clinical School, The University of Sydney, Sydney, NSW, Australia
- ¹⁹School of Health and Related Research, University of Sheffield, Sheffield, UK
- ²⁰Clinical Trials Evaluation Unit Bristol Medical School, University of Bristol, Bristol Royal Infirmary, Bristol, UK
- ²¹Nuffield Department of Surgical Sciences, University of Oxford, John Radcliffe Hospital, Oxford, UK
- ²²Medical Research Council, London, UK
- ²³Editorial Department, *The Lancet*, London, UK

*Corresponding author david.beard@ndorms.ox.ac.uk

Declared competing interests of authors: David J Beard reports grants from the National Institute for Health Research (NIHR) and Versus Arthritis (Chesterfield, UK) outside the submitted work. Marion K Campbell reports former NIHR Clinical Trials Unit (CTU) Standing Advisory Committee membership (2014–17). Jane M Blazeby reports current NIHR CTU Standing Advisory Committee membership (2015–19). Andrew J Carr reports grants from NIHR and the Wellcome Trust (London, UK) outside the submitted work, has a patent issued with BioPatch and is a member of Novartis Musculoskeletal Advisory Board and UK Research and Innovation Advanced Pain Discovery programme (January 2020–present). Charles Weijer reports personal fees from Cardialen, Inc. (Minneapolis, MN, USA), Eli Lilly & Company (Indianapolis IN, USA) and RTI International (Research Triangle, Park, NC, USA) outside the submitted work. Thomas Pinkney reports Health Technology Assessment (HTA) Clinical Evaluation and Trials Committee membership (November 2017–present). Jonathan Pugh reports grants from Wellcome Trust during the conduct of the study. Katie Gillies reports HTA Clinical Evaluation and Trials Committee membership (November 2020–present). Andrew Cook reports membership of the Efficacy and Mechanism Evaluation (EME) Funding Committee, EME Funding Committee Sub-Group Remit & Comp Check, HTA Prioritisation Committee B Methods Group (former) (October 2019–present), PHR Prioritisation Group (former) and Prioritisation Strategy Group (2006–9). Andrew Cook also declares membership of the secretariat of various committees for the HTA, EME and PHR programmes (2006–present). Richard Huxtable reports grants from NIHR during the conduct of the study. In addition, Richard Huxtable reports grants from the Wellcome Trust, the European Union, the Engineering and Physical Sciences Research Council (Swindon, UK), the Elizabeth Blackwell Institute for Health Research (Bristol, UK) and the National Research Foundation of Korea (Daejeon, Republic of Korea), and personal fees from the Wellcome Trust, outside the submitted work. Natalie Blencowe reports trainee membership to the HTA Clinical Evaluation and Trials Committee (January–December 2020). Amar Rangan reports grants from NIHR, Orthopaedic Research UK (London, UK) and Horizon 2020, and grants and personal fees from DePuy Synthes (Raynham, MA, USA) outside the submitted work. Irene Tracey is a member of a Medical Research Council (MRC) Council (2017–present), a member of the Guarantors of Brain (London, UK) (2016–present), is a trustee of MQ: Transforming Mental Health (London, UK) (2016–present) and is a Lundbeck Brain Prize Committee Member (2015–present). Peter Brocklehurst reports personal fees from MRC and AG Biotest (Dreieich, Germany) and grants

from MRC, Wellcome Trust and NIHR outside the submitted work. In addition, Peter Brocklehurst reports clinical trial units funded by NIHR, and HTA Efficient Study Designs Board (former) (2016) and HTA Maternal, Neonatal and Child Health Panel (former) membership (2014–18). Manuela L Ferreira reports grants from the National Health and Medical Research Council of Australia (Canberra, ACT, Australia) during the conduct of the study. Barnaby C Reeves reports former membership of the Health Technology Assessment Commissioning Board (January 2012–31 March 2016) and the Health Technology Assessment Efficient Study Designs Board (October–December 2014). He also reports current membership of the Health Technology Assessment Interventional Procedures Committee B Methods Group and Systematic Reviews Programme Advisory Group (Systematic Reviews National Institute for Health Research Cochrane Incentive Awards and Systematic Review Advisory Group). Freddie Hamdy reports being an editor-in-chief of the *BJU International* journal (John Wiley & Sons, Inc., Hoboken, NJ, USA) (February 2020–present) and Advisory Board Member for Intuitive (Sunnyvale, CA, USA) (January 2020–present). Samuel CS Rowley reports personal fees from MRC and UK Research and Innovation during the conduct of the study. Jonathan A Cook reports Methodology State-of-the-Art Workshops (MSAW) grant funding from the MRC and NIHR for the project. Naomi Lee reports an annual salary from Elsevier (Amsterdam, the Netherlands)/*The Lancet*, during the conduct of the study.

Published September 2021

DOI: 10.3310/hta25530

Scientific summary

The ASPIRE study including expert workshop

Health Technology Assessment 2021; Vol. 25: No. 53

DOI: 10.3310/hta25530

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

Scientific summary

Background

Placebo comparisons are increasingly being considered for randomised trials assessing the efficacy of complex interventions, including surgery. A placebo control is a complex type of comparison group and, although powerful, presents many challenges in a surgical setting.

Aim

The aim of this workshop and report was to extract and summarise the current knowledge on the use and appropriateness of placebo controls for surgical trials. It was intended to provide advice for researchers, clinicians, patients and funders when considering or designing a placebo surgical study or involvement in such a study.

Structure and content of report

This report outlines the background to placebo control for surgery and what a placebo surgical control entails and provides a summary of the up-to-date understanding of the placebo phenomenon in the context of surgery. Placebo controls for surgical evaluation are not always acceptable, nor are they always the most desirable or optimal option. The nature of surgical placebo is explored in terms of ethics arguments and regulatory requirements. The design of a placebo surgical control is also complex and consideration is given to this with clear guidelines on process. As placebo surgery is not without risk, methods are outlined on how to identify and mitigate risk for participants in placebo-controlled surgical trials. Last, attention is given as to how the results of such trials should be interpreted.

Findings

The use of a placebo control for the evaluation of a surgical procedure is justified provided that a strong scientific and ethics rationale can be provided. Feasibility work is recommended to explore the value of placebo randomised controlled trial (RCT) design and optimise the conduct. The workshop and ensuing publications provide an outline for best practice in the form of the ASPIRE (Applying Surgical Placebo in Randomised Evaluations) guidelines.

Conclusions

The guidelines are advised reading for those considering the use of a placebo control in a surgical RCT.

Outputs

The workshop has, to date, produced three substantial publications in high-impact journals, and the content of each helps to guide placebo control comparison and trial design in surgical trials [Beard DJ, Campbell MK, Blazeby JM, Carr AJ, Weijer C, Cuthbertson BH, *et al.* Considerations and methods for placebo controls in surgical trials (ASPIRE guidelines). *Lancet* 2020;**395**:828–38; Cousins S, Blencowe NS, Tsang C, Chalmers K, Mardanpour A, Carr AJ, *et al.* Optimizing the design of invasive placebo

interventions in randomized controlled trials. *Br J Surg* 2020;**107**:1114–22; and Cousins S, Blencowe NS, Tsang C, Lorenc A, Chalmers K, Carr AJ, *et al.* Reporting of key methodological issues in placebo-controlled trials of surgery needs improvement: a systematic review. *J Clin Epidemiol* 2020;**119**:109–16].

Funding

Funded by the Medical Research Council UK and the National Institute for Health Research as part of the Medical Research Council–National Institute for Health Research Methodology Research programme.

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.014

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, the Cochrane Library and Clarivate Analytics Science Citation Index.

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. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

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 or, commissioned/managed through the MRC–NIHR Methodology Research Programme (MRP), 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

This issue of the Health Technology Assessment journal series contains a project commissioned by the MRC–NIHR Methodology Research Programme (MRP). MRP aims to improve efficiency, quality and impact across the entire spectrum of biomedical and health-related research. In addition to the MRC and NIHR funding partners, MRP takes into account the needs of other stakeholders including the devolved administrations, industry R&D, and regulatory/advisory agencies and other public bodies. MRP supports investigator-led methodology research from across the UK that maximises benefits for researchers, patients and the general population – improving the methods available to ensure health research, decisions and policy are built on the best possible evidence.

To improve availability and uptake of methodological innovation, MRC and NIHR jointly supported a series of workshops to develop guidance in specified areas of methodological controversy or uncertainty (Methodology State-of-the-Art Workshop Programme). Workshops were commissioned by open calls for applications led by UK-based researchers. Workshop outputs are incorporated into this report, and MRC and NIHR endorse the methodological recommendations as state-of-the-art guidance at time of publication.

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 under a MRC–NIHR partnership. 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 MRC, NETSCC, 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 MRC, NETSCC, the HTA programme or the Department of Health and Social Care.

Copyright © 2021 Beard *et al.* This work was produced by Beard *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 adaptation 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

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

NIHR Journals Library Editors

Professor John Powell Chair of HTA and EME Editorial Board and Editor-in-Chief of HTA and EME journals. 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 (HS&DR, PGfAR, PHR journals) and Editor-in-Chief of HS&DR, 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 Senior Scientific Advisor, Wessex Institute, UK

Dr Peter Davidson Consultant Advisor, Wessex Institute, University of Southampton, UK

Ms Tara Lamont Senior Scientific Adviser (Evidence Use), Wessex Institute, University of Southampton, UK

Dr Catriona McDaid Senior Research Fellow, York Trials Unit, 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, Wessex Institute, Faculty of Medicine, University of Southampton, UK

Dr Rob Riemsma Reviews Manager, Kleijnen Systematic Reviews Ltd, UK

Professor Helen Roberts Professor of Child Health Research, UCL Great Ormond Street Institute of Child Health, 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