PROTOCOL

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LIST OF ABBREVIATIONS/GLOSSARY

Abbreviation	Explanation
AE	Adverse Event
ALND	Axillary Lymph Node Dissection
ANC	Axillary Node Clearance
BMI	Body Mass Index
CEAC	Cost-Effectiveness Acceptability Curves
CHI	Community Health Index
CI	Chief Investigator
CONSORT	*Con*solidated *S*tandards *o*f *R*eporting *T*rials
CRF	Case Report Form
CTU	Clinical Trials Unit
DASH	Disabilities of the Arm, Shoulder and Hand
DMC	Data Monitoring Committee
DN4	Doleur Neuropathique
GP	General Practitioner
HCRU	Health Care Resource Use
HES	Hospital Episode Statistics
HSCIC	Health & Social Care Information Centre
ICC	Intracluster coefficient
ICER	Incremental cost-effectiveness ratio
ICF	International Classification of Functioning, Disability and Health
ICPV	Independent Cancer Patients' Voice
ISRCTN	International Standard Randomised Controlled Trial Number
MCID	Minimal Clinically Important Difference
MDT	Multi-Disciplinary Team
MRC	Medical Research Council
NICE	National Institute for Health and Care Excellence
PI	Principal Investigator
PPI	Patient & Public Involvement
PSA	Probabilistic Sensitivity Analyses
PSS	Personal Social Services
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
RCT	Randomised Controlled Trial
R&D	Research and Development
REC	Research Ethics Committee
ROM	Range of Motion
RT	Radiotherapy
SAE	Serious Adverse Event
SLNB	Sentinel Lymph Node Biopsy
SOP	Standard Operating Procedure
SSI	Surgical Site Infection
TMG	Trial Management Group
TSC	Trial Steering Committee
UHCW	University Hospitals Coventry & Warwickshire NHS Trust
WCTU	Warwick Clinical Trials Unit
WHO	World Health Organisation
WLE	Wide Local Excision

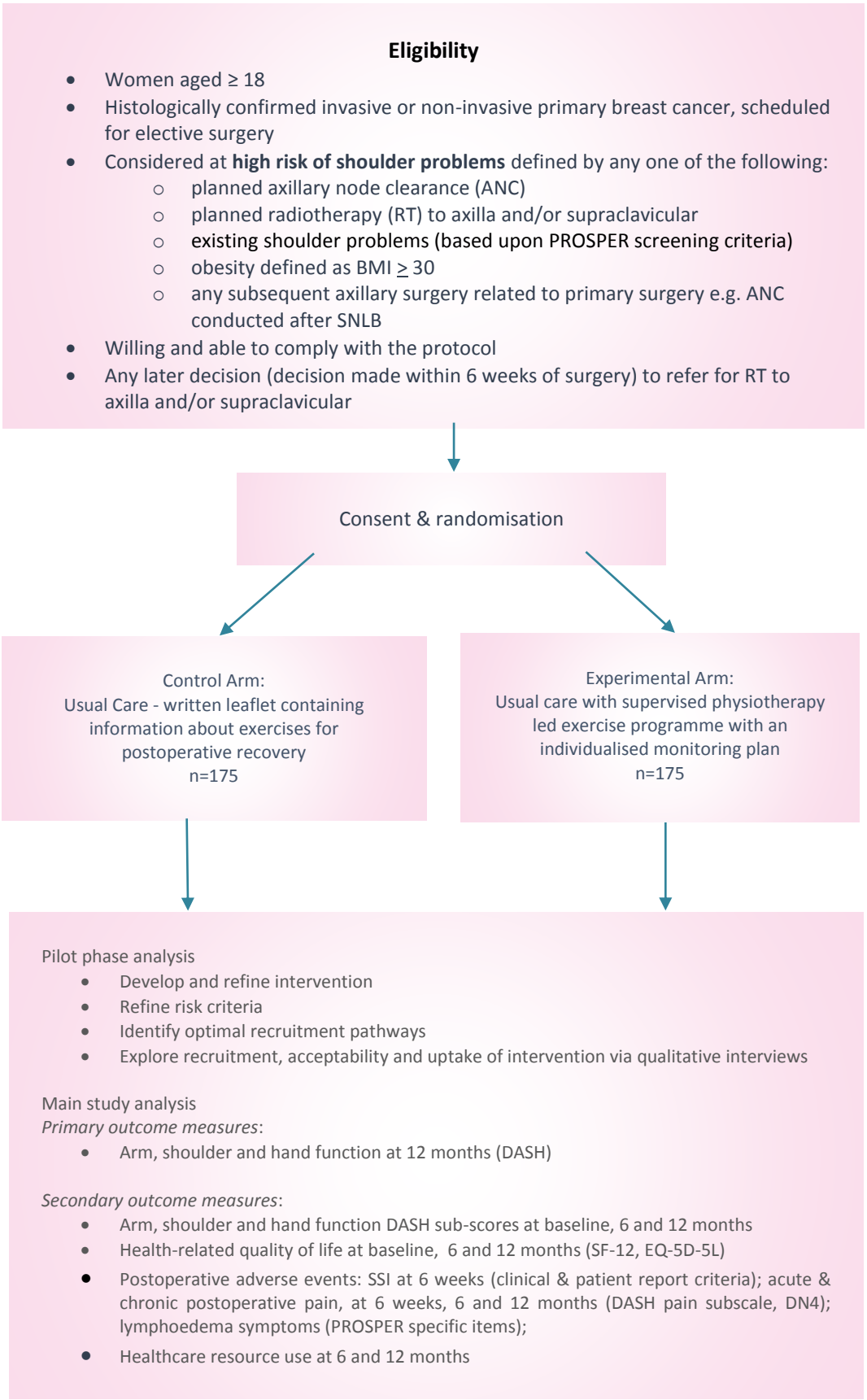
1. TRIAL SUMMARY

Title:	Prevention of Shoulder Problems Trial: exercise to prevent shoulder problems in patients undergoing breast cancer treatment.
Rationale:	Most women with breast cancer have surgery to the breast and axilla; some also have radiotherapy and chemotherapy. These treatments can affect the musculoskeletal system including the muscles, nerves and lymphatic vessels in the shoulder and upper body resulting in limited range of motion, weakness, persistent pain, altered sensations and lymphoedema (swelling due to accumulated lymphatic fluid). Studies suggest that between 10% and 67% of women have symptoms in their arm or shoulder up to 3 years after treatment. These persistent symptoms can limit daily activities, reduce quality of life and delay recovery. Structured exercise programmes, commenced within days or weeks of surgery, can improve shoulder movement and function and reduce complications. Usual NHS care is to provide information leaflets recommending upper body movements after breast cancer surgery to all women, and in many areas there is little access to physiotherapy, if at all. Current NHS pressures mean that many cancer centres now implement 'the 23-hour' care pathway, with the majority of women being discharged within hours or days after surgery without any physiotherapy support. Women who have extensive cancer treatment e.g. surgery to the axilla or radiotherapy, are at greater risk of developing shoulder problems. The PROSPER trial aims to prevent shoulder problems in women treated for breast cancer. The trial will investigate the clinical and cost-effectiveness of early supervised exercise compared to usual care, on outcomes of shoulder/arm function, health-related quality of life, chronic pain and other postoperative complications, following treatment for breast cancer. An internal pilot study will be undertaken to define risk criteria for women likely to experience shoulder problems following surgery, to determine recruitment pathways, and assess the acceptability and uptake of the exercise intervention.
Trial Design:	PROSPER is a multicentre 2-arm pragmatic randomised controlled trial (RCT) using 1:1 randomisation.
Trial arms:	Experimental arm: physiotherapy-led exercise programme with an individualised monitoring plan Control arm: usual care in the form of a written information leaflet
No. patients:	350: 175 per treatment arm
Stratification:	• First surgery vs repeat surgery • Centre • Informed of need for RT within 6 weeks of surgery
Objectives:	Pilot phase objectives: 1. To develop and refine a physiotherapy-led exercise programme, incorporating behavioural strategies, for women at risk of developing musculoskeletal problems after breast cancer treatment; 2. To test the acceptability of the exercise programme and outcome measures, and explore willingness to be randomised before and after surgery using qualitative interviews 3. Undertake an internal pilot study in up to 3 sites to test processes for the identification and assessment of high-risk patients (Year 1). Main trial objectives:

	4. Use findings from the internal pilot to expand and launch a larger multicentre definitive RCT across approximately 10 NHS breast cancer centres 5. To undertake clinical and cost-effectiveness analysis of the structured physiotherapy programme compared to best practice usual care.
Inclusion Criteria:	• Women, age ≥ 18 years • Histologically confirmed invasive or non-invasive primary breast cancer scheduled for surgical excision • Considered high risk of developing shoulder problems after surgery defined by one or more of the following: - planned axillary node clearance (ANC); - planned radiotherapy (RT) to axilla and/or supraclavicular; - existing shoulder problems (based upon PROSPER screening criteria); - obesity defined as BMI ≥30 - any subsequent axillary surgery related to primary surgery e.g. ANC conducted after sentinel lymph node biopsy (SLNB) • Willing and able to comply with the protocol • Written informed consent • Any later decision (made within 6 weeks of surgery) to refer for RT to axilla and/or supraclavicular *Note:* • Women who have had previous breast surgery (e.g. excision of benign tumour or breast cyst) are eligible for invitation; • Women who have had previous contralateral (opposite side) mastectomy are eligible for invitation.
Exclusion Criteria:	• Males • Women having immediate reconstructive surgery • Women having sentinel lymph node biopsy (SLNB) with or without breast surgery unless have other high risk criteria • Women having bilateral breast surgery • Evidence of known metastatic disease at time of recruitment
Outcome measures:	**Pilot phase:** • Develop a physiotherapy-led exercise intervention • Refine risk criteria identifying those at increased risk of acquiring shoulder problems following breast surgery • Identify optimal recruitment pathways for trial entry • Assess acceptability of trial recruitment pathways and exercise intervention via qualitative interviews (main trial). **Main trial:** Primary outcome: • Arm function measured using the Disabilities of Arm, Shoulder and Hand (DASH) questionnaire at 12 months Secondary outcomes: • Arm, shoulder and hand function DASH subscores at baseline, 6 and 12 months; • Health-related quality of life (QoL) measured using SF-12 and EQ-5D-5L at baseline, 6 months and 12 months;

	• Postoperative adverse events including: surgical site infection (SSI) at 6 weeks (clinical and patient reported criteria); acute and chronic postoperative pain at 6 weeks, 6 months & 12 months (DASH pain scale, DN4); lymphoedema symptoms (PROSPER specific items); • Healthcare resource use at 6 months and 12 months.
Analysis:	The primary analysis will be comparison of the two treatment groups, with results presented as mean differences between the trial groups, with 95% confidence intervals. Unadjusted mean change from baseline to 6 month and 12 month follow-up DASH scores will be compared by intervention arm. Potential factors to include in adjustment models, dependent upon distribution of baseline characteristics, include age, type of breast/axillary surgery and radiation therapy. Tests will be two-sided and considered to provide evidence for a statistically significant difference if *P* values are less than 0.05 (5% significance level). Where possible, reasons for missing data will be ascertained and reported. This will be assessed during the pilot phase to inform the main trial.

2. TRIAL SCHEMA



3. BACKGROUND

3.1 Epidemiology and burden of the condition

Breast cancer is the most common form of cancer in women in the UK. More women now survive, with two thirds of women living for 20 years beyond their diagnosis (1). It is extremely important that the NHS cares for women to ensure recovery and return to usual activities after cancer treatment. Most women have surgery to the breast and axilla (armpit), with some also requiring radiotherapy and chemotherapy. These treatments can affect the muscles, nerves and lymphatic vessels in the shoulder and upper body resulting in musculoskeletal problems such as: limited range of motion, weakness, persistent pain, altered sensations and lymphoedema (swelling due to accumulated lymphatic fluid). Studies suggest that between 10% and 64% of women have symptoms in their arm or shoulder up to 3 years after treatment (2). These persistent symptoms can delay recovery, limit daily activities, and reduce quality of life.

3.2 Existing knowledge

Surgery is the mainstay of treatment for breast cancer, supplemented with chemotherapy, radiotherapy and endocrine therapy, depending upon tumour stage and other clinical criteria. Upper limb problems, including decreased shoulder range of movement (ROM) and impaired strength, chronic pain, sensory disturbances and lymphoedema are common adverse effects after breast cancer treatment. Prevalence estimates for upper limb dysfunction vary, in part due to differences in definitions, methods of measurement and timing of postoperative follow-up. The most common complications include reduced shoulder range of movement (up to 67%), persistent pain and impaired arm strength (<28%) and related restrictions in function. Other postoperative complications, including cording and lymphoedema, contribute to these problems (3, 4). A nationwide Danish survey of 2500 women undergoing breast cancer surgery revealed that over a third of women report persistent pain and half reported sensory disturbances up to 7 years after treatment (2). Persistent upper limb dysfunction and pain are debilitating, having a negative impact upon sleep, quality of life, and both physical and emotional functioning. These persistent, yet potentially preventable, adverse sequelae of treatment are associated with disability and increased healthcare utilisation.

Previous trials investigating the efficacy of exercise have been criticised for being of poor methodological quality and uncertainty remains over the best exercises, the optimal timing of any exercise intervention, and the best strategy for maintaining adherence to exercise after breast cancer treatment (3). Early exercise e.g. vigorous shoulder ROM exercises (limited to 90 degrees) and stretching started within 48 hours of surgery, have been associated with increased risk of wound related complications, including seroma and infection (3, 5). In contrast, trials with limited ROM exercises in the first week post-surgery suggest that exercise interventions may be beneficial in regaining shoulder and arm ROM. However, additional important outcomes, such as upper limb strength and function, have been largely overlooked (3). Behavioural strategies incorporated within structured exercise programmes help promote adherence and sustainability over time, which may help reduce the healthcare burden from persistent adverse events and dysfunction.

3.2.1 Risk factors for shoulder problems

Risk factors for shoulder problems and upper body symptoms after breast cancer treatment include treatment-related factors e.g. type of axillary surgery, radiotherapy (to the axilla or the chest wall), and patient factors e.g. age, body mass index, and existing shoulder problems. Lee *et al.* (4) reviewed 32 studies to identify the prevalence of and independent prognostic factors associated with upper limb problems after surgery and/or radiation for early breast cancer.

Younger women may be more likely than older women (e.g <65 years versus ≥65 years) to experience any postoperative arm symptoms (4). Kootstra *et al*. (6) found that age was the strongest predictor of long term arm function, 7 years after treatment. However, mechanisms for developing arm problems at a younger age may in part be explained by tumour type and more invasive cancer treatment. Women undergoing mastectomy compared to breast conserving surgery are at greater risk of postoperative shoulder restrictions

(OR 5.67, 95% 1.03-31.16) (4). Differences in the subjective and objective measurement of shoulder function have been found to persist up to 18 months after mastectomy and breast conserving surgery (7). Women undergoing axillary lymph node dissection (ALND) are at greater risk of postoperative arm complaints compared to those having sentinel lymph node biopsy (OR 9.8; 95% CI 3.50, 27.45). Similarly, risk of shoulder restriction and chronic pain is greater after axillary sampling or clearance compared to SLNB (4, 6, 8). We have previously reported that women undergoing repeat surgery, thus hospital readmission within a short period of time after primary surgery, were at increased independent risk of reporting moderate to severe persistent chronic pain at 4 months after surgery (RR 2.77, 95% CI 0.98, 7.81(8)). Severe chronic postoperative pain in the upper body and axilla region is associated with anxiety and fear/avoidance of movement, which also can subsequently lead to loss of upper body function (8).

Radiation therapy and other factors

Radiation therapy (RT) increases the odds of shoulder restriction (pooled OR 1.67, 95% CI 0.98-2.86) and lymphoedema (pooled OR 1.46, 95% CI 1.16, 1.84) compared to women treated without adjuvant RT (4). Women reporting problems in the upper body and shoulder region *before* surgery are at increased risk of postoperative shoulder pain (8). Similarly, preoperative pain and chronic pain before surgery increases risk of postoperative symptoms (8, 9). Kootstra *et al.* (6) conducted a cohort study to investigate predictors of arm function at 2 and 7 years after treatment: Body Mass Index (BMI) at time of surgery had an independent negative effect on shoulder external rotation 7 years after breast cancer treatment. Increased BMI is also a risk factor for arm lymphoedema after surgery (10).

3.3 Hypothesis

The hypothesis for the study is that an early supervised exercise programme delivered to women at high risk of shoulder problems after breast cancer surgery can improve outcomes of shoulder function, health-related quality of life and reduce disability, chronic pain and related adverse events at 12 months after treatment. The aim of PROSPER is to investigate an early supervised exercise programme compared to best practice usual care within a randomised controlled trial (RCT), supported by qualitative methods and economic evaluation, to determine whether this is a feasible and cost effective intervention for the NHS.

3.4 Need for a trial

Breast cancer is the commonest cancer in women; around 85% of women in the UK diagnosed with breast cancer survive for at least 5 years after diagnosis (1). Given successes in increasing survival, it is therefore timely to identify strategies to improve their health-related quality of life. Upper limb pain and dysfunction post-surgery can have a debilitating effect on overall quality of life. Understanding and monitoring the acute and long term sequelae of cancer treatment is an increasingly high priority, with considerable clinical and research effort directed towards implementing surveillance programmes to manage and optimise recovery amongst cancer survivors. Reducing the public health burden from long term adverse consequences of cancer treatment will improve the health-related quality of life amongst breast cancer survivors, and may potentially expedite economic productivity through a more rapid return to work. Additionally, this may also reduce NHS-related costs associated with management of prolonged shoulder dysfunction and pharmacological interventions for chronic pain. Early postoperative intervention, through the introduction of structured, controlled upper arm movements in the acute postoperative period, may improve shoulder function after treatment for breast cancer.

Published systematic reviews have highlighted deficiencies in existing trials investigating exercise interventions, including the short-term nature of follow-up, which potentially misses the impact of longer term treatment sequelae (11). Some trial interventions have been very intensive, with multiple face-to-face physiotherapy sessions delivered over many weeks; this is unlikely to be a cost-effective strategy for the NHS (or indeed implementable if shown to be cost-effective). A 2010 Cochrane systematic review included only

one small UK trial published over 30 years ago (3). Although the bulk of available data suggest a benefit from early exercise, if exercise is too vigorous too early then this may lead to increased risk of wound-related complications (3). A UK trial (n=116 patients), published after the date of the Cochrane systematic review, found that participants were less likely to develop lymphoedema when exercises were limited to 90° elevation during the first week post-surgery compared to those who performed unrestricted exercises (12).

No large scale, high-quality, multicentre clinical trial investigating the cost-effectiveness of a structured physiotherapy intervention, underpinned using behavioural change techniques, has been conducted on women treated for breast cancer in the UK. Given the lack of knowledge regarding the intensity and duration of exercise intervention after breast cancer treatment, this trial will provide evidence on whether a rigorously designed physiotherapy intervention, incorporating behaviour change theory, improves postoperative outcome and will provide valuable knowledge on predictors for adherence to treatment over time.

3.5 Ethical considerations

The trial will be conducted in full conformance with the principles of the Declaration of Helsinki and to MRC Good Clinical Practice (GCP) guidelines. It will also comply with all applicable UK legislation and Warwick Medical School Clinical Trials Unit Standard Operating Procedures (SOPs). All data will be stored securely and held in accordance with the Data Protection Act 1998. There are no major ethical issues other than the potentially tight period between cancer diagnosis and planned date of cancer surgery. We will be sensitive to the fact that women may find this period difficult, and potentially have to deal with a large amount of new information. The qualitative interviews and focus groups to be conducted at the start of the study will explore how we can best facilitate recruitment to the trial without placing undue stress on participants, and will also identify barriers to participant recruitment.

3.6 CONSORT

The trial will be reported in line with the CONSORT (*Con*solidated *S*tandards *o*f *R*eporting *T*rials) statement (13).

4. TRIAL DESIGN

PROSPER is a multicentre pragmatic randomised controlled trial (RCT) which will compare best practice usual care of a written leaflet containing information about exercises after surgery with a physiotherapy-led exercise programme, which includes an individualised monitoring plan for women with primary breast cancer. An integrated pilot study will assess feasibility including the acceptability to, and uptake of the intervention, by patients. A total of 350 patients will be randomised in a 1:1 ratio.

4.1 Aims and objectives

The overall **aim** of the study is to investigate the clinical and cost-effectiveness of early supervised exercise compared to usual care, on outcomes of shoulder/arm function, health-related quality of life and chronic pain after treatment for breast cancer.

4.1.1 Pilot study objectives

- To develop and refine a physiotherapy-led exercise programme, incorporating behavioural strategies, for women at risk of developing musculoskeletal problems after breast cancer treatment;
- To assess the acceptability of the exercise programme and outcome measures, and explore willingness to be randomised around the time of breast cancer surgery using qualitative interviews;

- To refine risk criteria by testing processes for the identification and assessment of high-risk patients;
- To identify optimal participant recruitment pathways and undertake an internal pilot study in 3 clinical sites. This will include evaluation of entry (immediate and delayed) into the trial, depending upon clinical treatment.

4.1.2 Main trial objectives

- To test the feasibility of conducting a larger multicentre definitive RCT, using findings from the internal pilot phase, across approximately 10 NHS breast cancer centres to recruit 350 women;
- To undertake a clinical and cost-effectiveness analysis of the structured physiotherapy programme compared to best practice usual care.

4.2 Outcome measures

4.2.1 Pilot study

- To develop and refine the physiotherapy-led exercise intervention;
- To define risk criteria identifying those at increased risk of acquiring shoulder problems;
- To identify recruitment pathways in up to 3 clinical sites;
- To assess recruitment challenges and the acceptability of the exercise intervention via qualitative interviews.

4.2.2 Main study

Primary:

- Assessment of arm, shoulder and hand function at 12 months measured using the Disabilities of Arm, Shoulder and Hand (DASH) questionnaire.

Secondary:

- Assessment of arm, shoulder and hand function (DASH) subscales measured at baseline, 6 and 12 months. Subscales within the DASH capture impairment, activity limitations and participation restriction (14).
- Health related QoL as measured by SF-12 & EQ-5D-5L, measured at baseline, 6 and 12 months.
- Acute and chronic postoperative pain measured using pain items from DASH and Doleur Neuropathique (DN4) to capture neuropathic pain, measured at baseline, 6 weeks, 6 and 12 months.
- Surgical site infection measured at 6 weeks (clinical criteria).
- Postoperative symptoms, including indicators of lymphoedema at 6 weeks, 6 and 12 months (DASH and lymphoedema screening items (15).
- Health care resource use measured at 6 and 12 months (self-reported; HES data on pilot subsample).

4.2.3 Justification for selection of primary outcome

The primary outcome for PROSPER is upper limb function at 12 months. Upper limb function is the basis of both fine and gross motor skills which are critical to daily activities. Functional impairment to the arm can affect performance of simple daily activities, including dressing, writing, opening or closing jars, lifting and/or holding shopping bags, amongst others. Many assessment tools are shoulder-specific and do not assess these actions or activities. One review summarised the psychometric properties of 9 commonly used instruments

designed to measure symptoms and function of the shoulder (16); the DASH questionnaire was the most widely used and thoroughly tested instrument. This scale captures symptoms and function of the upper limb rather than the shoulder joint *per se,* which is important after breast cancer treatment. Although surgery and radiotherapy is targeted at the breast and axilla area, treatment side effects can impact upon the hand, arm and shoulder (e.g. potential trauma to the intercostobrachial nerve and lymphatic system), leading to problems with grip strength etc., and therefore function. Patient-reported outcome measures can be used to assess the difficulty of a variety of upper extremity activities during participation in daily roles – this is what is ultimately important to patients (17). Additionally, the WHO identifies three important health outcomes in the International Classification of Functioning Disability and Health (ICF) taxonomy on the consequences of disease: impairments, activity limitations and participation restrictions (18). The DASH includes 6 items on symptoms, 21 items on function and 3 items on social/role function. Although a single DASH score is calculated, psychometric assessment using discriminant content validation analysis has shown that the scale can be used to produce three health outcome scores: an impairment score, activity limitation score and participation restriction score (14). Finally, there is good evidence that the DASH can detect change, both minimally detectable change and minimally clinical important differences (19).

4.3 Patient selection & eligibility

4.3.1 Eligibility criteria

Patients are eligible to be included in the trial if they meet the following criteria:

4.3.1.1 Inclusion criteria

- Women ≥ 18 years
- Histologically confirmed invasive or non-invasive primary breast cancer scheduled for surgical excision of breast cancer
- Considered high risk of developing shoulder problems after surgery defined by one or more of the following:
  - planned axillary node clearance;
  - planned radiotherapy to the axilla and/or supraclavicular*;
  - existing shoulder problems (based upon PROSPER screening criteria);
  - obesity defined as BMI ≥30
  - any subsequent axillary surgery related to primary surgery e.g. ANC conducted after sentinel lymph node biopsy (SLNB).
- Willing and able to comply with the protocol
- Written informed consent

Note:

- *includes women **informed of need** for radiotherapy to the axilla and/or supraclavicular within **6 weeks** of surgery, thus potential late entry to the trial is allowed in this setting;
- Women who have had previous breast surgery (e.g. excision of benign tumour or breast cyst) are eligible for invitation, if they fulfil high risk criteria for shoulder problems;
- Women who have had previous contralateral (opposite side) mastectomy are eligible for invitation, if they fulfil high risk criteria for shoulder problems.

4.3.1.2 Exclusion criteria

- Males

- Women having immediate reconstructive surgery
- Women having sentinel lymph node biopsy (SLNB), with or without breast surgery, *unless* they fulfil other high risk criteria
- Women having bilateral breast surgery
- Evidence of metastatic disease at time of recruitment

4.3.2 Informed consent

It is the responsibility of the local Principal Investigator (or designee as listed on the Site Responsibilities Form) to obtain written informed consent in compliance with national requirements from each patient prior to entry into the trial. The trial must be discussed in detail with the patient, and the patient provided with a copy of the Patient Information Sheet. Patients should be offered sufficient time to consider the trial, allowing time for discussion with family/friends/GP. The patient must be given the opportunity to ask questions and to be satisfied with the responses prior to written consent being given. Due to variation in the clinical pathways and short time frame between diagnosis and surgery, information materials can be given and discussed preoperatively, but it may not always be possible to obtain written signed consent from all eligible patients before surgery. Additionally, patients can often be distressed and overwhelmed with clinical information during preoperative assessment clinics; therefore a subgroup of patients may need to be contacted afterwards by telephone to ask whether they are willing to participate in the trial, but written informed consent will be obtained before randomisation. We aim to recruit and randomise participants before surgery but this process will be explored during the pilot study.

A copy of the signed Consent Form(s) will be returned to the patient. Original Consent Forms must be retained on the hospital site; it is recommended that the original is retained in the trial site file, with a copy filed in the relevant patient's hospital notes. No Consent Forms should be sent to the PROSPER Trial Office at WCTU; any received will be returned to the PI for retention in the trial site file. If the Patient Information Sheet and/or Consent Form are modified due to new information becoming available during the course of the trial, sites will be notified of the procedure to follow for patients already consented and for prospective patients. Re-consent of participants may be required.

4.3.3 Recruitment

How potential participants will be identified and approached.

It is anticipated that potential participants will be identified from Multi-Disciplinary Team (MDT) meetings or by screening patients attending preoperative breast/oncology clinics. The initial screening process will be undertaken by a member of the clinical team, research nurse or facilitator (Site Investigator). This screening approach will identify eligibility based upon planned breast cancer treatment e.g. planned axillary clearance, radiotherapy to axilla and/or supraclavicular, or readmission for axillary surgery after a primary breast and/or SNLB surgery. One potential method may be to 'flag' patients by adding a brightly coloured sheet to the inside of medical notes stating that the patient is potentially eligible for invitation to the PROSPER trial. The sheet will specify a named person(s) to contact when the patient next attends for a clinic appointment.

Breast care nurses and surgeons or delegated personnel, will be asked to add simple pre-printed screening questions to existing clinical preoperative assessments, in order to screen for women with existing shoulder problems. This includes a simple screener asking about any previous treatment to the shoulder and pain level in the upper arm on the side of planned surgery. Women who are screened as being 'at risk' will be eligible for invitation to the trial, regardless of planned treatment pathways.

Radiotherapy Treatment – Delayed entry to the trial
Due to the complexity of clinical treatment pathways, we anticipate different points of entry to the study. Most women are informed of the need for radiotherapy before surgery, based upon the preoperative planned

treatment pathway. However, for some, the decision about the need for radiotherapy is confirmed **after surgery** e.g. during postoperative review at the MDT meeting. Any women informed of the need for radiotherapy to the axilla and/or supraclavicular within **6 weeks of surgery** will be eligible for invitation to participate. This is a pragmatic trial and it is important that inclusion criteria reflects 'real-life' contemporary clinical practice. This will be a stratification variable to ensure that women with **delayed entry** to the trial are equally distributed across intervention arms. Note that radiotherapy does not necessarily need to commence within this time frame.

Regardless of timing of entry, it is expected that all potentially eligible patients will be approached by clinical staff or research nurses/facilitators to ascertain their interest in taking part in the study. If the patient is interested, it is anticipated they will have further detailed discussion about the study with clinical staff or a research or breast care nurse, and will be given a Patient Information Sheet to take home.

Each recruitment site will be advised to give the patient a minimum of 24 hours to provide sufficient time to consider the trial and discuss with family, friends and other health professionals if preferred - this is in keeping with GCP guidelines. Some patients, but not all, will return to clinic and have the opportunity to ask any further questions or queries regarding the study. If the patient is willing to enter the trial, their written informed consent will be obtained by the Investigator prior to initiating any trial related procedures/activities.

We anticipate that a small number of patients will be contacted by telephone to give them verbal information about the study. Study information packs will be given in clinic where possible, but due to the short time frame between diagnosis and surgery, we may have to post packs and return signed consent forms before or on date of surgery. Permission will have been obtained at the initial discussion to pass their details onto the research team for the purposes of facilitating additional discussion.

Screening logs will be completed to capture limited details of patients who are eligible to be invited, the number approached and the number who declined to be given further information. As per described objectives, this process will be tested during the pilot phase of the study.

The aim for the main trial is to open approximately 10 NHS sites altogether to achieve the target sample size; however, if the nuances of the recruitment pathway at varying sites prove challenging, then additional sites may be approached.

The pre-randomisation procedure to ensure that all eligibility criteria are met.

The pre-consent procedure will involve completion of a simple screening sheet to record planned breast cancer treatment and risk assessment of shoulder problems; this will inform patient eligibility. Risk screening will be undertaken by the breast care nurse, other healthcare practitioner or by the research facilitator. The risk screening tool will include questions about any previous treatment for shoulder problems (pain/stiffness/weakness etc.), height and weight (BMI score). As described above, one objective of the pilot phase is to test and refine screening procedures and recruitment pathways. The aim is to standardise recruitment procedures across multiple sites, bearing in mind likely variation in clinical treatment pathways.

4.4 Randomisation

4.4.1 Randomisation procedure

The randomisation procedure will commence at the time consent has been given ('trial entry'). Given that breast cancer surgery is elective rather than emergency, a telephone rather than online randomisation service will be used. Before contacting the randomisation office at Warwick Clinical Trials Unit (WCTU), Site Investigators will complete a PROSPER Eligibility Form to confirm eligibility and informed consent. A Randomisation Form will also need to be completed to ensure essential information is available at point of

randomisation; this form will be used to collect patient data (patient initials; date of birth), stratification variables (e.g. type of surgery, timing of entry to the study in relation to surgery/radiotherapy) and centre details.

To preserve the patient's anonymity, only their allocated trial number and initials will be required on any clinical and patient documentation e.g. CRFs. With the patient's permission, a separate 'contact details' form will be used to record their name, address, telephone number and National Health Service (NHS) or Community Health Index (CHI) number to allow postal and telephone follow-up and also to allow data linkage with Health Episode Statistics (HES) data. Patients will be assured that their confidentiality will be respected at all times. Randomisation details can be phoned or faxed to the WCTU Randomisation Service:

Warwick Clinical Trials Unit
Telephone: +44 (0)24 7615 0402 (Mon-Fri, 9am-5pm)
Fax: +44 (0)24 7615 1586

The pilot phase will assess the stratification variables to ensure balanced distribution of patients allocated to each arm of the trial. Allocation will be reviewed by the independent Data Monitoring Committee during or after completion of the pilot study.

Once eligibility has been confirmed through the randomisation system, the patient will be allocated a unique Trial Number (TNO). An automated confirmation email will be generated which will contain the details of randomisation. Randomisation will be undertaken by a computer programme developed by the Warwick CTU programming team, managed by a Randomisation Officer. The randomisation system will ensure that there is no bias between the two trial groups. Patients will be randomised strictly sequentially, and treatment allocation between arms will be undertaken at a ratio of 1:1.

4.4.2 Randomisation documentation

After the participant has been randomised, the Investigator should send the patient's General Practitioner (GP) a letter and copy of the Patient Information Sheet to inform them of their participation in the PROSPER trial.

Eligibility/screening forms are kept in local site files. The participant's details must be entered onto the local site's Patient ID Log. The patient's trial number and initials will be used on all subsequent CRFs and correspondence relating to that patient.

At each site, screening logs must be maintained to document all patients considered for the trial but subsequently excluded. Where possible, the reason for non-entry to the trial must be documented. This must be sent to PROSPER Trial staff on a regular basis as requested. Patient names or hospital numbers must not be recorded on the Screening Log (use initials only).

4.5 Post-randomisation withdrawals, exclusions and moves out of region

Patients have the right to withdraw from the trial at any time for any reason. Patients should be encouraged to remain within the trial; however, if a patient wishes to withdraw from the trial, the PROSPER Trial Office should be notified immediately. Full details of the reasons for withdrawal must be recorded on the relevant documentation.

Patients may also decide to withdraw from the trial interventions or be withdrawn at the discretion of the Investigator and/or Trials Steering Committee due to safety concerns. If a patient withdraws from the trial intervention only (e.g. exercise programme), a Treatment Withdrawal Form should be completed with reason

for withdrawal. These patients are still eligible for follow-up unless the patient withdraws from the trial completely. Withdrawal forms will be designed to record information on level and reason for withdrawal (if known). Patients moving away from the region of the local site should NOT be withdrawn from the trial. Should this occur, please contact the PROSPER Trial Office with details of the relevant patient, and they will endeavour to assign the patient's follow-up to a site close to their new location.

4.6 Trial interventions

4.6.1 Control arm: Usual care

Patients allocated to the usual care arm will receive best practice usual care in the form of written leaflets containing information about exercises and recovery after surgery and treatments for breast cancer. These leaflets are usually given to patients before surgery. Guidance on best practice for written exercise materials is available from the NHS Breast Cancer Rehabilitation Pathway.

The most commonly used leaflets are 'Exercises after Breast Cancer Surgery (BCC6)' and 'Your Operation and Recovery (BCC151)' published by and freely available from the charity Breast Cancer Care (20). We have scoped different exercise information leaflets used by participating breast cancer centres and have selected these leaflets based upon content, style and clarity of presentation of information. Trial patient representatives and professionals, including physiotherapists specialising in shoulder/breast cancer treatment, were invited to contribute to this process. It is important to ensure that standard care reflects best practice across recruiting centres but also that materials are clear, readable and accessible to patients. Delivery of the control intervention will be done by breast care nursing staff or other healthcare professionals depending upon local practice.

4.6.2 Experimental arm: Exercise intervention

The PROSPER exercise programme was developed with input from experienced cancer and musculoskeletal physiotherapists who participated in an Intervention Development Day at the University of Warwick (18 March 2015). Patients randomised to the experimental arm will be allocated to a physiotherapy-led structured exercise programme which will comprise of between three and six sessions with a physiotherapist. When possible, the usual care information leaflets will be given preoperatively, to provide instruction until the first physiotherapy appointment. The therapy team will be informed when a trial participant has been randomised to the active intervention. The referral notification process, agreed with local therapy teams, will involve an 'urgent' referral to the named physiotherapist(s) trained in delivery of the PROSPER intervention.

The first physiotherapy session, to commence within seven to ten days after randomisation, will include a physiotherapy assessment of shoulder ROM, strength, pain and function. An individually tailored home exercise programme will be prescribed. This will include verbal education and written information provision on what to expect during the post-operative period, including advice about common post-operative complications as well as concerning generalised physical activity and/or work. We will utilise strategies to facilitate adherence to the exercise programme. The participant and physiotherapist will complete an exercise planner which involves goal setting, an assessment of their confidence in performing the prescribed exercises (strategies for building confidence will be used if needed), and stating where and when they will do their exercises. This document is then signed by the participant and physiotherapist acting as a contract, and is reviewed at subsequent visits. The physiotherapist will explain to the patient how their progress will be monitored and ensure that they know how to contact their physiotherapist should they need to; this may include further one-to-one treatment if needed. The participants will also be given an exercise diary to fill in following completion of their home exercises which will also be reviewed at the next appointment.
The second planned face to face physiotherapy appointment will occur approximately four to five weeks after randomisation and will involve assessment of progress and review of the home programme using the Exercise

Diary and Exercise Planner. It will progress exercises as appropriate and provide further education about monitoring progress, exercising during radiotherapy (where applicable), pacing, relaxation and coping with fatigue. A third planned physiotherapy session will occur approximately 12 to 16 weeks after randomisation to review and progress the home programme, including adding strengthening exercises to facilitate return to work, sport and hobbies. In later stage physiotherapy sessions, strategies for increasing and maintaining physical activity long term will be discussed and self-monitoring skills will be developed.

As per development work with the PROSPER PPI group and to reflect the pragmatic design of the trial, three additional physiotherapy consultations are available on request. These patients are at higher risk of developing upper limb problems. The timing and delivery of these appointments, either via telephone or face-to-face, is flexible to account for on-going treatment, physiotherapist judgement and patient preference. We recognise that for a very few women, further additional appointments may be necessary, and pragmatically these would be best delivered by their treating trial therapist. Ideally the intervention will be delivered within the first six months following surgery, but the trial allows women to contact their physiotherapist for additional support or advice for up to 12 months after randomisation. This means that any treatment-related shoulder problems occurring later in the recovery period will be dealt with by the trial physiotherapist, who is familiar to the woman. The actual number of physiotherapy sessions and method of contact will be closely monitored during the trial. As per study objectives, the physiotherapy intervention package will be tested and refined during the pilot phase.

4.6.2.1 Timing of delivery of exercise intervention

The timing of delivery of the intervention will depend upon knowledge of whether or not the patient requires radiotherapy to the axilla and/or supraclavicular, which will affect the timing of their entry to the trial. Wherever possible, the first physiotherapy assessment should be undertaken within **seven to ten days after surgery**. However, for those women who are informed about need for radiotherapy to the axilla and/or supraclavicular ***after*** their surgery, their risk status will change from low to high risk. These women are still eligible for invitation but will be recruited postoperatively. The first physiotherapy assessment should be undertaken within **six weeks of surgery**.

Group 1 - Immediate / early physiotherapy-led programme
This includes patients with planned axillary surgery or planned radiotherapy to the axilla and/or supraclavicular, regardless of type of breast surgery. Consequently, this encompasses women undergoing axillary surgery, including nodal clearance or extensive nodal sampling, **pre-planned radiotherapy** to the axilla and/or supraclavicular or those with existing shoulder problems. These patients are considered to be high risk based upon their expected treatment pathway or existing shoulder problems. Group 1 patients will be offered at least three physiotherapy face-to-face sessions, scheduled approximately for "baseline", four to five weeks postoperatively, and between 12-16 weeks postoperatively. As described in Section 4.6.2, the timing of these appointments are for guidance only, and will vary according to the requirements and availability of the patient.

Group 2 – Delayed physiotherapy-led programme (Radiotherapy)
Patients eligible for this group are those informed of the need for radiotherapy to the axilla and/or supraclavicular after their surgery. Patients in Group 2 may be at low risk initially and treated with usual care, but then transition to the high risk classification as a result of the later decision to refer them for radiotherapy. These women are eligible for PROSPER but will commence physiotherapy at a slightly later stage than Group 1. **The cut-point of six weeks from date of first operative procedure will be applied**. Physiotherapy sessions will be scheduled for as soon as possible after randomisation, 4-6 weeks, and 12-16 weeks thereafter respectively. This group will be treated with usual care up to the first six weeks, recruited to the trial, then allocated to either continue with usual care or the 'delayed onset' physiotherapy treatment pathway.

4.7 End of trial

Recruitment for the trial will end when 350 patients have been recruited. Participant follow-up will continue until 12 months after randomisation of the last patient recruited. The trial will be stopped prematurely if:

- Mandated by the Ethics Committee
- Following recommendations from the Data Monitoring Committee (DMC)
- Funding for the trial ceases
- Any other major clinical or therapeutic reason for the trial to be stopped prematurely.

The Research Ethics Committee will be notified in writing if the trial has been concluded or terminated early. No ongoing systematic treatment or follow-up will be offered after the trial has been completed, other than standard generic recommendations for exercise maintenance strategies as per the intervention manual.

5. METHODS AND ASSESSMENTS

5.1 Schedule of delivery of intervention and data collection

Table 1 summarises the schedule of events for the PROSPER trial. Usual care patients will be given their information leaflet and followed-up for 12 months as per the PROSPER timeline. Patients allocated to the exercise arm will complete patient adherence diaries and will be followed-up for 12 months as per the PROSPER timeline. The schedule for physiotherapy appointments is described above in Section 4.6.

5.2 PROSPER Patient Booklet

The first 'baseline' PROSPER patient questionnaire booklet will include the DASH, SF-12, EQ-5D-5L and other questionnaires relating to pain, infection and lymphoedema. These baseline questionnaires must be given to patients after written consent is obtained but prior to surgery – patients entering the trial via Group 2 (delayed physiotherapy-led programme) must complete these before their second surgery. A short 6-week questionnaire will be used to capture SSI, postoperative pain, and other adverse postoperative events; this will be a postal questionnaire in the first instance, although this can be completed by telephone or at clinic if there is an appointment at the appropriate time-point. Postal follow-up patient questionnaires will be administered at 6 and 12 months from randomisation. Self-reported symptoms of moderate to severe/extreme postoperative arm swelling and heaviness will be used as indicators of lymphoedema, based upon existing lymphoedema screening tools combined with the DASH impairment subscale. Items on Healthcare Resource Use (HRU) will be included in follow-up patient questionnaires. Participants will be asked to return completed questionnaires to the PROSPER Trial Office using prepaid return envelopes. A separate Data Management Plan will be written with policies for questionnaire reminders, including text message reminders, and telephone follow-up for core outcomes. The local researcher or delegated staff member should explain the requirements for completing follow-up questionnaires, to promote data collection and timely completion. A Freephone telephone number will be available for participants to contact the PROSPER Trial office directly should they have any queries whilst completing their Questionnaire Booklets.

5.3 Schedule of events

Once a patient has been confirmed eligible, informed consent will be obtained and the patient will be randomised. A PROSPER Questionnaire Booklet must be completed at baseline (before randomisation), and 6 and 12 months by postal questionnaire thereafter. A separate questionnaire must be completed at 6 weeks post-surgery.

Table 1: Schedule of Events

	Pre-randomisation	6 weeks from surgery	6 months from randomisation	12 months from randomisation
Inclusion criteria satisfied	√			
Informed trial consent taken	√			
Screened for risk of shoulder problems	√			
Planned surgery assessed	√			
Planned radiotherapy noted (if known)	√			
PROSPER Patient Questionnaire	DASH SF12 EQ-5D-5L Pain/DN4 Lymphoedema*	Pain / DN4 SSI Lymphoedema	DASH SF12 EQ-5D-5L Pain/DN4 Lymphoedema*	DASH SF12 EQ-5D-5L Pain/DN4 Lymphoedema*
Healthcare Resource Use			√	√

*Lymphoedema self-report screening items within Patient Questionnaire Booklet

Other considerations

a. The nature and time of radiotherapy treatment to the axilla and/or supraclavicular will be according to local protocols.
b. The baseline PROSPER Patient questionnaire can be completed either in clinic or at home to be returned by post to the PROSPER Trial Office.

6. ADVERSE EVENT MANAGEMENT

6.1 Definitions

6.1.1 Adverse Events (AE)

An Adverse Event (AE) is defined as any untoward medical occurrence in a participant and which does not necessarily have a causal relationship with this intervention. Expected common postoperative events include: superficial SSIs, seroma, bruising/haematoma and drain-site infections. With regards to the exercise intervention, some muscle soreness will be expected after stretching and strengthening exercises. Any other type of adverse events will be recorded and reported. After the pilot study, this reporting process will be presented and reviewed by the Trial Steering Committee (TSC).

6.1.2 Serious Adverse Events (SAEs)

In non-CTIMP trials, a serious adverse event (SAE) is defined as an untoward occurrence that:

(a) results in death;
(b) is life-threatening;
(c) requires hospitalisation or prolongation of existing hospitalisation;
(d) results in persistent or significant disability or incapacity;

(e) consists of a congenital anomaly or birth defect; or
(f) is otherwise considered medically significant by the investigator.

For the purposes of reporting, the following events will be recorded postoperatively but will not be considered SAEs, unless considered arising as a direct consequence of the trial intervention:

- superficial and deep SSIs;
- seroma;
- bruising/haematoma;
- drain-site infections;
- lymphodema;
- cording.

6.2 Serious Adverse Event reporting procedure

The reporting of SAEs for the PROSPER trial will be carried out according to Warwick CTU Standard Operating Procedures (SOP). A SAE occurring to a research participant should be reported to the main REC where in the opinion of the Chief Investigator the event was:

• **Related** – that is, it resulted from administration of any of the research procedures,
AND
• **Unexpected** – that is, the type of event is not listed in the protocol as an expected occurrence.

A "directly attributable" SAE will only be recorded and reported if the event occurs during contact time with the healthcare professional (physiotherapist) delivering the intervention or whilst undertaking study exercise, either supervised or unsupervised. This applies to a SAE which is life-threatening, requires hospitalisation, results in persistent or significant disability or incapacity, requires medical attention to prevent one of the above or is considered medically significant by the investigator. This does not apply to expected events such as delayed onset muscle soreness or infection (as described in Section 6.1 above).

SAEs will be reported using the PROSPER Serious Adverse Event Form. The Site Investigator or treating physiotherapist must report any SAEs to the trial coordinating centre within 24 hours of them becoming aware of the event. **The Serious Adverse Event form should be completed and faxed to the dedicated fax number at Warwick CTU: 02476 150549.** The Trial Coordinator will liaise with the Site Investigator or physiotherapist to compile all the necessary information. The trial coordinating centre is responsible for reporting related and unexpected serious adverse events to the sponsor and REC within required timelines.

All SAEs that occur in relation to the exercise intervention programme and during the monitoring follow-up period must be recorded, together with data including date of onset and resolution, outcome, severity and causality for the trial intervention.

7. DATA MANAGEMENT

7.1 Data acquisition

Personal data collected during the trial will be handled and stored in accordance with the 1998 Data Protection Act. The CRFs will be designed by the Trial Co-ordinator in conjunction with the Chief Investigator and Statistician. Completed patient and clinical CRFs will be stored by WCTU, and copies on site.

7.2 Confidentiality

The personal data recorded on all documents will be regarded as strictly confidential. To preserve the patient's anonymity, only their allocated trial number and initials will be recorded on any trial documentation. With the patient's permission, their name, date of birth, address, telephone number and health service (NHS) number/Community Health Index (CHI) number will be held on a secure database in the PROSPER Trial Office to allow postal follow-up and data linkage with Health and Social Care Information Centre (HSCIC) for HES data.

For qualitative interviews, patients will sign separate consent forms for permission regarding data use and storage. Qualitative interviews will be audio recorded and will be stored electronically and identified by trial number only. Patients will be assured that their confidentiality will be respected at all times.

The Local Investigator must maintain documents not for submission to the WCTU (e.g. patients' written consent forms) in strict confidence. In the case of special problems and/or governmental queries, it will be necessary to have access to the complete trial records, provided that patient confidentiality is protected. Warwick CTU will maintain the confidentiality of all patient data and will not disclose information by which patients may be identified to any third party, other than those directly involved in the intervention.

7.3 Data collection and management

Each site will be provided with an Investigator File containing copies of trial related documentation and CRFs. Data collected on each patient must be recorded by the local Principal Investigator (PI), or his/her designee (as documented on the site signature/delegation log), as accurately and completely as possible. The PI is responsible for the timing, completeness, legibility, accuracy and signing of trial-related documentation and he/she will retain a copy of each completed form. The PI must allow trial staff access to any required background data from hospital records (source data e.g. medical records) on request.

All fields MUST be completed. If an assessment or intervention was not done, please indicate why that was omitted on the CRF. Entries must be made in black ballpoint pen. Errors must be crossed out with a single line leaving the original data un-obscured (i.e. without overwriting), the correction inserted and the change initialled and dated. An explanatory note should be added if necessary. Correction fluid/tape/labels must not be used. All data submitted on trial documentation must be verifiable in the source documentation. Any deviation from this must be explained appropriately.

Completed CRFS should be returned to:
PROSPER Trial Office
Warwick Clinical Trials Unit
Warwick Medical School
University of Warwick
Gibbet Hill Road
Coventry, CV4 7AL

7.4 Database

The database will be developed by the Programming Team at WCTU and all specifications (i.e. database variables, validation checks, screens) will be agreed between the programmer and appropriate trial staff. The live database will only be accessible by authorised personnel.

7.5 Data Storage

All essential documentation and trial records will be stored by WCTU in conformance with the applicable regulatory requirements and access to stored information will be restricted to authorised personnel. Trial documentation and data will be archived for at least ten years after completion of the trial in accordance with WCTU SOPs.

7.6 Data access and quality assurance

On receipt, all forms will be checked for completeness and congruity. Forms containing empty data fields or data anomalies will be queried with the site for resolution. Data will be entered onto the trial database and any further anomalies will be identified and queried with the site. Periodically, data will undergo additional checks to ensure consistency between data submitted on CRFs.

Trial staff will maintain regular communication with sites, through routine calls, mailings and/or meetings. In the event of persistent issues with the quality and/or quality of data submitted, an on-site monitoring visit may be arranged. In such circumstances, patient notes and the investigator site file must be available during the visit. The representative from the PROSPER Trial Office will work with the site staff to resolve issues, offer appropriate training if necessary, and determine the site's future participation in the trial.

An audit may be arranged at a site if the Trial Management Group feels it is appropriate. Audits will be conducted by an independent team, determined by the Trial Management Group. Access to stored information will be restricted to authorised personnel.

7.7 Archiving

Trial documentation and data will be archived for at least ten years after completion of the trial in accordance with WCTU SOPs. Local site policies may be in situ, however we request that they will be expected to store PROSPER data on site for up to ten years, in order to address any future data queries.

8. STATISTICAL ANALYSIS

8.1 Stratification

The stratification variables relate to timing of surgery (first versus repeat), centre and timing of need for radiotherapy. The first variable adjusts for the requirement for additional surgery which will change risk status from low to high. The second stratification variable will ensure balanced allocation across each recruitment site. The third variable is an indicator for timing of delivery of the exercise intervention, whether participants will be randomised at the time of surgery (preoperatively up to the day of surgery) or within the first 6 weeks ***after*** surgery. For this category, patients will be treated by usual care until informed of need for RT which then changes their risk profile from low to high risk. The similarity across treatment arms will be maintained through stratification.

Thus, randomisation will be stratified by:

a) First surgery vs. repeat surgery
b) Centre
c) Informed of need for RT within 6 weeks of surgery.

8.2 Power and sample size

Our selection for the target sample size is 350 total number of patients, allocated in a 1:1 ratio. This is based on existing data from a trial using a similar sample and intervention (21). A between group difference of 7 points on the DASH at 6 months (mean 21.6 control, mean 14.6 intervention, pooled standard deviation (SD) of 19.5 at baseline, standardised mean difference 0.36). These estimates are based on published estimates of the efficacy of a similar intervention and population. This Dutch trial included women with breast cancer undergoing axillary node clearance, randomised to physiotherapy sessions over a 3 month period starting at 2 weeks postoperatively.

At 80% power and $p<0.05$, this yields a target of 242 in total. Accounting for therapist effects, with 9 patients per therapist in the intervention and control arm, an intracluster coefficient (ICC) of 0.01, yielding a design effect of 1.05), yields a target of 256 patients. The ICC estimate is based on our previous experience of exercise interventions in a range of musculoskeletal trials. We seek to randomly allocate intervention participants to physiotherapists. Based on our experience of similar standardised interventions, we anticipate very little therapist effect but in the eventuality of lower therapist effects, we would have greater power with the given numbers to detect the same difference. Finally, we anticipate loss to follow up of less than 10% based on our previous clinical studies experiences in this patient group, but we have inflated by 25% to cover the possibility that loss to follow up is greater, and thus allowing the potential to detect smaller effects if accrual and retention to go plan.

We have considered the recommended minimally clinically important difference (MCID) for the DASH (19). Studies of rheumatological and orthopaedic populations has suggested that the MCID is 10, and that the between group difference for trials should be set at 10. However, this fails to account for many of the eventualities that are occur in pragmatic trials, notably that there is not a no treatment control, and that some of the control group may be exposed by serendipity to an intervention of similar intensity, particularly in a high risk population.

8.3 Criteria for early termination of the trial

The purpose of the internal pilot study is to test whether the components of the main study work together and to check that patients are willing to be recruited and randomised. It is important to determine the consent rate for patients entering the trial as this will have a direct impact on how many centres we are likely to need in order to recruit the full sample (n=350 participants).

8.3.1 *Recruitment*

We aim to conduct the internal pilot study in Coventry, Oxford and one other recruitment centre (as requested by the funder). The intended sample size for the internal pilot study is 37 participants, approximately 10% of the full sample. These randomised patients will be retained in the full trial analysis. Decisions regarding stop-go criteria are given in Table 1.

Table 1. Pilot study recruitment targets

Target recruitment Year 1	**Actual recruitment Year 1**		
37 participants (100%)	28 – 37 participants (75-100% of pilot recruitment target)	19 – 27 participants (50-75% of target)	< 19 participants (<50% of target)
Stop-go criteria	Recruitment feasible; proceed to main trial	Review recruitment strategies per site. Report to TSC/DMC/HTA. Continue but modify protocol & monitor closely	Recruitment not feasible; decision not to proceed to main trial

8.3.2 *Acceptability of the exercise intervention*

The other important aim of the pilot study is to assess acceptability of the exercise intervention. This will be judged by assessing uptake to the intervention by recording data on number of face to face and telephone contacts between physiotherapists and participants. Adherence with an exercise intervention is important in determining its effect. Previous trials have used different criteria to judge uptake, attendance and engagement with exercise interventions. For example, number of contacts has been reported as: failure to attend any appointment; attended initial session only; partial completion of treatment; and fully completed treatment (22). In a current trial of exercise interventions offered to older adults (PreFIT Study HTA 0/14/41), the following criteria are being used: 'engagement with exercise intervention' = at least 1 contact with physiotherapist; and, 'intervention retention/adherence' = compliance with agreed number of sessions. Women randomised to the PROSPER intervention arm will be offered up to 6 sessions with a trained physiotherapist, although the number of recommended sessions will be individually tailored, based upon the initial baseline assessment. The initial face-to–face assessment will be defined as 'at least 1 contact with physiotherapist.'

8.4 Statistical analysis

8.4.1 Pilot phase

At the end of the internal pilot phase in Year 1, the overall recruitment to the three selected clinical centres will be calculated and compared to the target rate per centre per month. We estimate two patients per month per site. Actual uptake, reasons for refusal and rate of withdrawals from the pilot phase will inform the design and decision to proceed to the main trial ("Stop/Go" criteria), as described in Section 8.3. It will also inform the final number of sites to approach for the main trial. Currently, this has been estimated as ten centres but could be increased if required.

8.4.2 Main trial

The main 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 the 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 the 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 radiation therapy) estimates. These mean changes and their 95% confidence intervals will be plotted graphically so as that the change can be assessed over the course of the study. Secondary outcomes which are continuous 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 the clustering effect.

If there are more than three missing items, the DASH score cannot be computed. As a sensitivity analysis, the impact of the 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 analysis (23, 24). The detailed analyses and template tables will be reported in a detailed statistical analysis plan. This will be reviewed and approved by the DMC, prior to any final statistical analysis of the data.

8.5 Health Economic Evaluation

An economic evaluation will be integrated into the trial design. The economic evaluation will be conducted from the recommended NHS and personal social services (PSS) perspective (25). Data will be collected on the health and social service resources used in the treatment of each trial participant during the period between randomisation and 12 months post-randomisation. Primary research methods will be followed 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, participant monitoring activities, and any follow-up/management. Broader resource utilisation will be captured through three principal sources: (i) trial Case Report Forms (CRFs); (ii) patient questionnaires administered at baseline, 6 weeks, 6 months and 12 months post-randomisation; and (iii) information extracted from routine health service data collection systems. It may not be possible to obtain Hospital Episode Statistics (HES) data from the Health & Social Care Information Centre (HSCIC) for all trial participants within the tight timeframe of the study. However, we anticipate requesting inpatient and outpatient data on a small subset (pilot study participants) in order to assess level of concordance between HES and self-report data. Any discordance between the two sets of resource use data will inform subsequent calibrations of the self-reported resource use data in the larger trial cohort. Current UK unit costs, estimated through a combination of primary and secondary research methods, will be applied to each resource item to value total resource use in each arm of the trial. Health-related quality of life will be measured at baseline and at 6 and 12 months post-randomisation using the generic EuroQol EQ-5D-5L and SF-12 measures; national tariff sets will be used to generate quality-adjusted life-years (QALYs) (26-29).

An incremental cost-effectiveness analysis, expressed in terms of incremental cost per quality-adjusted life year (QALY) gained, will be performed. Results will be presented using incremental cost-effectiveness ratios (ICERs) and cost-effectiveness acceptability curves (CEACs) generated via non-parametric bootstrapping. This accommodates sampling (or stochastic) uncertainty and varying levels of willingness to pay for an additional QALY. A series of sensitivity analyses will be undertaken to explore the implications of uncertainty on the incremental cost-effectiveness ratios and to consider the broader issue of the generalisability of the study results. One such sensitivity analysis will involve adopting a societal perspective for the economic evaluation, which will incorporate direct costs to trial participants and their carers, informal care provided by family and friends, and productivity losses. Due to the known limitations of within-trial economic evaluations (30), we will also construct a decision-analytical model to model beyond the parameters of the proposed trial the cost-effectiveness of the physiotherapy-led exercise programme in this clinical population.

Long term costs and health consequences will be discounted to present values using discount rates recommended for health technology appraisal in the United Kingdom (25). A series of probabilistic sensitivity analyses will be undertaken to explore the implications of parameter uncertainty on the incremental cost-effectiveness ratios. Probabilistic sensitivity analyses (PSAs) will also explore the effects of extending the study perspective, target population, time horizon and decision context on the incremental cost-effectiveness ratios. In addition, cost-effectiveness acceptability curves will be constructed using the net benefits approach.

8.6 Qualitative sub-study

A qualitative sub-study will be undertaken in the first year with additional interviews planned later in the trial. An objective of the pilot study is to undertake patient interviews to explore willingness to be randomised into an exercise trial and to assess the acceptability of the physiotherapy-led exercise programme and outcome measures. Later interviews will explore the acceptability of and adherence to the exercise programme.

8.6.1 Aim

The overall aim of the qualitative research is to explore willingness to be randomised into an exercise trial around the time of breast cancer surgery and to assess the acceptability of the physiotherapy-led exercise programme and outcome measures, among women with a diagnosis of breast cancer.

8.6.2 Specific Objectives

Trial Recruitment (Interviews)

1) To explore willingness to be randomised into an exercise trial around the time of breast cancer surgery;
2) To explore women's views about exercise and to identify barriers and facilitators for recruitment into PROSPER, including views on the impact of shoulder problems related to breast cancer treatment;
3) To inform optimal timing of approach for explanation about the study and invitation to recruit;
4) To assess the acceptability of completing study questionnaires, the proposed exercise intervention and related materials.

Acceptability of the exercise intervention (Interviews /Focus Groups)

5) To obtain feedback on the acceptability of the exercise programme;
6) To explore women's views about barriers and motivators for adherence to the exercise programme;
7) To explore information provision towards the end of treatment; understanding of risk of shoulder problems; confidence regarding ability to self-manage / when to seek help.

8.6.3 Design

Qualitative study.

8.6.4 Method

In-depth, semi-structured interviews will be conducted and audio-recorded with participants eligible for recruitment to PROSPER, regardless of whether or not they choose to participate in the Trial. Interview topic guides will be used to ensure similar areas are covered in each interview within each group, based on those used in previous studies but also encouraging the informants to express their own views about PROSPER.

8.6.5 Sample and Frequency

Interviews will be held at various time points in the first year with different patient groups. During the first phase of year 1, women with newly diagnosed breast cancer will be invited from preoperative and postoperative clinics for interviews to explore issues in relation to proposed trial recruitment. We will seek to interview a sample of women who would, if approached to participate in the trial, accept or decline recruitment to PROSPER in order to obtain thorough data about the acceptability of the proposed recruitment method and intervention. Participants invited for actual recruitment to PROSPER will also be asked to indicate on their consent form if they would be willing to take part in an interview study. We will seek to interview around 10-15 women at different stages throughout year 1. Purposive sampling will be utilised, striving for a mix according to geographical location, age, employment status, socio-economic background and ethnicity. Interviews will also be held later in the trial (end of year 2/early year 3) to explore barriers and motivators for adherence to the exerise intervention in a small sample of participants randomised to the programme.

8.6.6 Analysis

Interviews will be recorded, transcribed and analysed using a Framework Approach. A thematic framework will be developed using a priori issues and questions from the aims of the study and new themes raised by participants within the interviews. The framework will be applied to the text of the interviews and the coded data from each interview will be arranged on a chart according to each issue/theme identified. Associations and differences between themes will be examined with a view to providing explanations of the participants' experiences and understandings. Comparisons will be made between groups of women and over time.

Computer software will be used to organise the data for analysis (e.g. NVivo). Analysis will be a collaborative process between the interviewer, the qualitative advisor, and the study team.

9. TRIAL ORGANISATION AND OVERSIGHT

9.1 Sponsor and governance arrangements

The University of Warwick and University Hospitals Coventry & Warwickshire NHS Trust will act as Co-Sponsors for the PROSPER study.

9.2 Regulatory authorities/ethical approval

PROSPER Trial has submitted for ethics approval from West Midlands - Solihull Research Ethics Committee in the UK. The local Principal Investigator must submit this protocol, any supporting documentation and any amendments, to the R&D Office at the Trust, as appropriate in accordance with local requirements and recommendations made by the REC. All required approval(s) for the trial will be sought using the Integrated Research Application System.

Before enrolling patients into the trial, each trial site must ensure that the local conduct of the trial has the approval of the relevant NHS Trust Research & Development (R&D) department. Sites will not be permitted to enrol patients into the trial until written confirmation of R&D approval is received by the PROSPER Trial Team.

All agreed substantial protocol amendments will be documented by the PROSPER Trial Office and will be submitted to the main REC for approval prior to submission to local parties as appropriate. Each trial site must ensure that they are using the most up to date version of the protocol, the Patient Information Sheet and Consent Form. All previous versions of the protocol, and other trial documents should be crossed out with 'this version is now superseded' written on cover page.

9.3 Indemnity

NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk. All sites should ensure that they carry insurance allowing them to conduct studies including this one. The University Hospitals Coventry & Warwickshire NHS Trust provides indemnity for any harm caused to participants by the design and/or management of the research protocol.

9.4 Trial timetable and milestones

Table 2: Trial timetable and key milestones

Month		Activity	Milestone	Responsibility
-3	Feb	Ethics preparation		CI
	Feb	Set-up main contract	Signed contract	CI/WCTU
	Feb	Advertise project staff		CI/WCTU
Project Year 1, 2015				
1-6 Set-up	Mar	Start Trial / appoint staff	Appoint staff	WCTU /TMG
	Apr	Ethics preparation & submission / R&D pilot	R&D submission	CI/TC
	May	Compose TSC /DMC		TMG
	May	Set up pilot site subcontracts		WCTU
	May	Prepare CRFs & exercise intervention manual		TC/RF
	May	Prepare & conduct qualitative interviews		RF
	June	Develop database /Refine intervention		WCTU
	July	Ethical revisions	MREC approval	CI/TC/TMG

7-12 Pilot	Aug	TSC review meeting / HTA Progress Report	1st TSC / HTA	CI/TMG
	Oct	Open pilot, centres 1 & 2, qualitative interviews		TC/RF
	Oct	Test assessment, recruitment & intervention		RF/CI
	Nov	Open pilot, centre 3		TC/RF
	Dec	Main trial preparation, contracts, R&D etc		TC
	Feb	R&D approvals prepared for main trial sites		TC/CI/RF
	Feb	Review pilot data, report feasibility to TSC	TSC /HTA reports	RF
Project Year 2, 2016				
13-18	Mar-May	Start launch of main trial, open centre 4	Launch main trial	TC
	Apr-Oct	Open remaining centres 5 -10	All by autumn2016	TC
	Apr-Oct	Deliver interventions, conduct QA checks	HTA Report	RF
19-24	Sep-Feb	Recruitment, delivery, monitoring & QA		RF/TC
	Sep-Feb	Postal CRF follow-up	HTA Report	TC
	Dec-Feb	Qualitative interviews with trial particpants		RF
Project Year 3, 2017				
25-30	Mar-Jun	End participant recruitment	350 recruited	TC/RF
31-36	Jun-Feb	Participant data collection & follow-up		TC/RF
	Dec	TSC report	TSC /HTA Reports	TMG/TSC
Project Year 4, 2018-9				
37-42	Mar-Aug	Complete follow-up at all sites		TC
		Final data entry and cleaning	HTA Report	TC
43-48	Sep-Feb	Statistical & HE analysis / Site closure		STAT/HE
		Prepare reports & manuscripts	HTA Report	CI/TMG/PPI

9.4.1 Key milestones

PROSPER will randomise 350 patients from national research networks in the UK. An integrated pilot study will test the acceptability and uptake of the exercise intervention during months 7-12. All centres will be asked to provide screening logs which should include number of patients screened, reasons for refusal and any issues at randomisation. Recruitment rates will be regularly checked to see if any additional training or interventions are required to improve rates at poorly recruiting sites, and to share best practice from the top recruiting sites.

Months 0-6: Grant activation and trial set up. Purchasing computers and equipment. Development and refinement of exercise intervention, and scoping of recruitment pathways; intervention meeting with clinical experts. Qualitative interviews to explore recruitment challenges. Preparation of trial documentation, including site initiation documents and case report forms. Site initiations for pilot centres. DMC/TSC meeting prior to starting recruitment.
Months 7-12: First pilot study patient randomised. Qualitative interviews to assess acceptability of intervention. Set up remainder of sites, and review recruitment. Review pilot data and report to TSC/DMC.
Months 13-18: Launch for main trial. Open remainder of sites and start recruitment into main trial.
Months 19-30: Complete recruitment (by month 26).
Months 36: TSC report
Months 37-42: Complete follow up at all sites and final data entry and cleaning
Months 43-48: Statistical analysis and health economic evaluation. Site closure. Host investigator day and prepare reports and manuscripts. Report to TSC/DMC according to agreed monitoring timetable.
Months 48-108: Follow-up of patients and data collection & data cleaning.
Months 84: Data cleaning and analyses of interim analysis of 3 year disease specific survival
Months 90 -108 Final analysis with 5-years minimum follow-up on all patients, preparation of HTA report and manuscript, presentation at Clinical National and International conferences, dissemination through patient and consumer groups.

9.5 Administration

The Chief Investigator for the trial is Dr Julie Bruce, University of Warwick. The trial will be co-ordinated from the PROSPER Trial Office at WCTU, under the direction of Dr Julie Bruce. Professor Sallie Lamb and Dr Esther Williamson from University of Oxford will provide physiotherapy expertise. Clinical responsibility will be undertaken by the surgical investigators of the Trial Management Group.

9.6 Trial Management Group (TMG)

The TMG includes a multidisciplinary team of researchers, statisticians, physiotherapist and economist who have considerable expertise in all aspects of design, running, quality assurance and analysis of the trial. This group includes co-investigators as well as experts co-opted for their expertise. It is anticipated that the TMG will meet monthly by teleconference. The Trial Management Group, consisting of the project staff and co-investigators involved in the day-to-day running of the trial, will meet regularly throughout the project. Significant issues arising from management meetings will be referred to the Trial Steering Committee or other clinical Investigators and lay contributors, as appropriate.

9.7 Trial Steering Committee (TSC)

The trial will be guided by a group of respected and experienced personnel and trialists as well as at least one 'lay' representative. The TSC will have an independent Chairperson. Face to face meetings will be held at regular intervals determined by need but not less than once a year. Routine business is conducted by email, post or teleconferencing. The Steering Committee, in the development of this protocol and throughout the trial will take responsibility for:

- Major decisions such as a need to change the protocol for any reason
- Monitoring and supervising the progress of the trial
- Reviewing relevant information from other sources
- Considering recommendations from the DMC
- Informing and advising on all aspects of the trial

The proposed membership of the TSC is shown on page 4.

9.8 Data Monitoring Committee (DMC)

The DMC will consist of independent experts with relevant surgical/health sciences research, and statistical experience. An independent data monitoring committee will be established for this trial. The DMC will review trial progress, recruitment, protocol compliance and interim analysis of outcomes (not formally tested outside of the trial statistical analysis plan to be agreed with the DMC), annually or more frequently if requested, in line with the trial milestones and agreed trial monitoring policy. The DMC will advise on whether the trial should continue, be amended or stopped prematurely.

The DMC will meet to review progress after the pilot study (aim to recruit 35 patients), and regularly thereafter. Confidential reports containing recruitment, protocol compliance, safety data and interim assessments of outcomes will be reviewed by the DMC. The DMC will advise the TSC, based on the trial data monitored and any future publications or emerging worldwide evidence. DMC meetings will also be attended by the Chief Investigator and Trial Co-ordinator (for non-confidential parts of the meeting) and the trial statistician. The proposed membership of the DMC is shown on page 4.

9.9 External Dissemination

The National Cancer Research Institute (NCRI) Breast Cancer Clinical Studies Group (CSG) will be informed about the PROSPER trial.

9.10 Essential Documentation

A Trial Master File will be set up according to WCTU SOP and held securely at the coordinating centre. The coordinating centre will provide Investigator Site Files to all recruiting centres involved in the trial.

10. MONITORING AND QUALITY ASSURANCE OF TRIAL PROCEDURES

This trial is being conducted under the auspices of MRC GCP according to the current guidelines for Good Clinical Research Practice in the public sector. Participating institutions will be monitored by the Warwick CTU personnel, to confirm compliance with the protocol and the protection of patients' rights as detailed in the Declaration of Helsinki. Copies of the Declaration may be obtained from the PROSPER Trial Office.

All Clinical Investigators taking part in the trial will attend a start-up meeting/initiation visit for training on study procedures and data collection methods. The Investigator at each institution must apply for and receive site specific R&D approval before they can recruit into the study. A risk assessment will be undertaken to detail the potential hazards of the trial and subsequent monitoring will be performed in line with Warwick CTU's monitoring procedures. On site monitoring visits will be conducted if it is felt there is a cause for concern at a particular site or if the site requests. All study documentation and source records must be securely retained for at least 10 years after the closure of the study. Documentation held at sites must be made available for any internal (R&D) audit purposes.

11. PATIENT AND PUBLIC INVOLVMENT (PPI)

Four PPI representatives, all of whom have been treated for breast cancer, have been consulted. Ms April Matthews and Ms Lynda Luke are members of 'Independent Cancer Patients' Voice', a patient advocate group independent of the main cancer charities. ICVP was started by breast cancer patients with a keen interest in research. The group focuses on ensuring that the needs of patients are addressed by clinical research. Dr Catherine Harkin is a general practitioner who suffered from chronic postoperative pain and 'frozen shoulder' which delayed her return to work after cancer treatment. Dr Harkin is involved with raising awareness of the incidence and burden from chronic pain after breast cancer treatment; she is also a PPI representative on the TMG. Our final PPI representative is Mrs Lyn Ankorn, a retired physiotherapist with an interest in cancer research. Our PPI representatives have read and contributed to the application. They have provided input and feedback on the exercise intervention, choice of outcome measures and commented on issues relating to participant recruitment.

PPI representatives have discussed the proposed interventions, and they have advised on issues relating to recruitment as they understand the worries and concerns faced by women during cancer treatment. Ms Matthews, Ms Luke and Mrs Ankorn will form a reading group to review study materials including participant information sheets, cover letters and intervention documentation. The reading group will review all plain English summaries. As co-author, Dr Harkin will review the final report and related publications. The reading group will contribute to research reports and press releases. The PROSPER Trial team will support PPI representatives to feedback to other cancer organisations e.g. Independent Cancer Patients' Voices, Breast Cancer Care etc. Several meetings have been held with PROSPER PPI representatives and have identified training needs. It is planned for PPI representatives to attend the INVOLVE conference.

12. DISSEMINATION AND PUBLICATION

The results of the trial will be firstly reported to trial collaborators. The main report will be drafted by the trial co-ordinating team at the WCTU, and the final version will be agreed by the HTA before submission for publication, on behalf of the collaboration. The success of the trial depends on the collaboration of researchers

from across the UK. Equal credit will be given to those who have wholeheartedly collaborated in the trial. The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org) (13).

The trial will show whether or not a physiotherapy led exercise programme with an individualised monitoring plan can improve upper arm function and quality of life, and reduce disability, pain and other adverse events following breast cancer treatment. Trials of structured exercise introduced in the early weeks after surgery have shown benefit in regaining shoulder and arm ROM, although important outcomes such as function have been largely overlooked, and this trial aims to fill the evidence gap. The results will be presented at national and international meetings and widely disseminated amongst the research community. This will generate publications in high impact journals. Patient involvement is fundamental to the PROSPER trial. Our patient representatives will ensure that the results of the study are disseminated through INVOLVE and their national contacts, other patient representatives and websites including www.independentcancerpatientsvoice.org.uk.

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14. APPENDICES