Exercise to prevent shoulder problems after breast cancer surgery: the PROSPER RCT

Julie Bruce,[1*] Bruno Mazuquin,[1] Pankaj Mistry,[1] Sophie Rees,[1] Alastair Canaway,[1] Anower Hossain,[1,2] Esther Williamson,[3,4] Emma J Padfield,[1] Ranjit Lall,[1] Helen Richmond,[5] Loraine Chowdhury,[1] Clare Lait,[6] Stavros Petrou,[1,7] Katie Booth,[1] Sarah E Lamb,[4] Raghavan Vidya[8] and Alastair M Thompson[9] on behalf of PROSPER Study Group

[1]Warwick Clinical Trials Unit, Division of Health Sciences, University of Warwick, Coventry, UK
[2]Institute of Statistical Research and Training (ISRT), University of Dhaka, Dhaka, Bangladesh
[3]Centre for Rehabilitation Research, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK
[4]College of Medicine and Health, University of Exeter, Exeter, UK
[5]Primary Healthcare Research Unit, Faculty of Medicine, Memorial University of Newfoundland, St John's, NL, Canada
[6]Gloucestershire Care Services NHS Trust, Gloucester, UK
[7]Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK
[8]Royal Wolverhampton NHS Trust, Wolverhampton, UK
[9]Baylor College of Medicine, Houston, TX, USA

*Corresponding author julie.bruce@warwick.ac.uk

Declared competing interests of authors: Julie Bruce is co-investigator on current research grants from the National Institute for Health Research (NIHR) (NIHR202618, HTA 17/129/02, NIHR128311, NIHR132046, HTA 131407 and HTA 10/42/02), British Heart Foundation (PG/19/22/34203) and Diabetes UK (17/0005690), and is supported by the NIHR Research Capability Funding via University Hospitals Coventry and Warwickshire NHS Trust. Clare Lait provides private physiotherapy to cancer patients outside the submitted work. Sarah E Lamb reports grants from the NIHR Health Technology Assessment (HTA) programme during the conduct of the study and was a member of the following boards: HTA Additional Capacity Funding Board (2012–15); HTA Clinical Trials Board (2010–15), HTA End of Life Care and Add on Studies (2015), HTA Funding Boards Policy Group (formerly Clinical Studies Group) (2010–15), HTA Post-board funding teleconference (policy group members to attend) (2010–15), HTA Maternal, Neonatal and Child Health Methods Group (2013–15), HTA Primary Care Themed Call Board (2013–14), HTA Prioritisation Group (2010–15) and NIHR Clinical Trials Unit Standing Advisory Committee (2012–16).

Published February 2022
DOI: 10.3310/JKNZ2003

Scientific summary

The PROSPER RCT

Health Technology Assessment 2022; Vol. 26: No. 15
DOI: 10.3310/JKNZ2003

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

Scientific summary

Background

Breast cancer is the most common cause of cancer in women in the UK. More women now survive for longer than was the case previously, with two-thirds of women living for 20 years beyond their diagnosis. Treatments usually involve surgery to the breast and axilla, with or without radiotherapy, chemotherapy and hormone treatment. These treatments can affect the muscles, nerves and lymphatic system in the upper limb, especially around the shoulder joint, resulting in musculoskeletal problems that can persist for many years. It is important to identify prevention strategies to promote recovery and return to usual activities after cancer treatment. We report an experimental study testing the hypothesis that an exercise programme for women at higher risk of developing shoulder and upper limb disability after breast cancer surgery is clinically effective and cost-effective compared with usual NHS care.

Aims and objectives

The aim was to undertake a multicentre, pragmatic randomised controlled trial (RCT) to determine the clinical effectiveness and cost-effectiveness of two interventions for women undergoing breast cancer treatment. We investigated whether or not an early, structured exercise programme, supported by a physiotherapist, was clinically effective and cost-effective compared with best practice usual care for women at high risk of developing shoulder problems after breast cancer treatment in terms of the outcomes of upper limb function, complications and quality of life.

The study objectives were to:

- develop and refine a complex intervention of physiotherapy-led exercise, incorporating behavioural strategies, for women at risk of developing musculoskeletal problems after breast cancer treatment
- assess the acceptability of the structured exercise programme and outcome measures
- optimise participant recruitment and refine trial processes during a 6-month internal pilot phase
- use findings from the internal pilot phase to undertake a definitive, full RCT in UK NHS breast cancer centres.

A health economic analysis and qualitative substudy were embedded in the trial. Qualitative research was undertaken throughout to inform intervention development and gain insight into the experiences of both women and physiotherapists taking part in the trial interventions.

Methods

Study design and setting

The study was a two-arm, pragmatic RCT with an embedded qualitative study and a parallel economic analysis. The unit of randomisation was the participant. The setting for the trial was secondary care in breast cancer centres in NHS trusts across England.

Participants

The participants were women aged $\geq$ 18 years who were newly diagnosed with histologically confirmed invasive or non-invasive breast cancer and were scheduled for surgical excision. Women considered at high risk of developing shoulder problems after surgery were eligible for invitation to take part in the trial. High risk was defined as planned axillary node clearance (ANC), planned radiotherapy to the axilla or

Copyright © 2022 Bruce *et al.* This work was produced by Bruce *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.

supraclavicular nodes, existing shoulder problems [as per PROSPER (PRevention Of Shoulder ProblEms tRial) criteria], obesity (body mass index $\geq$ 30 kg/m^2), or any subsequent axillary surgery after sentinel lymph node biopsy, or planned radiotherapy to the axilla or supraclavicular nodes within 6 weeks of surgery. Existing shoulder problems included any patient with a history of shoulder surgery, shoulder trauma injury (fracture or shoulder dislocation), frozen shoulder, osteoarthritis or rheumatoid arthritis affecting the shoulder, non-specific shoulder pain, stiffness, or decreased function. We allowed late entry to the trial for those informed postoperatively of the need for axilla/supraclavicular nodes radiotherapy, if the exercise intervention could be commenced within 6 weeks of the primary surgery.

Interventions

After risk screening, eligible patients were invited, recruited and randomised. All trial participants were provided with best practice usual care in the form of written information leaflets recommending exercises after surgery and generic postoperative advice. We used leaflets freely available from the UK charity Breast Cancer Care (London, UK). In addition to usual care, women randomised to the active intervention group were referred to a physiotherapy-led structured exercise programme, comprising between three and six sessions with a trained physiotherapist. The programme was individually tailored, and it progressed over time and incorporated behavioural support strategies to encourage adherence. Treatment was prescribed in accordance with a standardised protocol.

Outcomes

Our primary outcome was upper limb function at 12 months, measured using the Disabilities of the Arm, Shoulder and Hand (DASH) 30-item scale. Secondary outcomes included upper limb function (DASH subscales); acute, chronic and neuropathic pain [numerical rating scale (NRS), Douleur Neuropathique (DN4), Functional Assessment of Cancer Therapy-Breast4 (FACT-B4)]; complications [wound healing, surgical site infection (SSI)]; lymphoedema [Lymphoedema and Breast Cancer Questionnaire (LBCQ)]; health-related quality of life (HRQoL) [Short Form questionnaire-12 items (SF-12), EuroQol-5 Dimensions, five-level version (EQ-5D-5L)]; and health services resource use over 6 and 12 months in women undergoing breast cancer surgery. We captured patient-reported outcomes using participant questionnaires that were administered by post at follow-up time points. Health service use was collected using self-report and routine data from NHS Digital Hospital Episode Statistics (HES). Surgical and treatment-related data were gathered from medical records.

Sample size

The target sample size for the trial was 350 patients, allocated in a 1 : 1 ratio.

Randomisation and allocation sequence generation

The unit of randomisation was the individual participant. Three stratification variables were used: the centre, whether it was the participant's first or repeat surgery, and whether or not the participant had been informed of the need for radiotherapy within 6 weeks of surgery. Randomisation was based on a computer-generated randomisation algorithm held and controlled centrally within Warwick Clinical Trials Unit by an independent programmer.

Blinding

Owing to the nature of the exercise intervention, it was not possible to blind participants or physiotherapists delivering the intervention. Physiotherapists treated participants independently of the oncology team. We undertook data cleaning blind to treatment allocation. Senior members of the research team were blind to practice and treatment allocation for the duration of the trial. Treatment codes were accessed only after data lockdown occurred for analysis. Final statistical analysis was undertaken by a statistician independent of the core trial team.

Statistical analysis

The primary statistical analysis was intention to treat (ITT). We compared the primary outcome of DASH score at 12 months between the usual-care group and the exercise intervention group using an

ordinary linear regression model, as the clustering effect was found to be negligible. A complier-average causal effect (CACE) analysis was also conducted for the primary outcome. In addition, we analysed the change in DASH score from baseline to 6 and 12 months by treatment group. Models were adjusted for age, baseline DASH score, breast surgery, axillary surgery, radiotherapy and chemotherapy. A post hoc sensitivity analysis was undertaken to assess the impact of adjusting for only age, without any other clinical variable, at baseline. Mean changes and 95% confidence intervals (CIs) were plotted graphically to assess change over 12 months. The SF-12 was analysed using similar methods comparing scores between treatment groups.

Health economic analysis

We undertook a within-trial economic evaluation comparing the incremental costs and quality-adjusted life-years (QALYs) over a 12-month period from randomisation. The EQ-5D-5L was used to measure preference-based health-related quality of life over time and QALYs were constructed using the area under the curve approach. An NHS and Personal Social Services perspective was adopted. The health economic analysis used a 12-month time horizon; hence no discounting of costs or outcomes was required. Multiple imputation was used to address missing data and a hierarchical net benefit regression framework was used to jointly examine costs and consequences while accounting for clustering and baseline differences. Uncertainty around cost-effectiveness was characterised through the use of net benefit plots and cost-effectiveness acceptability curves, in addition to sensitivity analyses.

Results

We randomised 392 women from 17 breast cancer centres across England: 196 to each treatment group. We over-recruited to the trial to replace participants withdrawn at randomisation and those who did not return baseline data. Of the 392 participants randomised, 10 (3%) were withdrawn before treatment allocation: five from each intervention group. Of the remaining 382 participants allocated to treatment, 191 (50%) were randomised to usual-care leaflets only and 191 (50%) to the PROSPER exercise programme. The mean age of participants was 58 [standard deviation (SD) 12.1] years. Most were screened as being overweight or obese on recruitment (277/392; 70%) and/or having planned surgery for ANC (231/392; 59%). Most participants underwent ANC surgery (327/392; 83%) and 317 out of 392 (81%) had radiotherapy. A total of 32 out of 392 (8%) participants did not complete baseline questionnaires (usual-care group, $n = 16$; exercise group, $n = 16$). Thus, baseline data were available for 350 out of 392 (89%) of those randomised: 175 out of 196 (89%) for each treatment group. Postal questionnaire data were obtained for 303 out of 392 participants (77%) at 6 weeks, 278 out of 392 participants (71%) at 6 months and 274 out of 392 (70%) at 12 months. Of those returning baseline data, this equated to 303 out of 350 participants (87%) at 6 weeks, 278 out of 350 (79%) at 6 months and 274 out of 350 (78%) at 12 months. Of those randomised to the exercise group, uptake was high, with 181 out of 196 participants (92%) attending at least one appointment with a physiotherapist and 143 out of 196 participants (73%) completing the full exercise programme (i.e. attending three or more physiotherapy sessions). Physiotherapists had a total of 622 contacts (mean 3.7 contacts, median 3 contacts) with 181 trial participants who attended the exercise programme.

Primary outcome

At 12 months, improvement in upper limb function was greater in the exercise group [mean DASH score 16.3 (SD 17.6)] than in the usual-care group [mean DASH score 23.7 (SD 22.9)] in both the ITT [adjusted mean difference (MD) DASH score −7.81, 95% CI −12.44 to −3.17; $p = 0.001$] and CACE analyses (adjusted MD −8.74, 95% CI −13.71 to −3.77; $p \leq 0.001$).

Secondary outcomes

At 12 months, we observed that those in the exercise group, compared with those receiving usual care, exhibited a greater improvement in DASH activity limitations (adjusted MD −8.04, 95% CI −12.93 to −3.14; $p = 0.001$), a greater improvement in DASH participation restrictions (adjusted MD −5.77,

Copyright © 2022 Bruce *et al.* This work was produced by Bruce *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.

95% CI −10.67 to −0.88; $p = 0.02$) and a greater improvement in DASH impairment (adjusted MD −7.15, 95% CI −13.19 to −1.11; $p = 0.02$). At 6 months, only DASH activity limitation scores were improved more in the exercise group than in the usual-care group.

Postoperative pain scores for pain in the breast and armpit while at rest and during movement were significantly lower at 6 weeks and at 12 months postoperatively for those randomised to the exercise group than for those randomised to the usual-care group (adjusted MD numerical rating scale −0.68, 95% CI −1.23 to −0.12; $p = 0.02$). We observed more arm symptoms, with higher FACT-B4 scores, in the usual-care group than in the exercise group at 6 months (adjusted MD FACT-B4 −1.06, 95% CI −1.99 to −0.13; $p = 0.03$) and 12 months (adjusted MD FACT-B4 −2.02, 95% CI −3.11 to −0.93; $p = 0.001$). We found no difference in the odds of reporting neuropathic pain at any time point over the 12 months' follow-up.

There were no differences in the rate of wound healing, SSI, lymphoedema or other postoperative complications between treatment groups at 6 weeks, 6 months or 12 months. Physical HRQoL scores were higher in the exercise group than in the usual-care group at both 6 months (adjusted SF-12 physical health composite score MD 2.73, 95% CI 0.24 to 5.21; $p = 0.03$) and 12 months (adjusted physical health composite score MD 4.39, 95% CI 1.74 to 7.04; $p = 0.001$). There were no differences in mental health scores by treatment group over time. Those randomised to the exercise group were more confident in their ability to return to their usual activities and to regular physical activity than those randomised to usual care, across all time points.

Qualitative substudy

The findings from the pre-pilot interviews informed the design of patient and intervention materials and also informed aspects of intervention delivery. Through interviews with trial participants and physiotherapists, we found that physiotherapists could reassure participants that it was safe to move their arm in the acute postoperative period after their surgery. Exercise intervention participants were motivated to comply with exercises because they felt that they were doing something proactive to improve their well-being. Interviewed participants felt that being involved in the selection of exercises and feeling as if they were progressing in their own recovery journey restored a sense of control, which cancer treatment had removed. Physiotherapists described that they found delivering the intervention rewarding. They felt that the extra time and focus on patient choice helped them feel as if they were delivering high-quality care. Several considerations for future implementation were identified, such as the need to integrate physiotherapists into the cancer team and to provide them with emotional support.

Economic analysis

The primary analysis found that the exercise group dominated the usual-care group: the intervention group accrued lower costs (–£387, 95% CI –£2491 to £1718) and generated more QALYs (0.029, 95% CI 0.001 to 0.056) than the usual-care group over 12 months. The intervention was found to be more cost-effective than usual care, with the intervention having a 78% chance of being the more cost-effective option at the National Institute for Health and Care Excellence-recommended cost-effectiveness threshold of £20,000 per QALY, and an 84% chance at £30,000 per QALY. The economic analyses suggest that exercise was cost-effective and our results were robust to a range of sensitivity analyses. The intervention itself was relatively cheap to implement (an additional £129 per person) and was associated with lower health-care costs and improved HRQoL. Given that the EQ-5D-5L utility scores were diverging at the final time point, it is reasonable to conclude that these estimates are conservative as benefits will likely accrue beyond the end of the trial.

Harms

No serious adverse events directly related to the interventions were reported. Six adverse events in six participants were reported by physiotherapists treating participants in the exercise group: four of the six participants who experienced an adverse event continued with the exercise programme.

Limitations

Completion of postal questionnaires at baseline and subsequent follow-up completion rates were lower than anticipated. This was largely because of treatment burden. However, we were sufficiently powered for the primary analyses at 12 months.

Conclusions

This multicentre RCT recruited 392 women at high risk of developing shoulder problems after breast cancer treatment. We found that an early, structured exercise programme improved upper limb function, pain and quality of life at 1 year after breast cancer surgery compared with usual care. Supported exercise started from the first postoperative week was safe: no serious adverse events were reported and exercise did not increase the risk of lymphoedema. Exercise was relatively cheap to implement (£129 per participant) and associated with lower health-care costs than usual care and improved HRQoL. Thus, our economic analyses found evidence that exercise was beneficial, with favourable estimates of cost-effectiveness relative to usual care.

Future work

We found robust evidence to support referral for early physiotherapy for women at an increased risk of developing shoulder problems after non-reconstructive breast surgery. Future work should examine strategies to support women to maintain compliance with exercise in the long term. Finally, work should focus on knowledge mobilisation to implement this exercise intervention in clinical practice within the NHS setting to prevent upper limb disability.

Trial registration

This trial is registered as ISRCTN35358984.

Funding

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 26, No. 15. See the NIHR Journals Library website for further project information.

Copyright © 2022 Bruce *et al.* This work was produced by Bruce *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.

Health Technology Assessment

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, 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 13/84/10. The contractual start date was in March 2015. The draft report began editorial review in March 2020 and was accepted for publication in June 2021. 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 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, 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, NETSCC, the HTA programme or the Department of Health and Social Care.

Copyright © 2022 Bruce *et al*. This work was produced by Bruce *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

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 (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 Consultant Advisor, Wessex Institute, University of Southampton, UK

Ms Tara Lamont Senior Adviser, Wessex Institute, 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, 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, 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