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A randomised controlled trial of exercise to prevent shoulder problems in women undergoing breast cancer treatment: study protocol for the Prevention of Shoulder Problems Trial (PROSPER)

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Complete List of Authors:	Bruce, Julie; University of Warwick, Warwick Clinical Trials Unit Williamson, Esther; Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, United Kingdom. , Centre for Rehabilitation Research in Oxford Lait, Clare; Gloucestershire Care Services NHS Trust Richmond, Helen ; University of Warwick, Warwick Clinical Trials Unit Betteley, Lauren; University of Warwick Warwick Medical School, Warwick Clinical Trials Unit Lall, Ranjit; University of Warwick, Warwick Clinical Trials Unit Petrou, Stavros; University of Warwick, Warwick Medical School Rees, Sophie; University of Warwick, Warwick Clinical Trials Unit Lamb, Sarah; University of Oxford, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences Thompson, Alastair; University of Texas M.D. Anderson Cancer Center, Department of Breast Surgical Oncology and Department of Translational Molecular Pathology
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Manuscripts

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3 **A randomised controlled trial of exercise to prevent shoulder problems in women**
4 **undergoing breast cancer treatment: study protocol for the Prevention of Shoulder**
5 **Problems Trial (PROSPER)**
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10 **Authors:** Julie Bruce¹, Esther Williamson², Clare Lait³, Helen Richmond¹, Lauren Betteley¹,
11 Ranjit Lall¹, Stavros Petrou¹, Sophie Rees¹, Sarah E Lamb^{1,2} and Alastair Thompson⁴ on
12 behalf of the PROSPER Study Group
13
14
15

16
17
18 **Author affiliations**
19

- 20
21 1. Warwick Clinical Trials Unit, Division of Health Sciences, University of Warwick,
22 Coventry CV4 7AL, UK
23
24 2. Nuffield Department of Orthopaedics Rheumatology & Musculoskeletal Sciences,
25 University of Oxford, Windmill Road, Oxford, OX3 7LD, UK
26
27 3. Gloucestershire Care Services NHS Trust, 1010 Gloucester Business Park, Pioneer
28 Avenue, Brockworth, Gloucester, GL3 4AW, UK
29
30 4. Department of Breast Surgical Oncology & Department of Translational Molecular
31 Pathology, University of Texas M.D. Anderson Cancer Center, 1400 Pressler Drive,
32 Houston, Texas, US
33
34
35
36
37
38

39 **Corresponding author:** Professor Julie Bruce; julie.bruce@warwick.ac.uk
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Abstract (300 words)

Introduction

Musculoskeletal shoulder problems are common after breast cancer treatment. Early postoperative exercises targeting the upper limb may improve shoulder function. This protocol describes a National Institute for Health Research funded randomised controlled trial to evaluate the clinical and cost-effectiveness of an early supervised exercise programme compared to usual care, for women at high risk of developing shoulder problems after breast cancer surgery.

Methods and Analysis

This pragmatic two-armed, multicentre RCT is underway within secondary care in the United Kingdom. PROSPER aims to recruit 350 women from approximately 15 UK centres with follow-up at 6 weeks, 6 and 12 months after randomisation. Recruitment processes and intervention development were optimised through qualitative research during a six-month internal pilot phase. Participants are randomised to the PROSPER intervention or best practice usual care only. The PROSPER intervention is delivered by physiotherapists and incorporates three main components: shoulder-specific exercises targeting range of movement and strength; general physical activity; and behavioural strategies to encourage adherence and support exercise behaviour. The primary outcome is upper arm function assessed using the Disabilities of the Arm Shoulder and Hand (DASH) questionnaire at 12 months post-randomisation. Secondary outcomes include DASH subscales, acute and chronic pain, complications, health related quality of life, and healthcare resource use. We will interview a subsample of participants (n=10 intervention; n=10 usual care) to explore their experiences of the trial interventions.

Ethics and Dissemination

Ethical approval was granted from the NHS National Research Ethics Service Committee West Midlands (15/WM/0224) on 20.07.2015. The PROSPER study is the first multicentre UK clinical trial to investigate the clinical and cost-effectiveness of supported exercise in the prevention of shoulder problems in high risk women undergoing breast cancer surgery. The

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3 findings will inform future clinical practice and provide valuable insight into the role of
4
5 physiotherapy-supported exercise in breast cancer rehabilitation.

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7 **Trial registration:** ISRCTN35358984

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9 **Protocol version:** Version 2.1; dated 11/01/2017

10
11 **Funding:** NIHR HTA (Project Number 13/84/10)

12 13 14 **Strengths and limitations of this study**

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16 Strengths:

- 17
18 • A large pragmatic study delivering a complex intervention to prevent postoperative health
19
20 problems in newly diagnosed cancer patients within secondary care;
- 21
22 • A strength of the evaluation is the mixed methods approach incorporating embedded
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24 qualitative research and economic analysis

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26 Limitations:

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28 • Recruited participants undergo multiple cancer treatments thus experience a
29
30 complicated postoperative recovery pathway.

Background

Breast cancer is the most common cancer in women in the UK with a 30% increase in incidence since the early 1970s (1). Due to advances in screening and treatment, the survival rate has progressively risen and now two thirds of women will survive for 20 years beyond their breast cancer diagnosis (1). The mainstay treatment is surgery to the breast and axilla, supplemented with chemotherapy, radiotherapy and endocrine therapy, depending upon tumour stage and other clinical criteria. As a consequence of these treatments, upper limb problems such as decreased shoulder range of movement (ROM), impaired strength, chronic pain, sensory disturbances and lymphoedema are common adverse treatment effects (2, 3). Studies suggest that up to 67% of women have arm or shoulder symptoms up to 3 years after treatment (4). Persistent upper limb dysfunction and pain are debilitating, have a negative impact upon sleep, quality of life, physical functioning and emotional wellbeing. Given successes in increasing survival, it is timely to identify strategies to improve the health-related quality of life of women after breast cancer treatment.

Several risk factors for shoulder and upper body problems after breast cancer treatment have been identified, including treatment-related factors, such as type of axillary surgery and radiotherapy (RT), and patient factors such as age, body mass index (BMI), and pre-existing shoulder problems (4, 5). Women undergoing mastectomy compared to breast conserving surgery are at greater risk of postoperative shoulder restrictions (odds ratio (OR) 5.7, 95% confidence interval (CI) 1.03, 31.2) (4). Additionally, those undergoing axillary lymph node clearance (ANC) are at greater risk of postoperative arm complaints compared to those having sentinel lymph node biopsy (SLNB; OR 9.8; 95% CI 3.5, 27.5) (4-6). Radiotherapy (RT), particularly to the axilla or chest wall, increases the odds of shoulder restriction (pooled OR 1.7, 95% CI 1.0, 2.9) and lymphoedema (pooled OR 1.5, 95% CI 1.2, 1.8) compared to women treated without adjuvant RT (4). Women reporting problems in the upper body and shoulder region before surgery are also at increased risk of chronic postoperative pain (5, 7).

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3 BMI at time of surgery has been shown to have an independent negative effect on shoulder
4 external rotation up to seven years after breast cancer treatment, and increased BMI is a risk
5 factor for chronic postoperative pain and arm lymphoedema (7, 8). It is important that the UK
6 National Health Service (NHS) provides optimal care for these women at high risk of
7 developing shoulder problems to ensure recovery and return to usual activities after cancer
8 treatment.
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17 A Cochrane review identified 24 studies (2132 participants) investigating exercise following
18 breast cancer surgery (9). Six studies (n=354), conducted outside of the UK, found that
19 structured postoperative exercise significantly improved shoulder ROM in the short and long
20 term when compared to usual care (9). Ten studies (n=1304) have evaluated timing of
21 exercise delivery; programmes initiated immediately postoperatively (1-3 days) versus
22 delayed exercise suggest that early postoperative exercise does significantly improve long-
23 term shoulder ROM. However, some studies reported an increased risk of wound-related
24 complications with early exercise, such as seroma and surgical site infection (9). The largest
25 UK trial to date (n=116 patients), published after the Cochrane review, found that
26 participants were less likely to develop lymphoedema when exercises were limited to 90° of
27 shoulder elevation during the first postoperative week compared to those performing
28 unrestricted exercises (10). These previous trials investigating the efficacy of exercise
29 following breast cancer surgery have been criticised for being of poor methodological quality
30 and for omitting important patient-reported outcomes such as function and health-related
31 quality of life (9). Furthermore, there is ongoing uncertainty around the optimal type, dose,
32 and timing of exercise after breast cancer treatment. Moreover, none of the trials conducted
33 to date have investigated the cost-effectiveness of structured exercise programmes after
34 breast cancer treatment.
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Rationale for a trial

To date, no large scale, high-quality, multicentre RCT investigating the clinical effectiveness of a structured physiotherapy intervention for women undergoing breast cancer surgery has been conducted. Given the lack of knowledge regarding the intensity and duration of exercise interventions after breast cancer surgery, this trial will provide evidence on whether a rigorously designed physiotherapy-led intervention, incorporating behaviour change theory, improves postoperative function and related outcomes, and whether this is cost-effective to deliver in the NHS setting.

Methods

Aim

The overall aim of PROSPER is to investigate the clinical and cost-effectiveness of an early supervised exercise programme compared to best practice usual care for women at high risk of shoulder problems after treatment for breast cancer, on outcomes of upper arm function, complications and quality of life. Specific trial objectives are:

1. To develop and refine a complex intervention of physiotherapy-led exercise for women at risk of developing musculoskeletal problems after breast cancer treatment;
2. To assess the acceptability of the exercise programme and outcome measures, optimise participant recruitment and refine trial processes during a six-month internal pilot phase at three clinical centres;
3. Use findings from the internal pilot phase to undertake a definitive RCT in approximately 15 UK NHS breast cancer centres.

This protocol follows guidance from the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)(11). Core trial information is presented in Table 1 (WHO Trial Registration Data Set). Figure 1 details the schedule of enrolment, interventions and assessment.

Trial design and setting

A multicentre, pragmatic, parallel, two-arm RCT with an internal pilot study and embedded economic evaluation and qualitative studies. The trial framework is superiority rather than equivalence or exploratory. The trial is currently open and recruiting from 17 NHS tertiary breast cancer centres across England. Participants are randomised in a 1:1 ratio between intervention and control arms.

Patient and public involvement (PPI) in trial design

Four female PPI representatives, all of whom were treated for breast cancer, were consulted during the initial grant preparation, intervention development and trial set up. Our PPI representatives contributed to the design of the intervention and advised on recruitment-related issues; they provided valuable insight into the worries and concerns experienced during cancer treatment.

Eligibility Criteria

Women are eligible to participate in PROSPER if they are: diagnosed with histologically confirmed invasive or non-invasive primary breast cancer scheduled for surgical excision; aged 18 years or over; can comply with the protocol; willing to provide written informed consent; and considered as being at high risk of developing postoperative shoulder problems (Table 2). This is a pragmatic trial and it is important that inclusion criteria reflect contemporary clinical practice. Therefore, women are also eligible where a later decision is made for postoperative radiotherapy (RT) to the axilla and/or supraclavicular region, thus changing their risk status from low to high. 'Late entry' women are eligible for the trial if the decision for postoperative RT is made within six weeks of surgery. Women who have had previous breast surgery (such as excision of a benign tumour or breast cyst) and those women who have had previous contralateral (opposite side) mastectomy, are eligible for invitation providing they fulfil high risk criteria for shoulder problems. Women having

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3 immediate reconstruction or bilateral breast surgery are ineligible as the usual NHS
4 postoperative care pathway often includes routine postoperative physiotherapy. Exclusion
5 criteria are presented in Table 2.
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10 **Participant screening, recruitment and consent**

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12 Participants are screened and identified from multi-disciplinary team (MDT) meetings and
13 preoperative breast/oncology clinic lists in secondary care. The initial screening process is
14 undertaken by a member of the clinical team, research nurse or trained designee. Potentially
15 eligible patients are approached by clinical or research staff and are given a Patient
16 Information Sheet (PIS) with further explanation of the trial. Figure 2 summarises participant
17 flow.
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26 **Allocation sequence generation and randomisation**

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28 Randomisation is based upon a computer-generated algorithm held and controlled centrally
29 by the Warwick Clinical Trials Unit (WCTU) programming team, independent from the
30 PROSPER trial team. The WCTU telephone randomisation service is used whereby
31 randomisation occurs after eligibility and informed consent has been obtained. Concealment
32 of allocation is maintained. An automated confirmation email of intervention allocation is
33 generated to the study team. Randomisation is stratified by the following variables: (i) first
34 versus repeat surgery; (ii) centre; and (iii) whether informed of the need for radiotherapy
35 within six weeks of surgery. The first variable adjusts for the requirement for any additional
36 surgery which may change risk status from low to high (e.g. second procedure ANC or
37 reexcision of surgical margins). The second stratification variable ensures balanced
38 allocation across each recruitment site. The third variable accounts for late entry to the trial,
39 thus relates to the timing of intervention delivery and whether participants are randomised
40 preoperatively (up to the day of surgery) or within the first six weeks postoperatively. Due to
41 the nature of the study intervention, it is not possible to blind participants or treating
42 physiotherapists to treatment allocation. However, outcome data collection, data entry, data
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3 cleaning and interim statistical analyses are conducted without knowledge of treatment
4 allocation (blinded).
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6 **Interventions**

7 **Control Arm: Usual Care**

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10 Participants allocated to the usual care arm receive best practice usual care in the form of
11 written leaflets containing information about exercises, recovery after surgery, and
12 treatments for breast cancer. During the pilot phase, different exercise information leaflets
13 were reviewed and considered; we also consulted best practice guidance for written patient
14 information materials (12). The most commonly used information leaflets were 'Exercises
15 after Breast Cancer Surgery (BCC6)' and 'Your Operation and Recovery (BCC151)'
16 published by Breast Cancer Care (BCC) (13). The BCC leaflets were selected because of
17 content, style and clarity of presentation of information. These leaflets are given to patients
18 before surgery by breast care nurses, or other healthcare professionals, depending upon
19 local practice.
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32 **Intervention Arm: PROSPER exercise programme**

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34 Participants randomised to the active intervention receive usual care leaflets in addition to
35 the PROSPER intervention: a structured individualised exercise programme, comprising a
36 minimum of three face-to-face and maximum of six sessions or contacts with a
37 physiotherapist. A detailed description of intervention development has been submitted for
38 publication. In brief, the PROSPER programme comprises specific exercises targeting
39 shoulder range of motion and upper arm muscle strength, general physical activity, and
40 behavioural adherence strategies. The intervention is predominantly delivered in
41 physiotherapy outpatient departments.
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52 The first physiotherapy session is arranged seven to ten days after surgery, for assessment
53 of shoulder ROM, pain, function, patients' goals and assessment of confidence to carry out
54 prescribed exercises. Participants are prescribed an individually tailored home exercise
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3 programme and provided with guidance on rehabilitation, management of postoperative
4 complications and returning to general physical activity and/or work. The second
5 appointment is between four to six weeks postoperatively to review progress and prescribe
6 shoulder strengthening exercises. The programme is progressed by increasing exercise
7 repetitions, sets and resistance. The third appointment is recommended for between 12 to
8 16 weeks postoperatively, for further progression to facilitate return to work, sport and
9 hobbies. For women with later entry on the basis of postoperative radiotherapy, these
10 timings will be slightly delayed, but the exercise programme should commence at the earliest
11 opportunity, thus within six weeks of surgery.
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22 As per development work with patient representatives, and to reflect the pragmatic trial
23 design, three additional physiotherapy consultations are available on request. The timing
24 and delivery of additional appointments, either via telephone or face-to-face, are flexible to
25 account for on-going treatment, physiotherapist judgement and patient preference. Ideally
26 the intervention will be completed within the first six months following surgery, but women
27 can contact their physiotherapist for up to 12 months after randomisation. Thus any late
28 treatment-related shoulder problems will be dealt with by the trial physiotherapist. Number
29 and method of physiotherapy contacts will be closely monitored during the trial.
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40 **Outcomes**

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42 Figure 1 presents the study outcome measures and standardised assessment scales by
43 assessment time point. Questionnaires are completed at baseline on recruitment, then at 6
44 weeks, 6 and 12 months after randomisation by post. The primary outcome is upper limb
45 function at 12 months measured using the Disabilities of Arm, Shoulder and Hand (DASH)
46 questionnaire. The DASH is a 30-item patient-reported outcome measure designed to
47 capture difficulty in performing various upper arm activities (14). A single DASH score is
48 generated, although psychometric assessment using discriminant content validation analysis
49 has shown that the scale can be used to produce three health outcome sub-scores for
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3 impairment, activity limitation and participation restriction, as per the WHO International
4 Classification of Functioning Disability and Health (ICF) taxonomy (15). Secondary outcomes
5 include health-related quality of life, DASH sub-scores, and surgical adverse events
6 including pain (acute, chronic, neuropathic pain) surgical site infection and lymphoedema.
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8 Data on exercise/mobility are collected to allow comparisons in activity. Healthcare resource
9 use is recorded for economic analyses.
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16 **Internal pilot study**

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18 A six-month internal pilot phase was conducted at three breast cancer units (Coventry,
19 Oxford and Wolverhampton) to evaluate processes for patient identification, eligibility and
20 refinement of recruitment estimates. The intended sample size for the internal pilot study
21 was 30 participants, approximately 10% of the full sample. Acceptability of the PROSPER
22 intervention was explored through qualitative research involving audio-recorded individual
23 interviews with seven participants. Data from the pilot phase helped to refine recruitment and
24 trial processes. Patients recruited to the pilot phase continue with the follow-up schedule and
25 will be retained in the full trial analysis.
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36 **Sample Size**

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38 The PROSPER trial aims to recruit 350 patients, allocated in a 1:1 ratio. The sample size
39 calculation is based on a Dutch trial of thirty women with breast cancer, randomised to
40 physiotherapy over a three month period, reporting a between group difference of 7 points
41 on the DASH at 6 months (16). At 80% power and $p < 0.05$, this yields a target of 242
42 participants in total. Accounting for therapist effects, an intraclass coefficient (ICC) of 0.01
43 (yielding a design effect of 1.05), gives a target of 256 participants. The ICC estimate is
44 based on our previous experience of exercise interventions in a range of musculoskeletal
45 trials. We anticipate loss to follow up of less than 10% based on our previous clinical trials
46 however, have inflated this to 25% to cover the possibility that numbers lost to follow up are
47 greater than anticipated e.g. due to ongoing cancer treatment.
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5 The study is powered to detect a 7 point difference on the DASH. Studies of rheumatological
6 and orthopaedic populations have suggested that the minimally clinically important
7 difference (MCID) for the DASH is 10, and that the between group difference for trials should
8 be set at 10 (17). However, this fails to account for many of the eventualities that occur in
9 pragmatic trials, notably that there is not a 'no treatment' control arm, and therefore that
10 some of the control group may be exposed by serendipity to an intervention of similar
11 intensity, particularly in a high risk population.
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20 **Data analysis**

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22 Statistical analysis will be intention-to-treat and will comply with the CONSORT guidelines.
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24 The primary outcome data will be summarised using mean, standard deviation, median and
25 range values. The clustering effect will be assessed prior to analysis of the data. In the
26 presence of a clustering effect, the primary outcome will be analysed using multi-level linear
27 regression models. If there is negligible clustering effect, it will be analysed using ordinary
28 linear regression models. In each case, the mean change from baseline (to 6 and 12
29 months) will be summarised for each of the treatment arms and differences between the
30 interventions using unadjusted and adjusted (for age, type of surgery and radiotherapy)
31 estimates. These mean changes and their 95% confidence intervals will be plotted
32 graphically so that change can be assessed over the course of the study. Continuous
33 secondary outcomes will be assessed in a similar way to the primary outcome. Categorical
34 data will be analysed using random effect/ordinary logistic models, depending on the
35 presence of a clustering effect.
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50 A DASH score cannot be computed if there are more than three missing items. As a
51 sensitivity analysis, the impact of missing data will be assessed using multiple imputation.
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53 The impact of non-compliance with the intervention will be examined using the complier
54 average causal effect (CACE) analysis (18, 19). We have reviewed definitions of compliance
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3 for CACE analyses used in other therapy trials (20, 21). Complete compliance with the
4 PROSPER intervention is defined as having three or more contacts with the PROSPER
5 therapist; an additional analysis will be undertaken to explore partial compliance, defined as
6 less than three sessions. Analyses and template tables will be reported in a detailed
7 statistical analysis plan for review and approval by the DMC, prior to final statistical analysis
8 of the data. Planned sensitivity analyses include: a) the impact of low/high recruitment
9 centres on clustering effect; and b) assessment of differences between date of
10 randomisation and date of surgery across groups, as surgical trials vary in relation to timing
11 of follow-up.
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22 *Economic Evaluation*

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24 The primary economic evaluation will be conducted from the NHS and personal social
25 services (PSS) perspective (22) using the intention-to-treat approach (23). Data will be
26 collected on the health and social service resources used in the treatment of each trial
27 participant from randomisation to 12 months post-randomisation. Primary research methods
28 will be used to estimate the costs of delivering the physiotherapy-led exercise programme,
29 including development and training of accredited providers, the cost of delivering the
30 individual sessions and participant monitoring activities. Broader resource utilisation will be
31 captured through three main sources: (i) clinical data extraction forms; (ii) patient postal
32 questionnaires at 6 months and 12 months post-randomisation; and if feasible within the trial
33 timeline, (iii) routine health data sources from NHS Digital. Current UK unit costs, will be
34 applied to each resource item to estimate costs in each trial arm. Health-related quality of life
35 will be measured at baseline and at 6 and 12 months post-randomisation using the generic
36 EuroQol EQ-5D-5L and SF-12 measures; national tariff sets will be used to generate quality-
37 adjusted life-years (QALYs) (24-28).
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54 An incremental cost-effectiveness analysis, expressed in terms of incremental cost per
55 QALY gained, will be performed. Detailed methods of analysis will be pre-specified within a
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3 health economics analysis plan approved by the trial team prior to analysis to ensure
4 appropriate methods are used. Results will be presented using incremental cost-
5 effectiveness ratios (ICERs) and cost-effectiveness acceptability curves generated via the
6 net-benefit framework. A series of sensitivity analyses will be undertaken to explore the
7 implications of uncertainty on the ICERs and to consider the broader issue of the
8 generalisability of the study results. Due to the known limitations of within-trial economic
9 evaluations (29), a decision-analytical model may be constructed to examine the longer term
10 costs and outcomes beyond the end of the trial. Costs and outcomes beyond the first year
11 will be discounted to present values (22) and probabilistic sensitivity analyses will be
12 undertaken to explore the impact of uncertainty on the ICERs.
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24 **Qualitative sub-study**

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26 An embedded qualitative study will be undertaken to gain insight into the experiences of
27 women participating in trial interventions. We will explore the acceptability of the exercise
28 programme and compare and contrast experiences with women allocated to the control
29 intervention.
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36 *Design of sub-study*

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38 In-depth, semi-structured interviews will be conducted and audio-recorded. Interview topic
39 guides will be used to ensure similar areas are covered in each interview. Participants
40 consenting to the main trial are asked to indicate willingness to take part in a future interview
41 to explore postoperative experiences. A total of twenty interviews are planned, with ten
42 women from each intervention arm. Purposive sampling will be used, striving for a mix of
43 geographical location, age, employment status, socio-economic background and ethnicity.
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51 *Analysis*

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53 Interviews will be recorded, transcribed and analysed using a Framework Approach. A
54 thematic framework will be developed using pre-determined themes plus new themes raised
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3 by participants. The framework will be applied to the interview text and coded data will be
4 arranged on a chart according to each theme identified. Themes will be examined with a
5 view to providing explanations of the participants' experiences and understandings.
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8 **Data security and management**

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10 Participant data is stored on a secure database in accordance with the Data Protection Act
11 (1998). A unique trial identification number is used on all participant communication. Clinical
12 and patient forms are being checked for completeness and congruity before data entry onto
13 the PROSPER trial database. Data will undergo additional checks to ensure consistency
14 between data submitted and original paper forms. Trial documentation and data will be
15 archived for at least ten years after completion of the trial in accordance with WCTU
16 standard operating procedures.
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26 **Trial monitoring**

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28 The Trial Management Group (TMG) will oversee all aspects of design, delivery, quality
29 assurance and data analysis. A Trial Steering Committee (TSC), with independent
30 Chairperson, will monitor the trial at least once per year. An independent DMC will review
31 trial progress, recruitment, protocol compliance and interim analysis of outcomes, annually
32 or more frequently as requested. Recruitment data from the internal pilot study were
33 reviewed by independent committees and by the funder to approve the launch of the main
34 trial.
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44 **Adverse event management**

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3 A safety reporting protocol has been developed for related and unexpected serious adverse
4 events (SAEs) and directly attributable adverse events (AEs). An AE is defined as any
5 untoward medical occurrence in a subject which does not necessarily have a causal
6 relationship with the intervention. Any adverse event that occurs whilst undertaking
7 PROSPER exercises, either during an appointment, or whilst exercising unsupervised at
8 home, require reporting to the trial team. The trial Chief Investigator, with input from the
9 WCTU Quality Assurance team, determine whether AEs require reporting to the trial
10 sponsor, DMC and Ethics Committee, in accordance with the full safety reporting protocol.
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22 **Research ethics approval**

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24 Ethical approval was granted from the NHS National Research Ethics Service (NRES)
25 Committee West Midlands (Solihull) (15/WM/0224) on 20th July 2015. Site-specific
26 approvals have been obtained from NHS Research, Development and Innovation
27 departments.
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34 **Dissemination policy**

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36 The study team are committed to full disclosure of the results of the trial. Findings will be
37 reported in accordance with CONSORT guidelines (30) and we aim to publish in high impact
38 journals. Our patient representatives will assist with dissemination of study results through
39 INVOLVE, other cancer patient groups and organisations including
40 www.independentcancerpatientsvoice.org.uk. The funder will take no role in the analysis or
41 interpretation of trial results.
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50 **Discussion**

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52 The PROSPER trial will be the largest UK RCT examining the effectiveness of an early,
53 supervised exercise and behavioural support intervention for women at risk of developing
54 shoulder problems after breast cancer surgery. Previous trials in this field have been
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3 criticised for being of poor methodological quality and lacking in important outcome
4 measures, such as patient-reported shoulder function and health-related quality of life.
5 PROSPER will provide empirical data on whether a physiotherapy-led exercise programme
6 is effective for reducing shoulder disability when delivered in a pragmatic NHS clinical
7 setting. The design and development of this complex intervention was underpinned by
8 multiple stages of work, in line with MRC guidance on the development of complex
9 interventions.
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16 17 18 **Acknowledgements**

19 We extend very grateful thanks to all the trial participants. We are also grateful to all the
20 physiotherapy staff, surgical oncology teams, breast cancer nurses and research
21 departments collaborating on this study.
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26 27 **Collaborators**

28 PROSPER Study Group: Chief Investigator: Professor Julie Bruce. Co-investigators (Grant
29 holders): Professor Sarah E Lamb, Dr Esther Williamson, Dr Ranjit Lall, Professor Stavros
30 Petrou, Mr Alastair M Thompson, Dr John Williams and Dr Catherine Harkin (deceased).
31
32

33 Trial Coordination/Administration: Mrs Emma J Withers, Mrs Lauren Betteley, Mr Craig
34 Turner, Mrs Loraine Chowdhury.
35
36

37 Senior Project Managers: Mrs Susie Hennings, Mrs Helen Higgins.
38

39 Research Fellows/Associates: Dr Helen Richmond, Mrs Clare Lait (Physiotherapist), Dr
40 Sophie Rees (Qualitative), Mr Pankaj Mistry (Medical Statistics), Dr Alastair Canaway
41 (Health Economics).
42
43
44

45 Patient representatives: Dr Catherine Harkin (Deceased), Mrs Marie van Laar, Mrs Lyn
46 Ankcorn.
47
48

49 Surgical Leads: Miss Abigail Tomlins, Miss Raghavan Vidya, Ms Pankaj G Roy, Miss Kat
50 McEvoy.
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3 Intervention development: Mrs Clare Lait, Dr Esther Williamson, Dr Cynthia Srikesavan, Mrs
4 Jane Moser, Dr Meredith Newman, Dr Sophie Rees, Mrs Lauren Betteley, Dr Helen
5 Richmond, Dr Beth Fordham, Professor Sarah E Lamb and Professor Julie Bruce.

6
7
8 Data Programming team: Mr Ade Willis, Mr Henry Adjei.

9
10 Quality Assurance: Ms Claire Daffern.

11
12
13
14 **Contributors:** JB obtained study funding with support from SEL, EW, RL, SP, AMT and JW.
15
16 JB, SEL, EW, CL, RL, AMT, LB, SR and SP participated in the design of the study. EJW and
17
18 LB coordinate study administration, acquisition of trial data and administrative support
19
20 (CT/LC). PM will undertake statistical analysis, under direction of RL, senior trial statistician.
21
22 AC is responsible for health economic analysis, supported by SP, senior health economist.
23
24 JB and HR drafted the manuscript. All authors critically revised the manuscript for intellectual
25
26 content and approved the final manuscript. This trial protocol is published on behalf of the
27
28 PROSPER Study Group.

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35
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37
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41
42 from Advantage West Midlands (AWM). The trial sponsor is the University of Warwick and
43
44 University Hospitals Coventry and Warwickshire NHS Trust.

45 46 47 48 **Trial Registration:**

49
50 International Standard Randomised Controlled Trial Number: ISRCTN 35358984.

51 52 53 **Competing interests**

54
55 One author provides private physiotherapy to cancer patients (CL).

Data sharing statement

The trial statisticians and iDMC will have access to the dataset for the analysis of trial outcomes. The CI will have access to the data and take full responsibility for the analysis and publication of results. Once the main analyses have been undertaken, data will be available to other investigators subject to approval of data analysis plans by the steering committee and compliance with the University of Warwick Standard Operating Procedures on Data Management and Sharing. We will comply with Data Sharing Policies that may be instituted by the Funder (NIHR) during the lifetime of the project. The full PROSPER intervention manual and related materials will be available for wider access on completion of the main trial, according to funder and institutional repository requirements.

Data Monitoring Committee: Professor Malcolm Reed (Chair), Dr Rhian Gabe, Dr Matthew Maddocks.

Trial Steering Committee: Professor Steven Duffy (Chair), Dr Anna Kirby, Dr Karen Robb. We dedicate this article to Professor Adele Frances (Deceased) who served on the PROSPER TSC from 2015-2016.

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Table 1 World Health Organisation Trial Registration Data Set

Data category	Information
Primary registry and trial identifying number	ISRCTN35358984
Date of registration in primary registry	Project Number 13/84/10
Secondary identifying numbers	HTA
Source of monetary or material support	National Institute for Health Research (NIHR) Health Technology Assessment (HTA)
Joint sponsor	University of Warwick / University Hospitals Coventry & Warwickshire NHS Trust
Contact for public queries	prosper@warwick.ac.uk
Contact for scientific queries	Prof Julie Bruce, Warwick Clinical Trials Unit, University of Warwick
Public Title	Exercise to prevent shoulder problems in patients undergoing breast cancer treatment
Scientific Title	The PRevention Of Shoulder ProbleMs Study (PROSPER): a randomised controlled clinical trial comparing physiotherapy-led exercise versus usual care in women at high risk of shoulder problems after breast cancer surgery
Countries of recruitment	UK
Health condition or problem studied	Breast cancer
Interventions	Advice only: Breast Cancer Care leaflets Comparator: Physiotherapy-led structured exercise programme incorporating behavioural

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	strategies
Key inclusion and exclusion criteria	Age: 18 years or over, no upper age restriction Sex: Female Inclusion: confirmed invasive/non-invasive primary breast cancer schedule for surgical excision, at high risk of shoulder problems as defined by criteria given in Table 2. Exclusion: males, and women with exclusion criteria as described in Table 2.
Study type	Interventional Allocation: randomised; individual assignment. Primary purpose: prevention. Phase III
Date of first enrolment	January 2016
Target sample size	350
Recruitment status	Recruiting to July 2017
Primary outcome	Arm, shoulder and hand function as measured using the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire at 12 months
Key secondary outcomes	DASH subscales, pain (acute, chronic, neuropathic), health-related quality of life, surgical site infection, lymphoedema and other complications, health care resource use.

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	Exercise/activity data to inform adherence to interventions.
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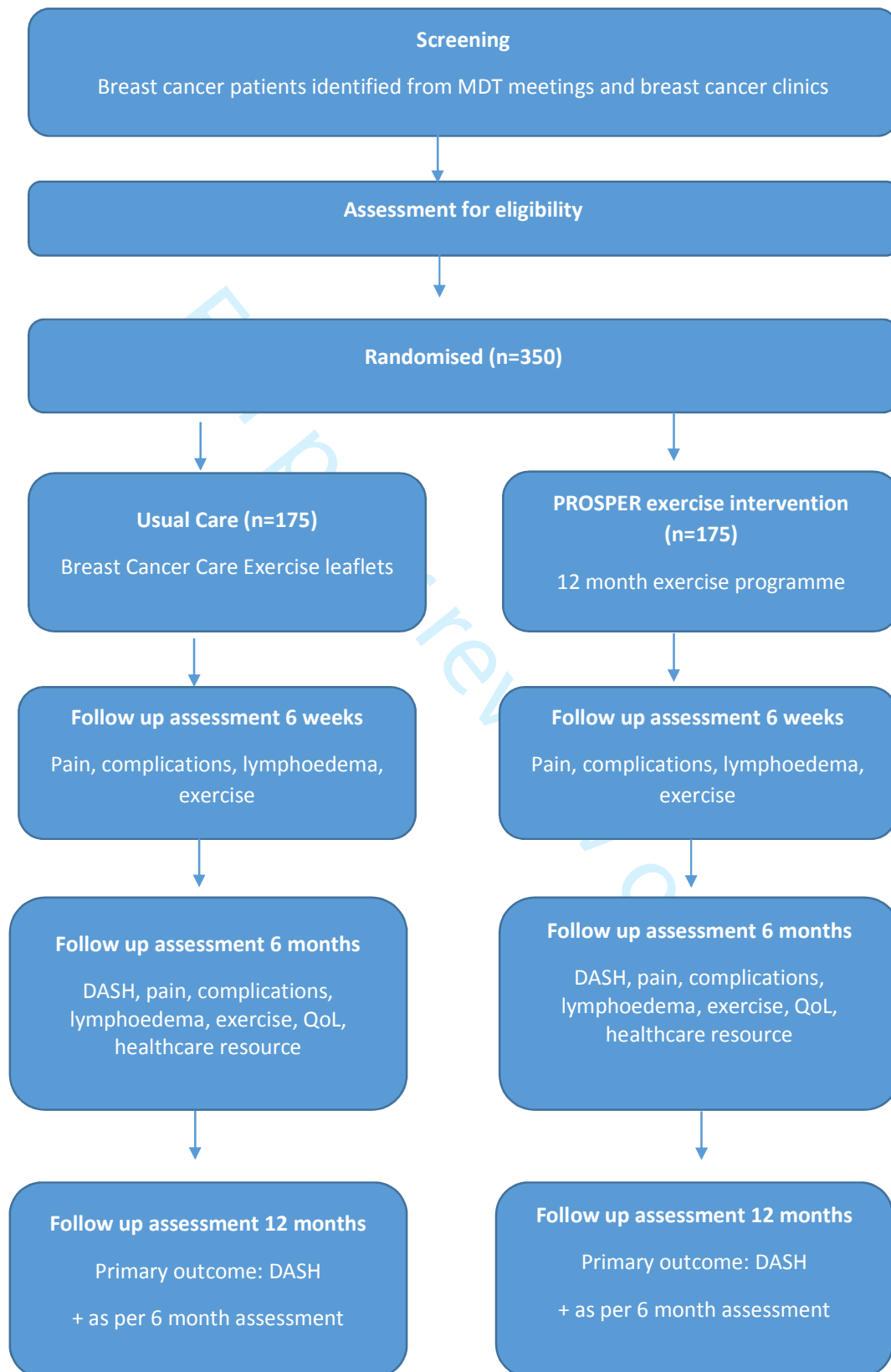
For peer review only

Table 2. Trial inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Aged ≥18 years old	Males
Histologically confirmed invasive or non-invasive primary breast cancer scheduled for surgical excision of breast cancer	Women having immediate reconstructive surgery
Considered high risk of developing shoulder problems after surgery defined by one or more of the following: <ul style="list-style-type: none"> • Planned axillary node clearance • Planned radiotherapy to the axilla and/or supraclavicular* • Existing shoulder problems (based upon PROSPER screening criteria) 	Women having sentinel lymph node biopsy (SLNB), with or without breast surgery, unless they fulfil other high risk criteria
Obesity defined as BMI >30	Women having bilateral breast surgery
Any subsequent axillary surgery related to primary surgery e.g. ANC conducted after sentinel lymph node biopsy (SLNB)	Evidence of metastatic disease at time of recruitment
Able to provide written informed consent	
Willing and able to comply with the protocol	
<i>*includes women informed of need for radiotherapy to the axilla and/or supraclavicular within six weeks of surgery, thus potential late entry to the trial is allowed in this setting</i>	

Figure 1. Study outcome measures and assessment time points

Time point	Study period				
	Enrolment	Allocation	Post-allocation		
	$-t_1$	0	t_1 6 weeks	t_2 6 months	t_3 12 months
Enrolment:					
Eligibility screen	√				
Informed consent	√				
Randomisation	350	√			
Interventions					
Usual Care (UC)	175	All participants	←→		
UC + PROSPER intervention	175		←→		
Assessments:					
Baseline	√				
Primary outcome	Function	DASH			√
Secondary outcomes	Function	DASH subscales	-	√	√
	Acute & chronic pain	FACT-B+4; NRS	√	√	√
	Neuropathic pain	DN4	√	√	√
	Complications	SSI + self-report	√	√	√
	Lymphoedema	Self-report	√	√	√
	Health-related QoL	SF12 / EQ-5D-5L	-	√	√
	Resource use	Self-report	-	√	√
	General activity & exercise	PASE items	√	√	√
<p><i>DASH: Disabilities of Arm, Shoulder and Hand questionnaire; DN4: Doleur Neuropathique; SF12: Short Form-12; SSI: surgical site infection; EQ-5D-5L: Euroqol; t: time point; QoL: Quality of Life; PASE: Physical Activity Scale for the Elderly.</i></p>					

Figure 2. Trial flow diagram



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	Table 1
Protocol version	3	Date and version identifier	3 & 22
Funding	4	Sources and types of financial, material, and other support	25 & Table 1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	24-25
	5b	Name and contact information for the trial sponsor	Table 1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	25-6
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	24

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Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5 - 7
	6b	Explanation for choice of comparators	10 – 12
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8 - 9

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8 – 9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-12 + separate intervention papers
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	22
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Table 2
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

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3 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including 16
4 clinical and statistical assumptions supporting any sample size calculations

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6 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size 9
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8 **Methods: Assignment of interventions (for controlled trials)**
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10 Allocation:

11 Sequence generation 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any 9
12 factors for stratification. To reduce predictability of a random sequence, details of any planned restriction
13 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants
14 or assign interventions
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17 Allocation concealment mechanism 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, 9
18 opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
19
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21 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to 10
22 interventions
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24 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome 10
25 assessors, data analysts), and how
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27 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's 10
28 allocated intervention during the trial
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31 **Methods: Data collection, management, and analysis**
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33 Data collection methods 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related 11 & Table 2
34 processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of
35 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.
36 Reference to where data collection forms can be found, if not in the protocol
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38 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be 11 & 14
39 collected for participants who discontinue or deviate from intervention protocols
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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	20
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17-20
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17-20
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18-20
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	22
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	20
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	22
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12 & described in intervention papers
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	22
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	4



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3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
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6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	9 & 21
7				
8	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9
9				
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11	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	24
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14	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	26
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17	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12
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20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	3-4 & 20
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25		31b	Authorship eligibility guidelines and any intended use of professional writers	3
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27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	24
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Can be provided as Appendix if requested
32				
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35	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable
36				
37				

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

BMJ Open

A randomised controlled trial of exercise to prevent shoulder problems in women undergoing breast cancer treatment: study protocol for the Prevention of Shoulder Problems Trial (UK PROSPER Trial)

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-019078.R1
Article Type:	Protocol
Date Submitted by the Author:	01-Nov-2017
Complete List of Authors:	Bruce, Julie; University of Warwick, Warwick Clinical Trials Unit Williamson, Esther; Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, United Kingdom. , Centre for Rehabilitation Research in Oxford Lait, Clare; Gloucestershire Care Services NHS Trust Richmond, Helen ; University of Warwick, Warwick Clinical Trials Unit Betteley, Lauren; University of Warwick Warwick Medical School, Warwick Clinical Trials Unit Lall, Ranjit; University of Warwick, Warwick Clinical Trials Unit Petrou, Stavros; University of Warwick, Warwick Medical School Rees, Sophie; University of Warwick, Warwick Clinical Trials Unit Withers, Emma; University of Warwick, Warwick Clinical Trials Unit Lamb, Sarah; University of Oxford, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences Thompson, Alastair; University of Texas M.D. Anderson Cancer Center, Department of Breast Surgical Oncology and Department of Translational Molecular Pathology
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Surgery, Health services research, Oncology
Keywords:	Breast surgery < SURGERY, Clinical trials < THERAPEUTICS, Rehabilitation medicine < INTERNAL MEDICINE

SCHOLARONE™
Manuscripts

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3 **A randomised controlled trial of exercise to prevent shoulder problems in women**
4 **undergoing breast cancer treatment: study protocol for the Prevention of Shoulder**
5 **Problems Trial (UK PROSPER Trial)**
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10 **Authors:** Julie Bruce¹, Esther Williamson², Clare Lait³, Helen Richmond¹, Lauren Betteley¹,
11 Ranjit Lall¹, Stavros Petrou¹, Sophie Rees¹, Emma J Withers¹, Sarah E Lamb^{1,2} and Alastair
12 Thompson⁴ on behalf of the PROSPER Study Group.
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16
17
18 **Author affiliations**
19

- 20
21 1. Warwick Clinical Trials Unit, Division of Health Sciences, University of Warwick,
22 Coventry CV4 7AL, UK
23
24 2. Nuffield Department of Orthopaedics Rheumatology & Musculoskeletal Sciences,
25 University of Oxford, Windmill Road, Oxford, OX3 7LD, UK
26
27 3. Gloucestershire Care Services NHS Trust, 1010 Gloucester Business Park, Pioneer
28 Avenue, Brockworth, Gloucester, GL3 4AW, UK
29
30 4. Department of Breast Surgical Oncology & Department of Translational Molecular
31 Pathology, University of Texas M.D. Anderson Cancer Center, 1400 Pressler Drive,
32 Houston, Texas, US
33
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39 **Corresponding author:** Professor Julie Bruce; julie.bruce@warwick.ac.uk
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Abstract

Musculoskeletal shoulder problems are common after breast cancer treatment. Early postoperative exercises targeting the upper limb may improve shoulder function. This protocol describes a National Institute for Health Research (NIHR) funded randomised controlled trial (RCT) to evaluate the clinical and cost-effectiveness of an early supervised structured exercise programme compared to usual care, for women at high risk of developing shoulder problems after breast cancer surgery.

Methods

This pragmatic two-armed, multicentre RCT is underway within secondary care in the United Kingdom (UK). PROSPER aims to recruit 350 women from approximately 15 UK centres with follow-up at 6 weeks, 6 and 12 months after randomisation. Recruitment processes and intervention development were optimised through qualitative research during a six-month internal pilot phase. Participants are randomised to the PROSPER intervention or best practice usual care only. The PROSPER intervention is delivered by physiotherapists and incorporates three main components: shoulder-specific exercises targeting range of movement and strength; general physical activity; and behavioural strategies to encourage adherence and support exercise behaviour. The primary outcome is upper arm function assessed using the Disabilities of the Arm Shoulder and Hand (DASH) questionnaire at 12 months post-randomisation. Secondary outcomes include DASH subscales, acute and chronic pain, complications, health related quality of life, and healthcare resource use. We will interview a subsample of twenty participants to explore their experiences of the trial interventions.

Discussion

The PROSPER study is the first multicentre UK clinical trial to investigate the clinical and cost-effectiveness of supported exercise in the prevention of shoulder problems in high risk women undergoing breast cancer surgery. The findings will inform future clinical practice and provide valuable insight into the role of physiotherapy-supported exercise in breast cancer rehabilitation.

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3 **Trial registration:** ISRCTN35358984

4 **Protocol version:** Version 2.1; dated 11/01/2017

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6 **Funding:** NIHR HTA (Project Number 13/84/10)

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10 **Strengths and limitations of this study**

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12 **Strengths:**

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- 15 • A large pragmatic study delivering a complex intervention to prevent postoperative health
 - 16 problems in newly diagnosed cancer patients within secondary care;
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 - 18 • A strength of the evaluation is the mixed methods approach incorporating embedded
 - 19 qualitative research and economic analysis
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23 **Limitations:**

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- 25 • Recruited participants undergo multiple cancer treatments thus experience a
 - 26 complicated postoperative recovery pathway.
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Background

Breast cancer is the most common cancer in women in the UK with a 30% increase in incidence since the early 1970s (1). Due to advances in screening and treatment, the survival rate has progressively risen and now two thirds of women will survive for 20 years beyond their breast cancer diagnosis (1). The mainstay treatment is surgery to the breast and axilla, supplemented with chemotherapy, radiotherapy and endocrine therapy, depending upon tumour stage and other clinical criteria. As a consequence of these treatments, upper limb problems such as decreased shoulder range of movement (ROM), impaired strength, chronic pain, sensory disturbances and lymphoedema are common adverse treatment effects (2, 3). Studies suggest that up to 67% of women have arm or shoulder symptoms up to 3 years after treatment (4). Persistent upper limb dysfunction and pain are debilitating, have a negative impact upon sleep, quality of life, physical functioning and emotional wellbeing. Given successes in increasing survival, it is timely to identify strategies to improve the health-related quality of life of women after breast cancer treatment.

Several risk factors for shoulder and upper body problems after breast cancer treatment have been identified, including treatment-related factors, such as type of axillary surgery and radiotherapy (RT), and patient factors such as age, body mass index (BMI), and pre-existing shoulder problems (4, 5). Women undergoing mastectomy compared to breast conserving surgery are at greater risk of postoperative shoulder restrictions (odds ratio (OR) 5.7, 95% confidence interval (CI) 1.03, 31.2) (4). Additionally, those undergoing axillary lymph node clearance (ANC) are at greater risk of postoperative arm complaints compared to those having sentinel lymph node biopsy (SLNB; OR 9.8; 95% CI 3.5, 27.5) (4-6). Radiotherapy (RT), particularly to the axilla or chest wall, increases the odds of shoulder restriction (pooled OR 1.7, 95% CI 1.0, 2.9) and lymphoedema (pooled OR 1.5, 95% CI 1.2, 1.8) compared to women treated without adjuvant RT (4). Women reporting problems in the upper body and shoulder region before surgery are also at increased risk of chronic postoperative pain (5, 7).

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3 BMI at time of surgery has been shown to have an independent negative effect on shoulder
4 external rotation up to seven years after breast cancer treatment, and increased BMI is a risk
5 factor for chronic postoperative pain and arm lymphoedema (7, 8). It is important that the UK
6 National Health Service (NHS) provides optimal care for these women at high risk of
7 developing shoulder problems to ensure recovery and return to usual activities after cancer
8 treatment.
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17 A Cochrane review identified 24 studies (2132 participants) investigating exercise following
18 breast cancer surgery (9). Six studies (n=354), conducted outside of the UK, found that
19 structured postoperative exercise significantly improved shoulder ROM in the short and long
20 term when compared to usual care (9). Ten studies (n=1304) have evaluated timing of
21 exercise delivery; programmes initiated immediately postoperatively (1-3 days) versus
22 delayed exercise suggest that early postoperative exercise does significantly improve long-
23 term shoulder ROM. However, some studies reported an increased risk of wound-related
24 complications with early exercise, such as seroma and surgical site infection (9). The largest
25 UK trial to date (n=116 patients), published after the Cochrane review, found that
26 participants were less likely to develop lymphoedema when exercises were limited to 90° of
27 shoulder elevation during the first postoperative week compared to those performing
28 unrestricted exercises (10). These previous trials investigating the efficacy of exercise
29 following breast cancer surgery have been criticised for being of poor methodological quality
30 and for omitting important patient-reported outcomes such as function and health-related
31 quality of life (9). Furthermore, there is ongoing uncertainty around the optimal type, dose,
32 and timing of exercise after breast cancer treatment. Moreover, none of the trials conducted
33 to date have investigated the cost-effectiveness of structured exercise programmes after
34 breast cancer treatment.
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Rationale for a trial

To date, no large scale, high-quality, multicentre RCT investigating the clinical effectiveness of a structured physiotherapy intervention compared to usual care for women undergoing breast cancer surgery has been conducted. Given the lack of knowledge regarding the intensity and duration of exercise interventions after breast cancer surgery, this trial will provide evidence on whether a rigorously designed physiotherapy-led intervention, incorporating behaviour change theory, improves postoperative function and related outcomes, and whether this is cost-effective to deliver in the NHS setting.

Methods

Aim

The overall aim of PROSPER is to investigate the clinical and cost-effectiveness of an early supervised exercise programme compared to best practice usual care for women at high risk of shoulder problems after treatment for breast cancer, on outcomes of upper arm function, complications and quality of life. Specific trial objectives are:

1. To develop and refine a complex intervention of physiotherapy-led exercise for women at risk of developing musculoskeletal problems after breast cancer treatment;
2. To assess the acceptability of the structured exercise programme and outcome measures, optimise participant recruitment and refine trial processes during a six-month internal pilot phase at three clinical centres;
3. Use findings from the internal pilot phase to undertake a definitive full RCT in approximately 15 UK NHS breast cancer centres.

This protocol follows guidance from the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)(11). Core trial information is presented in Table 1 (WHO Trial Registration Data Set). Figure 1 details the schedule of enrolment, interventions and assessment.

Trial design and setting

A multicentre, pragmatic, parallel, two-arm RCT with an internal pilot study and embedded economic evaluation and qualitative studies. The trial framework is superiority rather than equivalence or exploratory. The trial is currently open and recruiting from 17 NHS tertiary breast cancer centres across England. Participants are randomised in a 1:1 ratio between intervention and control arms.

Patient and public involvement (PPI) in trial design

Four female PPI representatives, all of whom were treated for breast cancer, were consulted during the initial grant preparation, intervention development and trial set up. Our PPI representatives contributed to the design of the intervention and advised on recruitment-related issues; they provided valuable insight into the worries and concerns experienced during cancer treatment.

Eligibility Criteria

Women are eligible to participate in PROSPER if they are: diagnosed with histologically confirmed invasive or non-invasive primary breast cancer scheduled for surgical excision; aged 18 years or over; can comply with the protocol; willing to provide written informed consent; and considered as being at high risk of developing postoperative shoulder problems (Table 2). This is a pragmatic trial and it is important that inclusion criteria reflect contemporary clinical practice. Therefore, women are also eligible where a later decision is made for postoperative radiotherapy (RT) to the axilla and/or supraclavicular region, thus changing their risk status from low to high. 'Late entry' women are eligible for the trial if the decision for postoperative RT is made within six weeks of surgery. Women who have had previous breast surgery (such as excision of a benign tumour or breast cyst) and those women who have had previous contralateral (opposite side) mastectomy, are eligible for invitation providing they fulfil high risk criteria for shoulder problems. Women having

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3 immediate reconstruction or bilateral breast surgery are ineligible as the usual NHS
4 postoperative care pathway often includes routine postoperative physiotherapy. Exclusion
5 criteria are presented in Table 2.
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10 **Participant screening, recruitment and consent**

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12 Participants are screened and identified from multi-disciplinary team (MDT) meetings and
13 preoperative breast/oncology clinic lists in secondary care. The initial screening process is
14 undertaken by a member of the clinical team, research nurse or trained designee. Potentially
15 eligible patients are approached by clinical or research staff and are given a Patient
16 Information Sheet (PIS) with further explanation of the trial. Figure 2 summarises participant
17 flow.
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26 **Allocation sequence generation and randomisation**

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28 Randomisation is based upon a computer-generated algorithm held and controlled centrally
29 by the Warwick Clinical Trials Unit (WCTU) programming team, independent from the
30 PROSPER trial team. The WCTU telephone randomisation service is used whereby
31 randomisation occurs after eligibility and informed consent has been obtained. Concealment
32 of allocation is maintained. An automated confirmation email of intervention allocation is
33 generated to the study team. Randomisation is stratified by the following variables: (i) first
34 versus repeat surgery; (ii) centre; and (iii) whether informed of the need for radiotherapy
35 within six weeks of surgery. The first variable adjusts for the requirement for any additional
36 surgery which may change risk status from low to high (e.g. second procedure ANC or
37 reexcision of surgical margins). The second stratification variable ensures balanced
38 allocation across each recruitment site. The third variable accounts for late entry to the trial,
39 thus relates to the timing of intervention delivery and whether participants are randomised
40 preoperatively (up to the day of surgery) or within the first six weeks postoperatively. Due to
41 the nature of the study intervention, it is not possible to blind participants or treating
42 physiotherapists to treatment allocation. However, receipt and handling of outcome data
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3 collection is blinded, thus data entry of returned postal questionnaires, data cleaning and
4 interim statistical analyses are conducted without knowledge of treatment allocation
5 (blinded).
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10 **Interventions**

11 **Control Arm: Usual Care**

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13 All participants allocated to the usual care arm receive best practice usual care in the form of
14 written leaflets containing information about exercises, recovery after surgery, and
15 treatments for breast cancer. During the pilot phase, different exercise information leaflets
16 were reviewed and considered; we also consulted best practice guidance for written patient
17 information materials (12). The most commonly used information leaflets were 'Exercises
18 after Breast Cancer Surgery (BCC6)' and 'Your Operation and Recovery (BCC151)'
19 published by Breast Cancer Care (BCC) (13). The BCC leaflets were selected because of
20 content, style and clarity of presentation of information. These two information leaflets were
21 given to all patients before surgery by breast care nurses, or other healthcare professionals,
22 depending upon local practice.
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36 **Intervention Arm: PROSPER exercise programme**

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38 Participants randomised to the active intervention receive usual care leaflets in addition to
39 the PROSPER intervention: a structured individualised exercise programme, comprising a
40 minimum of three face-to-face and maximum of six sessions or contacts with a
41 physiotherapist. A more detailed description of intervention development and final content
42 has been submitted for publication. In brief, the PROSPER programme comprises specific
43 exercises targeting shoulder range of motion and upper arm muscle strength, general
44 physical activity, and behavioural adherence strategies. The intervention is predominantly
45 delivered in physiotherapy outpatient departments.
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3 The first physiotherapy session is arranged seven to ten days after surgery, for assessment
4 of shoulder ROM, postoperative pain, function, arm swelling, patients' goals and assessment
5 of confidence to carry out prescribed exercises. Participants are prescribed an individually
6 tailored home exercise programme and provided with guidance on rehabilitation,
7 management of postoperative complications and returning to general physical activity and/or
8 work. The second appointment is between four to six weeks postoperatively to review
9 progress and prescribe shoulder strengthening exercises. The programme is progressed by
10 increasing exercise repetitions, sets and resistance. The third appointment is recommended
11 for between 12 to 16 weeks postoperatively, for further progression to facilitate return to
12 work, sport and hobbies. For women with later entry on the basis of postoperative
13 radiotherapy, these timings will be slightly delayed, but the exercise programme should
14 commence at the earliest opportunity, thus within six weeks of surgery.
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28 As per development work with patient representatives, and to reflect the pragmatic trial
29 design, three additional physiotherapy consultations are available on request. The timing
30 and delivery of additional appointments, either via telephone or face-to-face, are flexible to
31 account for on-going treatment, physiotherapist judgement and patient preference. Ideally
32 the intervention will be completed within the first six months following surgery, but women
33 can contact their physiotherapist for up to 12 months after randomisation. Thus any late
34 treatment-related shoulder problems will be dealt with by the trial physiotherapist. Number
35 and method of physiotherapy contacts will be closely monitored during the trial.
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46 **Outcomes**

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48 Figure 1 and Table 3 present the study outcome measures and standardised assessment
49 scales by assessment time point. Questionnaires are completed at baseline on recruitment,
50 then at 6 weeks, 6 and 12 months after randomisation by post. The **primary outcome** is
51 upper limb function at 12 months measured using the Disabilities of Arm, Shoulder and Hand
52 (DASH) questionnaire. We considered other patient-reported outcome measures, including
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3 shoulder-specific scales, however selected the DASH because it captures symptoms and
4 function of the upper limb rather than the shoulder joint *per se*. There is good evidence to
5 suggest that women experience a variety of difficulties and restrictions after breast cancer
6 treatment, affecting the hand, arm and shoulder. Functional impairment to the arm can affect
7 performance of simple daily activities, including writing, opening or closing jars, lifting and/or
8 holding shopping bags.
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17 The DASH is a 30-item patient-reported outcome measure designed to capture difficulty in
18 performing various upper arm activities (14). A single DASH score is generated, although
19 psychometric assessment using discriminant content validation analysis has shown that the
20 scale can be used to produce three health outcome sub-scores for impairment, activity
21 limitation and participation restriction, as per the WHO International Classification of
22 Functioning Disability and Health (ICF) taxonomy (15).
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30 **Secondary outcomes** include health-related quality of life (EuroQol EQ-5D-5L and Short-
31 Form-12), DASH sub-scores, and surgical adverse events including pain (acute, chronic,
32 neuropathic pain) surgical site infection and lymphoedema. A numerical rating scale (NRS)
33 0-10 and Doleur Neuropathique Questionnaire (DN4) are used to collect pain intensity and
34 pain character. The Functional Assessment of Cancer Therapy-Breast (FACT-B4) subscale
35 captures arm tenderness, numbness, painful movement and stiffness. We added items to
36 capture arm heaviness and swelling as self-report indicators of lymphoedema.
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44 Data on exercise/mobility are collected to allow comparisons in physical activity (selected
45 items from the Physical Activity Scale for the Elderly (PASE)). Healthcare resource use is
46 recorded for economic analyses.
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52 **Sample Size**

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54 The PROSPER trial aims to recruit 350 patients, allocated in a 1:1 ratio. The sample size
55 calculation is based on a Dutch trial of thirty women with breast cancer, randomised to
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3 physiotherapy over a three month period, reporting a between group difference of 7 points
4 on the DASH at 6 months (16). At 80% power and $p < 0.05$, this yields a target of 242
5 participants in total. Accounting for therapist effects, an intraclass coefficient (ICC) of 0.01
6 (yielding a design effect of 1.05), gives a target of 256 participants. The ICC estimate is
7 based on our previous experience of exercise interventions in a range of musculoskeletal
8 trials. We anticipate loss to follow up of less than 10% based on our previous clinical trials
9 however, have inflated this to 25% to cover the possibility that numbers lost to follow up are
10 greater than anticipated e.g. due to ongoing cancer treatment.
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20 The study is powered to detect a 7 point difference on the DASH. Studies of rheumatological
21 and orthopaedic populations have suggested that the minimally clinically important
22 difference (MCID) for the DASH is 10, and that the between group difference for trials should
23 be set at 10 (17). However, this fails to account for many of the eventualities that occur in
24 pragmatic trials, notably that there is not a 'no treatment' control arm, and therefore that
25 some of the control group may be exposed by serendipity to an intervention of similar
26 intensity, particularly in a high risk population.
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36 **Internal pilot study**

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38 A six-month internal pilot phase was conducted at three breast cancer units (Coventry,
39 Oxford and Wolverhampton) to evaluate processes for patient identification, eligibility and
40 refinement of recruitment estimates. The intended sample size for the internal pilot study
41 was 30 participants, approximately 10% of the full sample. Acceptability of the PROSPER
42 intervention was explored through qualitative research involving audio-recorded individual
43 interviews with seven participants. Changes were made to patient-facing materials and to
44 exercise intervention materials. Easy to use pocket-sized laminated cards with details of
45 inclusion/exclusion criteria and shoulder screening criteria were produced for recruitment
46 staff. Additional telephone or face-to-face appointments were added to the exercise
47 intervention to allow for flexibility during ongoing cancer treatment. Data from the pilot phase
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3 helped to refine recruitment and trial processes. Patients recruited to the pilot phase
4 continue with the follow-up schedule and will be retained in the full trial analysis. The pilot
5 study was completed as planned and the funder approved progression to full trial.
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10 **Data analysis**

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12 Statistical analysis will be intention-to-treat and will comply with the CONSORT guidelines.
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14 The primary outcome data will be summarised using mean, standard deviation, median and
15 range values. The clustering effect will be assessed prior to analysis of the data. In the
16 presence of a clustering effect, the primary outcome will be analysed using multi-level linear
17 regression models. If there is negligible clustering effect, it will be analysed using ordinary
18 linear regression models. In each case, the mean change from baseline (to 6 and 12
19 months) will be summarised for each of the treatment arms and differences between the
20 interventions using unadjusted and adjusted (for age, type of surgery and radiotherapy)
21 estimates. These mean changes and their 95% confidence intervals will be plotted
22 graphically so that change can be assessed over the course of the study. Continuous
23 secondary outcomes will be assessed in a similar way to the primary outcome. Categorical
24 data will be analysed using random effect/ordinary logistic models, depending on the
25 presence of a clustering effect.
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40 A DASH score cannot be computed if there are more than three missing items. As a
41 sensitivity analysis, the impact of missing data will be assessed using multiple imputation.
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43 The impact of non-compliance with the intervention will be examined using the complier
44 average causal effect (CACE) analysis (18, 19). We have reviewed definitions of compliance
45 for CACE analyses used in other therapy trials (20, 21). Complete compliance with the
46 PROSPER intervention is defined as having three or more contacts with the PROSPER
47 therapist; an additional analysis will be undertaken to explore partial compliance, defined as
48 less than three sessions. Analyses and template tables will be reported in a detailed
49 statistical analysis plan for review and approval by the DMC, prior to final statistical analysis
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3 of the data. Planned sensitivity analyses include: a) the impact of low/high recruitment
4 centres on clustering effect; and b) assessment of differences between date of
5 randomisation and date of surgery across groups, as surgical trials vary in relation to timing
6 of follow-up.
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10 11 12 *Economic Evaluation* 13

14 The primary economic evaluation will be conducted from the NHS and personal social
15 services (PSS) perspective (22) using the intention-to-treat approach (23). Data will be
16 collected on the health and social service resources used in the treatment of each trial
17 participant from randomisation to 12 months post-randomisation. Primary research methods
18 will be used to estimate the costs of delivering the physiotherapy-led exercise programme,
19 including development and training of accredited providers, the cost of delivering the
20 individual sessions and participant monitoring activities. Broader resource utilisation will be
21 captured through three main sources: (i) clinical data extraction forms; (ii) patient postal
22 questionnaires at 6 months and 12 months post-randomisation; and if feasible within the trial
23 timeline, (iii) routine health data sources from NHS Digital. Current UK unit costs, will be
24 applied to each resource item to estimate costs in each trial arm. Health-related quality of life
25 will be measured at baseline and at 6 and 12 months post-randomisation using the generic
26 EQ-5D-5L and SF-12 measures; national tariff sets will be used to generate quality-adjusted
27 life-years (QALYs) (24-28).
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44 An incremental cost-effectiveness analysis, expressed in terms of incremental cost per
45 QALY gained, will be performed. Detailed methods of analysis will be pre-specified within a
46 health economics analysis plan approved by the trial team prior to analysis to ensure
47 appropriate methods are used. Results will be presented using incremental cost-
48 effectiveness ratios (ICERs) and cost-effectiveness acceptability curves generated via the
49 net-benefit framework. A series of sensitivity analyses will be undertaken to explore the
50 implications of uncertainty on the ICERs and to consider the broader issue of the
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3 generalisability of the study results. Due to the known limitations of within-trial economic
4 evaluations (29), a decision-analytical model may be constructed to examine the longer term
5 costs and outcomes beyond the end of the trial. Costs and outcomes beyond the first year
6 will be discounted to present values (22) and probabilistic sensitivity analyses will be
7 undertaken to explore the impact of uncertainty on the ICERs.
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14 **Qualitative sub-study**

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16 An embedded qualitative study will be undertaken to gain insight into the experiences of
17 women participating in trial interventions. We will explore the acceptability of the exercise
18 programme and compare and contrast experiences with women allocated to the control
19 intervention.
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26 *Design of sub-study*

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28 In-depth, semi-structured interviews will be conducted and audio-recorded. Interview topic
29 guides will be used to ensure similar areas are covered in each interview. Participants
30 consenting to the main trial are asked to indicate willingness to take part in a future interview
31 to explore postoperative experiences. A total of twenty interviews are planned, with ten
32 women from each intervention arm. Purposive sampling will be used, striving for a mix of
33 geographical location, age, employment status, socio-economic background and ethnicity.
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42 *Analysis*

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44 Interviews will be recorded, transcribed and analysed using a Framework Approach. A
45 thematic framework will be developed using pre-determined themes plus new themes raised
46 by participants. The framework will be applied to the interview text and coded data will be
47 arranged on a chart according to each theme identified. Themes will be examined with a
48 view to providing explanations of the participants' experiences and understandings.
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Data security and management

Participant data is stored on a secure database in accordance with the Data Protection Act (1998). A unique trial identification number is used on all participant communication. Clinical and patient forms are being checked for completeness and congruity before data entry onto the PROSPER trial database. Data will undergo additional checks to ensure consistency between data submitted and original paper forms. Trial documentation and data will be archived for at least ten years after completion of the trial in accordance with WCTU standard operating procedures.

Trial monitoring

The Trial Management Group (TMG) will oversee all aspects of design, delivery, quality assurance and data analysis. A Trial Steering Committee (TSC), with independent Chairperson, will monitor the trial at least once per year. An independent DMC will review trial progress, recruitment, protocol compliance and interim analysis of outcomes, annually or more frequently as requested. Recruitment data from the internal pilot study were reviewed by independent committees and by the funder to approve the launch of the main trial.

Adverse event management

A safety reporting protocol has been developed for related and unexpected serious adverse events (SAEs) and directly attributable adverse events (AEs). An AE is defined as any untoward medical occurrence in a subject which does not necessarily have a causal relationship with the intervention. Any adverse event that occurs whilst undertaking PROSPER exercises, either during an appointment, or whilst exercising unsupervised at home, require reporting to the trial team. The trial Chief Investigator, with input from the WCTU Quality Assurance team, determine whether AEs require reporting to the trial sponsor, DMC and Ethics Committee, in accordance with the full safety reporting protocol.

Research ethics approval

Ethical approval was granted from the NHS National Research Ethics Service (NRES) Committee West Midlands (Solihull) (15/WM/0224) on 20th July 2015. Site-specific approvals have been obtained from NHS Research, Development and Innovation departments.

Dissemination policy

The study team are committed to full disclosure of the results of the trial. Findings will be reported in accordance with CONSORT guidelines (30) and we aim to publish in high impact journals. Our patient representatives will assist with dissemination of study results through INVOLVE, other cancer patient groups and organisations including www.independentcancerpatientsvoice.org.uk. The funder will take no role in the analysis or interpretation of trial results.

Discussion

The PROSPER trial will be the largest UK RCT examining the effectiveness of an early, supervised exercise and behavioural support intervention for women at risk of developing shoulder problems after breast cancer surgery. Previous trials in this field have been criticised for being of poor methodological quality and lacking in important outcome measures, such as patient-reported shoulder function and health-related quality of life. PROSPER will provide empirical data on whether a physiotherapy-led exercise programme is effective for reducing shoulder disability when delivered in a pragmatic NHS clinical setting. The design and development of this complex intervention was underpinned by multiple stages of work, in line with MRC guidance on the development of complex interventions. A full description of the PROSPER exercise intervention has been submitted elsewhere for publication.

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Collaborators

PROSPER Study Group: Chief Investigator: Professor Julie Bruce. Co-investigators (Grant holders): Professor Sarah E Lamb, Dr Esther Williamson, Dr Ranjit Lall, Professor Stavros Petrou, Mr Alastair M Thompson, Dr John Williams and Dr Catherine Harkin (deceased).

Trial Coordination/Administration: Mrs Emma J Withers, Mrs Lauren Betteley, Mr Craig Turner, Mrs Loraine Chowdhury.

Senior Project Managers: Mrs Susie Hennings, Mrs Helen Higgins.

Research Fellows/Associates: Dr Helen Richmond, Mrs Clare Lait (Physiotherapist), Dr Sophie Rees (Qualitative), Mr Pankaj Mistry (Medical Statistics), Dr Alastair Canaway (Health Economics).

Patient representatives: Dr Catherine Harkin (Deceased), Mrs Marie van Laar, Mrs Lyn Ankcorn.

Surgical Leads: Miss Abigail Tomlins, Miss Raghavan Vidya, Ms Pankaj G Roy, Miss Kat McEvoy, Miss Rachel Soulsby.

Intervention development: Mrs Clare Lait, Dr Esther Williamson, Dr Cynthia Srikesavan, Mrs Jane Moser, Dr Meredith Newman, Dr Sophie Rees, Mrs Lauren Betteley, Dr Helen Richmond, Dr Beth Fordham, Professor Sarah E Lamb and Professor Julie Bruce.

Data Programming team: Mr Ade Willis, Mr Henry Adjei.

Quality Assurance: Ms Claire Daffern.

Contributors: JB obtained study funding with support from SEL, EW, RL, SP and AMT. JB, SEL, EW, CL, RL, AMT, LB, SR and SP participated in the design of the study. EJW and LB coordinate study administration, acquisition of trial data and administrative support (CT/LC). PM will undertake statistical analysis, under direction of RL, senior trial statistician. AC is

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3 responsible for health economic analysis, supported by SP, senior health economist. JB and
4 HR drafted the manuscript. All authors critically revised the manuscript for intellectual
5 content and approved the final manuscript. This trial protocol is published on behalf of the
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11
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18 University Hospitals Coventry and Warwickshire NHS Trust.
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28 **Trial Registration:**

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30 International Standard Randomised Controlled Trial Number: ISRCTN 35358984.
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33 **Competing interests**

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35 One author provides private physiotherapy to cancer patients (CL).
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39 **Data sharing statement**

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41 The trial statisticians and iDMC will have access to the dataset for the analysis of trial
42 outcomes. The CI will have access to the data and take full responsibility for the analysis
43 and publication of results. Once the main analyses have been undertaken, data will be
44 available to other investigators subject to approval of data analysis plans by the steering
45 committee and compliance with the University of Warwick Standard Operating Procedures
46 on Data Management and Sharing. We will comply with Data Sharing Policies that may be
47 instituted by the Funder (NIHR) during the lifetime of the project. The full PROSPER
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3 intervention manual and related materials will be available for wider access on completion of
4 the main trial, according to funder and institutional repository requirements.
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11
12 **Data Monitoring Committee:** Professor Malcolm Reed (Chair), Dr Rhian Gabe, Dr
13 Matthew Maddocks.
14

15 **Trial Steering Committee:** Professor Steven Duffy (Chair), Dr Anna Kirby, Dr Karen Robb.
16

17 We dedicate this article to Professor Adele Frances (Deceased) who served on the
18 PROSPER TSC from 2015-2016.
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Figure 1 Study outcome measures and assessment time points

Figure 2 Trial flow diagram

For peer review only

Table 1 World Health Organisation Trial Registration Data Set

Data category	Information
Primary registry and trial identifying number	ISRCTN35358984
Date of registration in primary registry	Project Number 13/84/10
Secondary identifying numbers	HTA
Source of monetary or material support	National Institute for Health Research (NIHR) Health Technology Assessment (HTA)
Joint sponsor	University of Warwick / University Hospitals Coventry & Warwickshire NHS Trust
Contact for public queries	prosper@warwick.ac.uk
Contact for scientific queries	Prof Julie Bruce, Warwick Clinical Trials Unit, University of Warwick
Public Title	Exercise to prevent shoulder problems in patients undergoing breast cancer treatment
Scientific Title	The PRevention Of Shoulder ProbleMs TRial (PROSPER): a randomised controlled clinical trial comparing physiotherapy-led exercise versus usual care in women at high risk of shoulder problems after breast cancer surgery
Countries of recruitment	UK
Health condition or problem studied	Breast cancer
Interventions	Advice only: Breast Cancer Care leaflets Comparator: Physiotherapy-led structured exercise programme incorporating behavioural

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	strategies
Key inclusion and exclusion criteria	Age: 18 years or over, no upper age restriction Sex: Female Inclusion: confirmed invasive/non-invasive primary breast cancer schedule for surgical excision, at high risk of shoulder problems as defined by criteria given in Table 2. Exclusion: males, and women with exclusion criteria as described in Table 2.
Study type	Interventional Allocation: randomised; individual assignment. Primary purpose: prevention. Phase III
Date of first enrolment	January 2016
Target sample size	350
Recruitment status	Recruiting to July 2017
Primary outcome	Arm, shoulder and hand function as measured using the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire at 12 months
Key secondary outcomes	DASH subscales, pain (acute, chronic, neuropathic), health-related quality of life, surgical site infection, lymphoedema and other complications, health care resource use.

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	Exercise/activity data to inform adherence to interventions.
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For peer review only

Table 2. Trial inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Aged ≥ 18 years old	Males
Histologically confirmed invasive or non-invasive primary breast cancer scheduled for surgical excision of breast cancer	Women having immediate reconstructive surgery
Considered high risk of developing shoulder problems after surgery defined by one or more of the following: <ul style="list-style-type: none"> • Planned axillary node clearance • Planned radiotherapy to the axilla and/or supraclavicular* • Existing shoulder problems (based upon PROSPER screening criteria) 	Women having sentinel lymph node biopsy (SLNB), with or without breast surgery, unless they fulfil other high risk criteria
Obesity defined as BMI >30	Women having bilateral breast surgery
Any subsequent axillary surgery related to primary surgery e.g. ANC conducted after sentinel lymph node biopsy (SLNB)	Evidence of metastatic disease at time of recruitment
Able to provide written informed consent	
Willing and able to comply with the protocol	
<i>*includes women informed of need for radiotherapy to the axilla and/or supraclavicular within six weeks of surgery, thus potential late entry to the trial is allowed in this setting</i>	

Table 3. Outcome assessment

Outcome	Domain	Scale / measure	T ₀ baseline	t ₁ 6 weeks	t ₂ 6 months	t ₃ 12 months
Primary	Function	DASH				√
Secondary	Function	DASH subscales	√		√	√
	Acute & chronic pain	FACT-B+4; NRS	√	√	√	√
	Neuropathic pain	DN4	√	√	√	√
	Complications	SSI + self-report		√	√	√
	Lymphoedema	Self-report	√	√	√	√
	Health-related QoL	SF12 / EQ-5D-5L	√		√	√
	Resource use	Self-report			√	√
	General activity & exercise	PASE items	√	√	√	√

DASH: Disabilities of Arm, Shoulder and Hand questionnaire; DN4: Doleur Neuropathique; SF12: Short Form-12; SSI: surgical site infection; EQ-5D-5L: Euroqol; t: time point; QoL: Quality of Life; PASE: Physical Activity Scale for the Elderly.

Figure 1. Study outcome measures and assessment time points

Time point	Study period				
	Enrolment	Allocation	Post-allocation		
	$-t_1$	0	t_1 6 weeks	t_2 6 months	t_3 12 months
Enrolment:					
Eligibility screen	√				
Informed consent	√				
Randomisation	350	√			
Interventions					
Usual Care (UC)	175	All participants	←→		
UC + PROSPER intervention	175		←→	→	

Figure 1 Study outcome measures and assessment time points

87x46mm (300 x 300 DPI)

Figure 2. Trial flow diagram

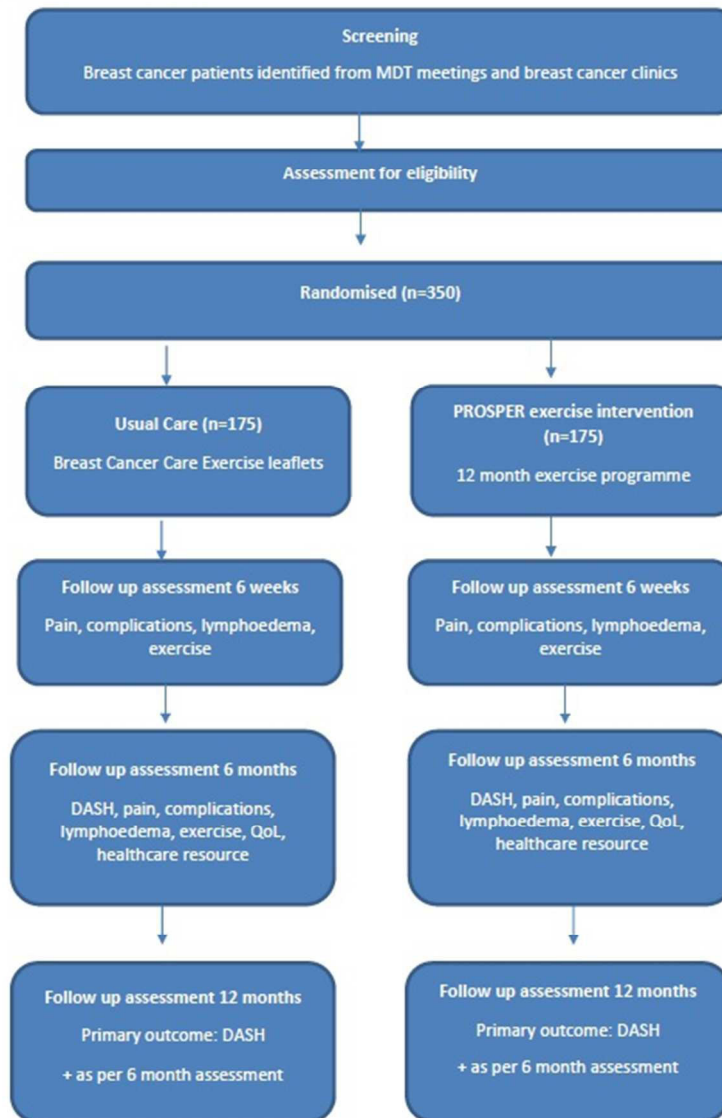


Figure 2 Trial flow diagram

50x65mm (300 x 300 DPI)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	Table 1
Protocol version	3	Date and version identifier	3 & 22
Funding	4	Sources and types of financial, material, and other support	25 & Table 1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	24-25
	5b	Name and contact information for the trial sponsor	Table 1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	25-6
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	24

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5 - 7
	6b	Explanation for choice of comparators	10 – 12
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8 - 9

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8 – 9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-12 + separate intervention papers
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	22
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Table 2
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11 & Table 2
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11 & 14

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3	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	20
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7	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17-20
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10		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17-20
11				
12		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18-20
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15	Methods: Monitoring			
16				
17	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	22
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22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	20
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25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	22
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12 & described in intervention papers
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32	Ethics and dissemination			
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34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	22
35				
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37	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	4
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3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
4				
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6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	9 & 21
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9	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9
10				
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12	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	24
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15	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	26
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18	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12
19				
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21	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	3-4 & 20
22				
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25		31b	Authorship eligibility guidelines and any intended use of professional writers	3
26				
27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	24
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Can be provided as Appendix if requested
32				
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35	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable
36				
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*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

BMJ Open

A randomised controlled trial of exercise to prevent shoulder problems in women undergoing breast cancer treatment: study protocol for the Prevention of Shoulder Problems Trial (UK PROSPER Trial)

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-019078.R2
Article Type:	Protocol
Date Submitted by the Author:	04-Jan-2018
Complete List of Authors:	Bruce, Julie; University of Warwick, Warwick Clinical Trials Unit Williamson, Esther; Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, United Kingdom. , Centre for Rehabilitation Research in Oxford Lait, Clare; Gloucestershire Care Services NHS Trust Richmond, Helen ; University of Warwick, Warwick Clinical Trials Unit Betteley, Lauren; University of Warwick Warwick Medical School, Warwick Clinical Trials Unit Lall, Ranjit; University of Warwick, Warwick Clinical Trials Unit Petrou, Stavros; University of Warwick, Warwick Medical School Rees, Sophie; University of Warwick, Warwick Clinical Trials Unit Withers, Emma; University of Warwick, Warwick Clinical Trials Unit Lamb, Sarah; University of Oxford, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences Thompson, Alastair; University of Texas M.D. Anderson Cancer Center, Department of Breast Surgical Oncology and Department of Translational Molecular Pathology
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Surgery, Health services research, Oncology
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Manuscripts

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3 **A randomised controlled trial of exercise to prevent shoulder problems in women**
4 **undergoing breast cancer treatment: study protocol for the Prevention of Shoulder**
5 **Problems Trial (UK PROSPER Trial)**
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10 **Authors:** Julie Bruce¹, Esther Williamson², Clare Lait³, Helen Richmond¹, Lauren Betteley¹,
11 Ranjit Lall¹, Stavros Petrou¹, Sophie Rees¹, Emma J Withers¹, Sarah E Lamb^{1,2} and Alastair
12 Thompson⁴ on behalf of the PROSPER Study Group.
13
14
15

16
17
18 **Author affiliations**
19

- 20
21 1. Warwick Clinical Trials Unit, Division of Health Sciences, University of Warwick,
22 Coventry CV4 7AL, UK
23
24 2. Nuffield Department of Orthopaedics Rheumatology & Musculoskeletal Sciences,
25 University of Oxford, Windmill Road, Oxford, OX3 7LD, UK
26
27 3. Gloucestershire Care Services NHS Trust, 1010 Gloucester Business Park, Pioneer
28 Avenue, Brockworth, Gloucester, GL3 4AW, UK
29
30 4. Department of Breast Surgical Oncology & Department of Translational Molecular
31 Pathology, University of Texas M.D. Anderson Cancer Center, 1400 Pressler Drive,
32 Houston, Texas, US
33
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39 **Corresponding author:** Professor Julie Bruce; julie.bruce@warwick.ac.uk
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Abstract

Musculoskeletal shoulder problems are common after breast cancer treatment. Early postoperative exercises targeting the upper limb may improve shoulder function. This protocol describes a National Institute for Health Research (NIHR) funded randomised controlled trial (RCT) to evaluate the clinical and cost-effectiveness of an early supervised structured exercise programme compared to usual care, for women at high risk of developing shoulder problems after breast cancer surgery.

Methods

This pragmatic two-armed, multicentre RCT is underway within secondary care in the United Kingdom (UK). PROSPER aims to recruit 350 women from approximately 15 UK centres with follow-up at 6 weeks, 6 and 12 months after randomisation. Recruitment processes and intervention development were optimised through qualitative research during a six-month internal pilot phase. Participants are randomised to the PROSPER intervention or best practice usual care only. The PROSPER intervention is delivered by physiotherapists and incorporates three main components: shoulder-specific exercises targeting range of movement and strength; general physical activity; and behavioural strategies to encourage adherence and support exercise behaviour. The primary outcome is upper arm function assessed using the Disabilities of the Arm Shoulder and Hand (DASH) questionnaire at 12 months post-randomisation. Secondary outcomes include DASH subscales, acute and chronic pain, complications, health related quality of life, and healthcare resource use. We will interview a subsample of twenty participants to explore their experiences of the trial interventions.

Discussion

The PROSPER study is the first multicentre UK clinical trial to investigate the clinical and cost-effectiveness of supported exercise in the prevention of shoulder problems in high risk women undergoing breast cancer surgery. The findings will inform future clinical practice and provide valuable insight into the role of physiotherapy-supported exercise in breast cancer rehabilitation.

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3 **Trial registration:** ISRCTN35358984

4 **Protocol version:** Version 2.1; dated 11/01/2017

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6 **Funding:** NIHR HTA (Project Number 13/84/10)

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10 **Strengths and limitations of this study**

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12 **Strengths:**

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- 15 • A large pragmatic study delivering a complex intervention to prevent postoperative health
 - 16 problems in newly diagnosed cancer patients within secondary care;
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 - 18 • A strength of the evaluation is the mixed methods approach incorporating embedded
 - 19 qualitative research and economic analysis
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23 **Limitations:**

- 24
- 25 • Recruited participants undergo multiple cancer treatments thus experience a
 - 26 complicated postoperative recovery pathway.
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Background

Breast cancer is the most common cancer in women in the UK with a 30% increase in incidence since the early 1970s (1). Due to advances in screening and treatment, the survival rate has progressively risen and now two thirds of women will survive for 20 years beyond their breast cancer diagnosis (1). The mainstay treatment is surgery to the breast and axilla, supplemented with chemotherapy, radiotherapy and endocrine therapy, depending upon tumour stage and other clinical criteria. As a consequence of these treatments, upper limb problems such as decreased shoulder range of movement (ROM), impaired strength, chronic pain, sensory disturbances and lymphoedema are common adverse treatment effects (2, 3). Studies suggest that up to 67% of women have arm or shoulder symptoms up to 3 years after treatment (4). Persistent upper limb dysfunction and pain are debilitating, have a negative impact upon sleep, quality of life, physical functioning and emotional wellbeing. Given successes in increasing survival, it is timely to identify strategies to improve the health-related quality of life of women after breast cancer treatment.

Several risk factors for shoulder and upper body problems after breast cancer treatment have been identified, including treatment-related factors, such as type of axillary surgery and radiotherapy (RT), and patient factors such as age, body mass index (BMI), and pre-existing shoulder problems (4, 5). Women undergoing mastectomy compared to breast conserving surgery are at greater risk of postoperative shoulder restrictions (odds ratio (OR) 5.7, 95% confidence interval (CI) 1.03, 31.2) (4). Additionally, those undergoing axillary lymph node clearance (ANC) are at greater risk of postoperative arm complaints compared to those having sentinel lymph node biopsy (SLNB; OR 9.8; 95% CI 3.5, 27.5) (4-6). Radiotherapy (RT), particularly to the axilla or chest wall, increases the odds of shoulder restriction (pooled OR 1.7, 95% CI 1.0, 2.9) and lymphoedema (pooled OR 1.5, 95% CI 1.2, 1.8) compared to women treated without adjuvant RT (4). Women reporting problems in the upper body and shoulder region before surgery are also at increased risk of chronic postoperative pain (5, 7).

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3 BMI at time of surgery has been shown to have an independent negative effect on shoulder
4 external rotation up to seven years after breast cancer treatment, and increased BMI is a risk
5 factor for chronic postoperative pain and arm lymphoedema (7, 8). It is important that the UK
6 National Health Service (NHS) provides optimal care for these women at high risk of
7 developing shoulder problems to ensure recovery and return to usual activities after cancer
8 treatment.
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17 A Cochrane review identified 24 studies (2132 participants) investigating exercise following
18 breast cancer surgery (9). Six studies (n=354), conducted outside of the UK, found that
19 structured postoperative exercise significantly improved shoulder ROM in the short and long
20 term when compared to usual care (9). Ten studies (n=1304) have evaluated timing of
21 exercise delivery; programmes initiated immediately postoperatively (1-3 days) versus
22 delayed exercise suggest that early postoperative exercise does significantly improve long-
23 term shoulder ROM. However, some studies reported an increased risk of wound-related
24 complications with early exercise, such as seroma and surgical site infection (9). The largest
25 UK trial to date (n=116 patients), published after the Cochrane review, found that
26 participants were less likely to develop lymphoedema when exercises were limited to 90° of
27 shoulder elevation during the first postoperative week compared to those performing
28 unrestricted exercises (10). These previous trials investigating the efficacy of exercise
29 following breast cancer surgery have been criticised for being of poor methodological quality
30 and for omitting important patient-reported outcomes such as function and health-related
31 quality of life (9). Furthermore, there is ongoing uncertainty around the optimal type, dose,
32 and timing of exercise after breast cancer treatment. Moreover, none of the trials conducted
33 to date have investigated the cost-effectiveness of structured exercise programmes after
34 breast cancer treatment.
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Rationale for a trial

To date, no large scale, high-quality, multicentre RCT investigating the clinical effectiveness of a structured physiotherapy intervention compared to usual care for women undergoing breast cancer surgery has been conducted. Given the lack of knowledge regarding the intensity and duration of exercise interventions after breast cancer surgery, this trial will provide evidence on whether a rigorously designed physiotherapy-led intervention, incorporating behaviour change theory, improves postoperative function and related outcomes, and whether this is cost-effective to deliver in the NHS setting.

Methods

Aim

The overall aim of PROSPER is to investigate the clinical and cost-effectiveness of an early supervised exercise programme compared to best practice usual care for women at high risk of shoulder problems after treatment for breast cancer, on outcomes of upper arm function, complications and quality of life. Specific trial objectives are:

1. To develop and refine a complex intervention of physiotherapy-led exercise for women at risk of developing musculoskeletal problems after breast cancer treatment;
2. To assess the acceptability of the structured exercise programme and outcome measures, optimise participant recruitment and refine trial processes during a six-month internal pilot phase at three clinical centres;
3. Use findings from the internal pilot phase to undertake a definitive full RCT in approximately 15 UK NHS breast cancer centres.

This protocol follows guidance from the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)(11). Core trial information is presented in Table 1 (WHO Trial Registration Data Set). Figure 1 details the schedule of enrolment, interventions and assessment.

Table 1 World Health Organisation Trial Registration Data Set

Data category	Information
Primary registry and trial identifying number	ISRCTN35358984
Date of registration in primary registry	Project Number 13/84/10
Secondary identifying numbers	HTA
Source of monetary or material support	National Institute for Health Research (NIHR) Health Technology Assessment (HTA)
Joint sponsor	University of Warwick / University Hospitals Coventry & Warwickshire NHS Trust
Contact for public queries	prosper@warwick.ac.uk
Contact for scientific queries	Prof Julie Bruce, Warwick Clinical Trials Unit, University of Warwick
Public Title	Exercise to prevent shoulder problems in patients undergoing breast cancer treatment
Scientific Title	The PRevention Of Shoulder ProbleMs TRial (PROSPER): a randomised controlled clinical trial comparing physiotherapy-led exercise versus usual care in women at high risk of shoulder problems after breast cancer surgery
Countries of recruitment	UK
Health condition or problem studied	Breast cancer
Interventions	Advice only: Breast Cancer Care leaflets Comparator: Physiotherapy-led structured exercise programme incorporating behavioural

	strategies
Key inclusion and exclusion criteria	Age: 18 years or over, no upper age restriction Sex: Female Inclusion: confirmed invasive/non-invasive primary breast cancer schedule for surgical excision, at high risk of shoulder problems as defined by criteria given in Table 2. Exclusion: males, and women with exclusion criteria as described in Table 2.
Study type	Interventional Allocation: randomised; individual assignment. Primary purpose: prevention. Phase III
Date of first enrolment	January 2016
Target sample size	350
Recruitment status	Recruiting to July 2017
Primary outcome	Arm, shoulder and hand function as measured using the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire at 12 months
Key secondary outcomes	DASH subscales, pain (acute, chronic, neuropathic), health-related quality of life, surgical site infection, lymphoedema and other complications, health care resource use.

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	Exercise/activity data to inform adherence to interventions.
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For peer review only

Trial design and setting

A multicentre, pragmatic, parallel, two-arm RCT with an internal pilot study and embedded economic evaluation and qualitative studies. The trial framework is superiority rather than equivalence or exploratory. The trial is currently open and recruiting from 17 NHS tertiary breast cancer centres across England. Participants are randomised in a 1:1 ratio between intervention and control arms.

Patient and public involvement (PPI) in trial design

Four female PPI representatives, all of whom were treated for breast cancer, were consulted during the initial grant preparation, intervention development and trial set up. Our PPI representatives contributed to the design of the intervention and advised on recruitment-related issues; they provided valuable insight into the worries and concerns experienced during cancer treatment.

Eligibility Criteria

Women are eligible to participate in PROSPER if they are: diagnosed with histologically confirmed invasive or non-invasive primary breast cancer scheduled for surgical excision; aged 18 years or over; can comply with the protocol; willing to provide written informed consent; and considered as being at high risk of developing postoperative shoulder problems (Table 2). This is a pragmatic trial and it is important that inclusion criteria reflect contemporary clinical practice. Therefore, women are also eligible where a later decision is made for postoperative radiotherapy (RT) to the axilla and/or supraclavicular region, thus changing their risk status from low to high. 'Late entry' women are eligible for the trial if the decision for postoperative RT is made within six weeks of surgery. Women who have had previous breast surgery (such as excision of a benign tumour or breast cyst) and those women who have had previous contralateral (opposite side) mastectomy, are eligible for invitation providing they fulfil high risk criteria for shoulder problems. Women having immediate reconstruction or bilateral breast surgery are ineligible as the usual NHS

postoperative care pathway often includes routine postoperative physiotherapy. Exclusion criteria are presented in Table 2.

Table 2. Trial inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Aged ≥ 18 years old	Males
Histologically confirmed invasive or non-invasive primary breast cancer scheduled for surgical excision of breast cancer	Women having immediate reconstructive surgery
Considered high risk of developing shoulder problems after surgery defined by one or more of the following: <ul style="list-style-type: none"> • Planned axillary node clearance • Planned radiotherapy to the axilla and/or supraclavicular* • Existing shoulder problems (based upon PROSPER screening criteria) 	Women having sentinel lymph node biopsy (SLNB), with or without breast surgery, unless they fulfil other high risk criteria
Obesity defined as BMI >30	Women having bilateral breast surgery
Any subsequent axillary surgery related to primary surgery e.g. ANC conducted after sentinel lymph node biopsy (SLNB)	Evidence of metastatic disease at time of recruitment
Able to provide written informed consent	
Willing and able to comply with the protocol	
<i>*includes women informed of need for radiotherapy to the axilla and/or supraclavicular within six weeks of surgery, thus potential late entry to the trial is allowed in this setting</i>	

Participant screening, recruitment and consent

Participants are screened and identified from multi-disciplinary team (MDT) meetings and preoperative breast/oncology clinic lists in secondary care. The initial screening process is undertaken by a member of the clinical team, research nurse or trained designee. Potentially

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3 eligible patients are approached by clinical or research staff and are given a Patient
4 Information Sheet (PIS) with further explanation of the trial. Figure 2 summarises participant
5 flow.
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10 **Allocation sequence generation and randomisation**

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12 Randomisation is based upon a computer-generated algorithm held and controlled centrally
13 by the Warwick Clinical Trials Unit (WCTU) programming team, independent from the
14 PROSPER trial team. The WCTU telephone randomisation service is used whereby
15 randomisation occurs after eligibility and informed consent has been obtained. Concealment
16 of allocation is maintained. An automated confirmation email of intervention allocation is
17 generated to the study team. Randomisation is stratified by the following variables: (i) first
18 versus repeat surgery; (ii) centre; and (iii) whether informed of the need for radiotherapy
19 within six weeks of surgery. The first variable adjusts for the requirement for any additional
20 surgery which may change risk status from low to high (e.g. second procedure ANC or
21 reexcision of surgical margins). The second stratification variable ensures balanced
22 allocation across each recruitment site. The third variable accounts for late entry to the trial,
23 thus relates to the timing of intervention delivery and whether participants are randomised
24 preoperatively (up to the day of surgery) or within the first six weeks postoperatively. Due to
25 the nature of the study intervention, it is not possible to blind participants or treating
26 physiotherapists to treatment allocation. However, receipt and handling of outcome data
27 collection is blinded, thus data entry of returned postal questionnaires, data cleaning and
28 interim statistical analyses are conducted without knowledge of treatment allocation
29 (blinded).
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50 **Interventions**

51 **Control Arm: Usual Care**

52 All participants allocated to the usual care arm receive best practice usual care in the form of
53 written leaflets containing information about exercises, recovery after surgery, and
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3 treatments for breast cancer. During the pilot phase, different exercise information leaflets
4 were reviewed and considered; we also consulted best practice guidance for written patient
5 information materials (12). The most commonly used information leaflets were 'Exercises
6 after Breast Cancer Surgery (BCC6)' and 'Your Operation and Recovery (BCC151)'
7 published by Breast Cancer Care (BCC) (13). The BCC leaflets were selected because of
8 content, style and clarity of presentation of information. These two information leaflets were
9 given to all patients before surgery by breast care nurses, or other healthcare professionals,
10 depending upon local practice.
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20 **Intervention Arm: PROSPER exercise programme**

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22 Participants randomised to the active intervention receive usual care leaflets in addition to
23 the PROSPER intervention: a structured individualised exercise programme, comprising a
24 minimum of three face-to-face and maximum of six sessions or contacts with a
25 physiotherapist. As per Medical Research Council and TiDieR guidance, a more detailed
26 description of the intervention development and final content has been described separately
27 (submitted for publication). . We selected exercises and components based upon systematic
28 reviews and clinical guidelines. A Cochrane review investigated the effectiveness of exercise
29 interventions in preventing, minimising or improving upper-limb dysfunction due to breast
30 cancer treatment (9) . This review included 24 trials and classified exercise type as active,
31 active-assisted, passive range of movement, manual stretching, active stretching and
32 resistance exercises. We considered these components in relation to evidence of
33 effectiveness on shoulder range of movement and strength. This process was also
34 augmented by eliciting opinions from clinical experts in the field of cancer rehabilitation and
35 health psychology. The final PROSPER programme comprises specific exercises targeting
36 shoulder range of motion and upper arm muscle strength, general physical activity, and
37 behavioural adherence strategies.
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Overview of exercise intervention

The intervention is predominantly delivered in physiotherapy outpatient departments. The first physiotherapy session is arranged seven to ten days after surgery, for assessment of shoulder ROM, postoperative pain, function, arm swelling, patients' goals and assessment of confidence to carry out prescribed exercises. Participants are prescribed an individually tailored home exercise programme and provided with guidance on rehabilitation, management of postoperative complications and returning to general physical activity and/or work. The intervention targets three movement directions using a combination of active-assisted ROM, active ROM and stretches: shoulder flexion (forward), shoulder abduction (side), and abduction with external rotation (open chest). The second appointment is between four to six weeks postoperatively to review progress and prescribe shoulder strengthening exercises. The programme is progressed by increasing exercise repetitions, sets and resistance. The third appointment is recommended for between 12 to 16 weeks postoperatively, for further progression to facilitate return to work, sport and hobbies. For women with later entry on the basis of postoperative radiotherapy, these timings will be slightly delayed, but the exercise programme should commence at the earliest opportunity, thus within six weeks of surgery.

As per development work with patient representatives, and to reflect the pragmatic trial design, three additional physiotherapy consultations are available on request. The timing and delivery of additional appointments, either via telephone or face-to-face, are flexible to account for on-going treatment, physiotherapist judgement and patient preference. Ideally the intervention will be completed within the first six months following surgery, but women can contact their physiotherapist for up to 12 months after randomisation. Thus any late treatment-related shoulder problems will be dealt with by the trial physiotherapist. Number and method of physiotherapy contacts will be closely monitored during the trial.

Outcomes

Figure 1 and Table 3 present the study outcome measures and standardised assessment scales by assessment time point. Questionnaires are completed at baseline on recruitment, then at 6 weeks, 6 and 12 months after randomisation by post. The **primary outcome** is upper limb function at 12 months measured using the Disabilities of Arm, Shoulder and Hand (DASH) questionnaire (14). We considered other patient-reported outcome measures, including shoulder-specific scales, however selected the DASH because it captures symptoms and function of the upper limb rather than the shoulder joint *per se*. There is good evidence to suggest that women experience a variety of difficulties and restrictions after breast cancer treatment, affecting the hand, arm and shoulder. Functional impairment to the arm can affect performance of simple daily activities, including writing, opening or closing jars, lifting and/or holding shopping bags.

Table 3. Outcome assessment

Outcome	Domain	Scale / measure	T ₀ baseline	t ₁ 6 weeks	t ₂ 6 months	t ₃ 12 months
Primary	Function	DASH				√
Secondary	Function	DASH subscales	√		√	√
	Acute & chronic pain	FACT-B+4; NRS DN4	√	√	√	√
	Neuropathic pain		√	√	√	√
	Complications	SSI + self-report		√	√	√
	Lymphoedema	Self-report	√	√	√	√
	Health-related QoL	SF12 / EQ-5D-5L	√		√	√
	Resource use	Self-report			√	√
General activity & exercise	PASE items	√	√	√	√	

DASH: Disabilities of Arm, Shoulder and Hand questionnaire; DN4: Doleur Neuropathique; SF12: Short Form-12; SSI: surgical site infection;

EQ-5D-5L: Euroqol; t: time point; QoL: Quality of Life; PASE: Physical Activity Scale for the Elderly

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3 The DASH is a 30-item patient-reported outcome measure designed to capture difficulty in
4 performing various upper arm activities (14, 15). A single DASH score is generated, although
5 psychometric assessment using discriminant content validation analysis has shown that the
6 scale can be used to produce three health outcome sub-scores for impairment, activity
7 limitation and participation restriction, as per the WHO International Classification of
8 Functioning Disability and Health (ICF) taxonomy (16).
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16 **Secondary outcomes** include health-related quality of life (EuroQol EQ-5D-5L and Short-
17 Form-12), DASH sub-scores, and surgical adverse events including pain (acute, chronic,
18 neuropathic pain) surgical site infection and lymphoedema. A numerical rating scale (NRS)
19 0-10 and Doleur Neuropathique Questionnaire (DN4) are used to collect pain intensity and
20 pain character. The Functional Assessment of Cancer Therapy-Breast (FACT-B4) subscale
21 captures arm tenderness, numbness, painful movement and stiffness. We added items to
22 capture arm heaviness and swelling as self-report indicators of lymphoedema. Data on
23 exercise/mobility are collected to allow comparisons in physical activity (selected items from
24 the Physical Activity Scale for the Elderly (PASE)). The PASE was designed for use with
25 older adults has been validated for use in clinical trials recruiting patients aged 55 years and
26 older (17). Healthcare resource use is recorded for economic analyses.
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40 **Sample Size**

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42 The PROSPER trial aims to recruit 350 patients, allocated in a 1:1 ratio. The sample size
43 calculation is based on a Dutch trial of thirty women with breast cancer, randomised to
44 physiotherapy over a three month period, reporting a between group difference of 7 points
45 on the DASH at 6 months (18). At 80% power and $p < 0.05$, this yields a target of 242
46 participants in total. Accounting for therapist effects, an intracluster coefficient (ICC) of 0.01
47 (yielding a design effect of 1.05), gives a target of 256 participants. The ICC estimate is
48 based on our previous experience of exercise interventions in a range of musculoskeletal
49 trials. We anticipate loss to follow up of less than 10% based on our previous clinical trials
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3 however, have inflated this to 25% to cover the possibility that numbers lost to follow up are
4 greater than anticipated e.g. due to ongoing cancer treatment.
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9 The study is powered to detect a 7 point difference on the DASH. Studies of rheumatological
10 and orthopaedic populations have suggested that the minimally clinically important
11 difference (MCID) for the DASH is 10, and that the between group difference for trials should
12 be set at 10 (19). However, this fails to account for many of the eventualities that occur in
13 pragmatic trials, notably that there is not a 'no treatment' control arm, and therefore that
14 some of the control group may be exposed by serendipity to an intervention of similar
15 intensity, particularly in a high risk population.
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24 **Internal pilot study**

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26 A six-month internal pilot phase was conducted at three breast cancer units (Coventry,
27 Oxford and Wolverhampton) to evaluate processes for patient identification, eligibility and
28 refinement of recruitment estimates. The intended sample size for the internal pilot study
29 was 30 participants, approximately 10% of the full sample. Acceptability of the PROSPER
30 intervention was explored through qualitative research involving audio-recorded individual
31 interviews with seven participants. Changes were made to patient-facing materials and to
32 exercise intervention materials. Easy to use pocket-sized laminated cards with details of
33 inclusion/exclusion criteria and shoulder screening criteria were produced for recruitment
34 staff. Additional telephone or face-to-face appointments were added to the exercise
35 intervention to allow for flexibility during ongoing cancer treatment. Data from the pilot phase
36 helped to refine recruitment and trial processes. Patients recruited to the pilot phase
37 continue with the follow-up schedule and will be retained in the full trial analysis. The pilot
38 study was completed as planned and the funder approved progression to full trial.
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Data analysis

Statistical analysis will be intention-to-treat and will comply with the CONSORT guidelines. The primary outcome data will be summarised using mean, standard deviation, median and range values. The clustering effect will be assessed prior to analysis of the data. In the presence of a clustering effect, the primary outcome will be analysed using multi-level linear regression models. If there is negligible clustering effect, it will be analysed using ordinary linear regression models. In each case, the mean change from baseline (to 6 and 12 months) will be summarised for each of the treatment arms and differences between the interventions using unadjusted and adjusted (for age, type of surgery and radiotherapy) estimates. These mean changes and their 95% confidence intervals will be plotted graphically so that change can be assessed over the course of the study. Continuous secondary outcomes will be assessed in a similar way to the primary outcome. Categorical data will be analysed using random effect/ordinary logistic models, depending on the presence of a clustering effect.

A DASH score cannot be computed if there are more than three missing items. As a sensitivity analysis, the impact of missing data will be assessed using multiple imputation. The impact of non-compliance with the intervention will be examined using the complier average causal effect (CACE) analysis (20, 21). We have reviewed definitions of compliance for CACE analyses used in other therapy trials (22, 23). Complete compliance with the PROSPER intervention is defined as having three or more contacts with the PROSPER therapist; an additional analysis will be undertaken to explore partial compliance, defined as less than three sessions. Analyses and template tables will be reported in a detailed statistical analysis plan for review and approval by the DMC, prior to final statistical analysis of the data. Planned sensitivity analyses include: a) the impact of low/high recruitment centres on clustering effect; and b) assessment of differences between date of randomisation and date of surgery across groups, as surgical trials vary in relation to timing of follow-up.

Economic Evaluation

The primary economic evaluation will be conducted from the NHS and personal social services (PSS) perspective (24) using the intention-to-treat approach (25). Data will be collected on the health and social service resources used in the treatment of each trial participant from randomisation to 12 months post-randomisation. Primary research methods will be used to estimate the costs of delivering the physiotherapy-led exercise programme, including development and training of accredited providers, the cost of delivering the individual sessions and participant monitoring activities. Broader resource utilisation will be captured through three main sources: (i) clinical data extraction forms; (ii) patient postal questionnaires at 6 months and 12 months post-randomisation; and if feasible within the trial timeline, (iii) routine health data sources from NHS Digital. Current UK unit costs, will be applied to each resource item to estimate costs in each trial arm. Health-related quality of life will be measured at baseline and at 6 and 12 months post-randomisation using the generic EQ-5D-5L and SF-12 measures; national tariff sets will be used to generate quality-adjusted life-years (QALYs) (26-30).

An incremental cost-effectiveness analysis, expressed in terms of incremental cost per QALY gained, will be performed. Detailed methods of analysis will be pre-specified within a health economics analysis plan approved by the trial team prior to analysis to ensure appropriate methods are used. Results will be presented using incremental cost-effectiveness ratios (ICERs) and cost-effectiveness acceptability curves generated via the net-benefit framework. A series of sensitivity analyses will be undertaken to explore the implications of uncertainty on the ICERs and to consider the broader issue of the generalisability of the study results. Due to the known limitations of within-trial economic evaluations (31), a decision-analytical model may be constructed to examine the longer term costs and outcomes beyond the end of the trial. Costs and outcomes beyond the first year

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3 will be discounted to present values (24) and probabilistic sensitivity analyses will be
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5 undertaken to explore the impact of uncertainty on the ICERs.
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8 **Qualitative sub-study**

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10 An embedded qualitative study will be undertaken to gain insight into the experiences of
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12 women participating in trial interventions. We will explore the acceptability of the exercise
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14 programme and compare and contrast experiences with women allocated to the control
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16 intervention.
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18 *Design of sub-study*

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20 In-depth, semi-structured interviews will be conducted and audio-recorded. Interview topic
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22 guides will be used to ensure similar areas are covered in each interview. Participants
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24 consenting to the main trial are asked to indicate willingness to take part in a future interview
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26 to explore postoperative experiences. A total of twenty interviews are planned, with ten
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28 women from each intervention arm. Purposive sampling will be used, striving for a mix of
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30 geographical location, age, employment status, socio-economic background and ethnicity.
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36 *Analysis*

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38 Interviews will be recorded, transcribed and analysed using a Framework Approach. A
39
40 thematic framework will be developed using pre-determined themes plus new themes raised
41
42 by participants. The framework will be applied to the interview text and coded data will be
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44 arranged on a chart according to each theme identified. Themes will be examined with a
45
46 view to providing explanations of the participants' experiences and understandings.
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50 **Data security and management**

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52 Participant data is stored on a secure database in accordance with the Data Protection Act
53
54 (1998). A unique trial identification number is used on all participant communication. Clinical
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56 and patient forms are being checked for completeness and congruity before data entry onto
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3 the PROSPER trial database. Data will undergo additional checks to ensure consistency
4 between data submitted and original paper forms. Trial documentation and data will be
5 archived for at least ten years after completion of the trial in accordance with WCTU
6 standard operating procedures.
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10 11 12 **Trial monitoring**

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14 The Trial Management Group (TMG) will oversee all aspects of design, delivery, quality
15 assurance and data analysis. A Trial Steering Committee (TSC), with independent
16 Chairperson, will monitor the trial at least once per year. An independent DMC will review
17 trial progress, recruitment, protocol compliance and interim analysis of outcomes, annually
18 or more frequently as requested. Recruitment data from the internal pilot study were
19 reviewed by independent committees and by the funder to approve the launch of the main
20 trial.
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30 31 **Adverse event management**

32 A safety reporting protocol has been developed for related and unexpected serious adverse
33 events (SAEs) and directly attributable adverse events (AEs). An AE is defined as any
34 untoward medical occurrence in a subject which does not necessarily have a causal
35 relationship with the intervention. Any adverse event that occurs whilst undertaking
36 PROSPER exercises, either during an appointment, or whilst exercising unsupervised at
37 home, require reporting to the trial team. The trial Chief Investigator, with input from the
38 WCTU Quality Assurance team, determine whether AEs require reporting to the trial
39 sponsor, DMC and Ethics Committee, in accordance with the full safety reporting protocol.
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51 52 **Research ethics approval**

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54 Ethical approval was granted from the NHS National Research Ethics Service (NRES)
55 Committee West Midlands (Solihull) (15/WM/0224) on 20th July 2015. Site-specific
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3 approvals have been obtained from NHS Research, Development and Innovation
4 departments.
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8 9 **Dissemination policy**

10 The study team are committed to full disclosure of the results of the trial. Findings will be
11 reported in accordance with CONSORT guidelines (32) and we aim to publish in high impact
12 journals. Our patient representatives will assist with dissemination of study results through
13 INVOLVE, other cancer patient groups and organisations including
14 www.independentcancerpatientsvoice.org.uk. The funder will take no role in the analysis or
15 interpretation of trial results.
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24 25 **Discussion**

26 The PROSPER trial will be the largest UK RCT examining the effectiveness of an early,
27 supervised exercise and behavioural support intervention for women at risk of developing
28 shoulder problems after breast cancer surgery. Previous trials in this field have been
29 criticised for being of poor methodological quality and lacking in important outcome
30 measures, such as patient-reported shoulder function and health-related quality of life.
31 Another challenge encountered in previous clinical trials of this population is low participant
32 recruitment, partly due to the short time frame between diagnosis and surgery but also
33 perhaps compounded by reluctance to undertake active exercise when faced with a
34 distressing and potentially life-threatening cancer diagnosis. PROSPER aims to recruit 350
35 newly diagnosed breast cancer patients to provide empirical data on whether a
36 physiotherapy-led exercise programme is effective for reducing shoulder disability, when
37 delivered in a pragmatic NHS clinical setting. The design and development of this complex
38 intervention was underpinned by multiple stages of work, in line with MRC guidance on the
39 development of complex interventions. A full description of the content of the PROSPER
40 exercise intervention has been submitted elsewhere for publication.
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3 **Figure 1** Study outcome measures and assessment time points

4 **Figure 2** Trial flow diagram

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8 **Acknowledgements**

9
10 We extend very grateful thanks to all the trial participants. We are also grateful to all the
11 physiotherapy staff, surgical oncology teams, breast cancer nurses and research
12 departments collaborating on this study.
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14

15
16 **Collaborators**

17
18 PROSPER Study Group: Chief Investigator: Professor Julie Bruce. Co-investigators (Grant
19 holders): Professor Sarah E Lamb, Dr Esther Williamson, Dr Ranjit Lall, Professor Stavros
20 Petrou, Mr Alastair M Thompson, Dr John Williams and Dr Catherine Harkin (deceased).
21
22

23
24 Trial Coordination/Administration: Mrs Emma J Withers, Mrs Lauren Betteley, Mr Craig
25 Turner, Mrs Loraine Chowdhury.
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29 Senior Project Managers: Mrs Susie Hennings, Mrs Helen Higgins.

30
31 Research Fellows/Associates: Dr Helen Richmond, Mrs Clare Lait (Physiotherapist), Dr
32 Sophie Rees (Qualitative), Mr Pankaj Mistry (Medical Statistics), Dr Alastair Canaway
33 (Health Economics).
34
35

36
37 Patient representatives: Dr Catherine Harkin (Deceased), Mrs Marie van Laar, Mrs Lyn
38 Ankcorn.
39

40
41 Surgical Leads: Miss Abigail Tomlins, Miss Raghavan Vidya, Ms Pankaj G Roy, Miss Kat
42 McEvoy, Miss Rachel Soulsby.
43

44
45 Intervention development: Mrs Clare Lait, Dr Esther Williamson, Dr Cynthia Srikesavan, Mrs
46 Jane Moser, Dr Meredith Newman, Dr Sophie Rees, Mrs Lauren Betteley, Dr Helen
47 Richmond, Dr Beth Fordham, Professor Sarah E Lamb and Professor Julie Bruce.
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51 Data Programming team: Mr Ade Willis, Mr Henry Adjei.

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53 Quality Assurance: Ms Claire Daffern.
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3 **Contributors:** JB obtained study funding with support from SEL, EW, RL, SP and AMT. JB,
4 SEL, EW, CL, RL, AMT, LB, SR and SP participated in the design of the study. EJW and LB
5 coordinate study administration, acquisition of trial data and administrative support (CT/LC).
6 PM will undertake statistical analysis, under direction of RL, senior trial statistician. AC is
7 responsible for health economic analysis, supported by SP, senior health economist. JB and
8 HR drafted the manuscript. All authors critically revised the manuscript for intellectual
9 content and approved the final manuscript. This trial protocol is published on behalf of the
10 PROSPER Study Group.
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32 and not necessarily those of the NHS, the NIHR or the Department of Health.
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47 **Trial Registration:**

48 International Standard Randomised Controlled Trial Number: ISRCTN 35358984.
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52 **Competing interests**

53 One author provides private physiotherapy to cancer patients (CL).
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Data sharing statement

The trial statisticians and iDMC will have access to the dataset for the analysis of trial outcomes. The CI will have access to the data and take full responsibility for the analysis and publication of results. Once the main analyses have been undertaken, data will be available to other investigators subject to approval of data analysis plans by the steering committee and compliance with the University of Warwick Standard Operating Procedures on Data Management and Sharing. We will comply with Data Sharing Policies that may be instituted by the Funder (NIHR) during the lifetime of the project. The full PROSPER intervention manual and related materials will be available for wider access on completion of the main trial, according to funder and institutional repository requirements.

Data Monitoring Committee: Professor Malcolm Reed (Chair), Dr Rhian Gabe, Dr Matthew Maddocks.

Trial Steering Committee: Professor Steven Duffy (Chair), Dr Anna Kirby, Dr Karen Robb. We dedicate this article to Professor Adele Frances (Deceased) who served on the PROSPER TSC from 2015-2016.

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Figure 1. Study outcome measures and assessment time points

Time point	Study period				
	Enrolment	Allocation	Post-allocation		
	$-t_1$	0	t_1 6 weeks	t_2 6 months	t_3 12 months
Enrolment:					
Eligibility screen	√				
Informed consent	√				
Randomisation	350	√			
Interventions					
Usual Care (UC)	175	All participants	←→		
UC + PROSPER intervention	175		←→	←→	→

Figure 1 Study outcome measures and assessment time points

87x46mm (300 x 300 DPI)

Figure 2. Trial flow diagram

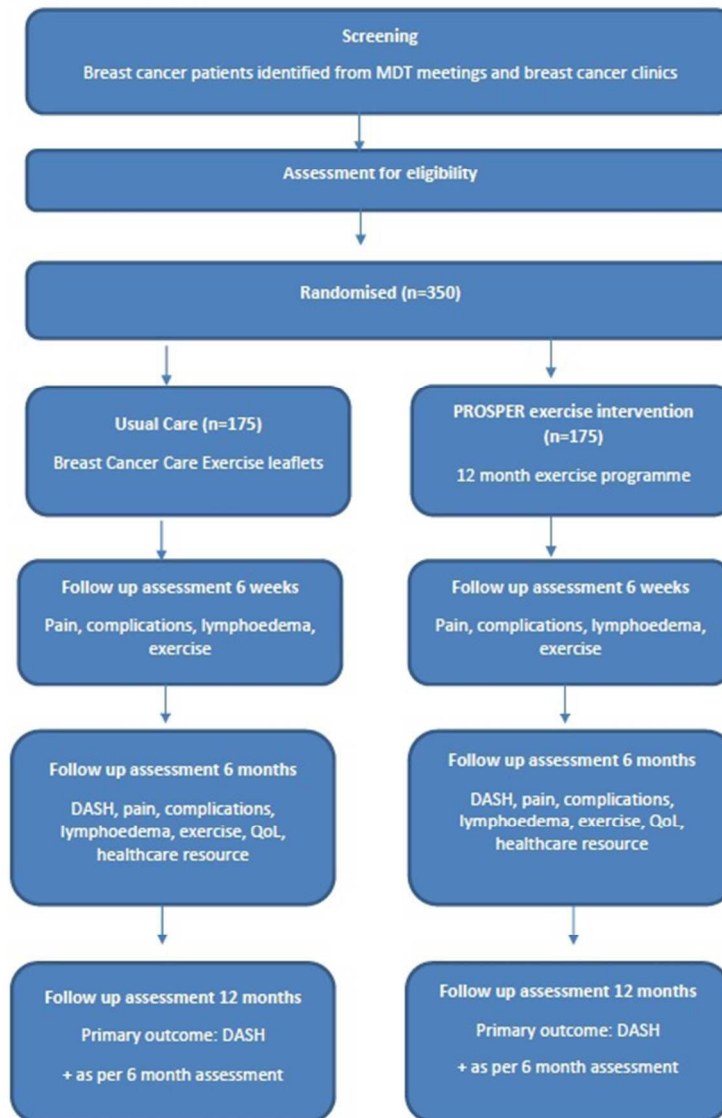


Figure 2 Trial flow diagram

50x65mm (300 x 300 DPI)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	Table 1
Protocol version	3	Date and version identifier	3 & 22
Funding	4	Sources and types of financial, material, and other support	25 & Table 1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	24-25
	5b	Name and contact information for the trial sponsor	Table 1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	25-6
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	24

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5 - 7
	6b	Explanation for choice of comparators	10 – 12
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8 - 9

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8 – 9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-12 + separate intervention papers
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	22
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Table 2
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

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Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations 16

Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size 9

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions 9

Allocation concealment mechanism 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned 9

Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions 10

Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how 10

17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial 10

Methods: Data collection, management, and analysis

Data collection methods 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol 11 & Table 2

18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols 11 & 14

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3	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	20
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7	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17-20
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10		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17-20
11				
12		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18-20
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15	Methods: Monitoring			
16				
17	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	22
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22		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	20
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25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	22
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12 & described in intervention papers
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32	Ethics and dissemination			
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34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	22
35				
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37	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	4
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3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
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5		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	9 & 21
6				
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8	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9
9				
10				
11	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	24
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14	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	26
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17	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12
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20	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	3-4 & 20
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23		31b	Authorship eligibility guidelines and any intended use of professional writers	3
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25		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	24
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29	Appendices			
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31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Can be provided as Appendix if requested
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35	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable
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*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.