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# BMJ Open

**RadBone: Bone Toxicity following Pelvic Radiotherapy. A prospective randomised controlled feasibility study evaluating a musculoskeletal health package in women with gynaecological cancers undergoing pelvic radiotherapy.**

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Manuscripts

**Title:** RadBone: Bone Toxicity following Pelvic Radiotherapy. A prospective randomised controlled feasibility study evaluating a musculoskeletal health package in women with gynaecological cancers undergoing pelvic radiotherapy.

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**Abstract:**

**Introduction:** Patients receiving radiotherapy are at risk of developing Radiotherapy Related Insufficiency Fractures (RRIFs), which are associated with increased morbidity and pose a significant burden to patients' quality of life and to the health system. Therefore, effective preventive techniques are urgently required. The RadBone randomized controlled trial (RCT) aims to determine the feasibility and acceptability of a musculoskeletal health package (MHP) intervention in women undergoing pelvic radiotherapy for gynaecological malignancies and to preliminary explore clinical effectiveness of the intervention.

**Methods and Analysis:** The RadBone RCT will evaluate the addition to standard care of a MHP consisting of a physical assessment of the musculoskeletal health, a three-month prehabilitation personalised exercise package, as well as an evaluation of the fracture risk and if required the prescription of appropriate bone treatment including calcium, vitamin D and - for high-risk individuals- bisphosphonates. Forty participants will be randomized in each group (MHP or observation) and will be followed for 18 months. The primary outcome of this RCT will be feasibility, including the eligibility, screening and recruitment rate, intervention fidelity and attrition rates; acceptability; and health economics. Clinical effectiveness and bone turnover markers will be evaluated as secondary outcomes.

**Ethics and dissemination:** This study has been approved by the Greater Manchester East Research Ethics Committee (Reference: 20/NW/0410, November 2020). The results will be published in peer reviewed journals, will be presented in national and international conferences, and will be communicated to relevant stakeholders. Moreover, a plain English report will be shared with the study participants, patients' organizations, and media.

**Clinical trial registration:** NCT04555317.

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3 **Keywords:** radiotherapy, insufficiency fractures, musculoskeletal health, gynaecological  
4 cancer, randomised control trial.  
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### 10 **Strengths and Limitations of this study**

- 12 • The RadBone is the first randomized controlled trial to explore the feasibility and  
13 clinical effectiveness of a musculoskeletal health package aimed to prevent  
14 radiotherapy related insufficiency fractures (RRIFs).  
15
- 16 • A feasibility economic evaluation will allow future assessment of this complex  
17 intervention's cost-effectiveness.  
18
- 19 • Planned longitudinal proteomic analyses may reveal mechanistic insights and  
20 promising treatment targets.  
21
- 22 • A prospectively published detailed protocol increases the transparency and allows for  
23 peer review of the methodology used.  
24
- 25 • This study is not blinded and lacks an active comparator. Therefore, it is susceptible to  
26 performance and detection bias.  
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30 **Word count: 2,982**  
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## Introduction

In 2015 there were 2.5 million people in the UK with a diagnosis of cancer and this number is expected to rise to 4 million by 2030<sup>1</sup>. As a result of the continuing improvement in early detection of disease and improved treatment efficacy, a significant proportion are living long beyond their cancer diagnosis. However, estimates suggest that currently over 500,000 people living with and beyond cancer have one or more physical or psychosocial consequences of their cancer or its treatment that affect their lives on a long-term basis. These consequences also have a substantial implication in terms of NHS resources.

Patients receiving radiotherapy are at risk of developing radiotherapy related bone toxicity, in particular radiotherapy related insufficiency fractures (RRIFs). Incidence of RRIFs following pelvic radiotherapy has been reported as between 1.7 and 89% and occurring between 3 to 20 months post radiotherapy. The wide variation in reported incidence depends on imaging modality and radiological reporting standards, symptomatic versus asymptomatic fractures, radiotherapy dose and underlying tumour type (reviewed in<sup>2</sup>). A recent meta-analysis of over 400 patients with RRIFs following pelvic radiotherapy for gynaecological cancers suggested an overall incidence of 14%<sup>3</sup>. Over 30 studies have been published since the 1990's describing more than 1000 patients with pelvic RRIFs. This literature is notable for being almost exclusively retrospective in nature, a sparsity of baseline assessment of bone density and fracture risk, the absence of Patient Reported Outcome Measures (PROMs) used to assess Quality of Life (QOL) and no primary preventative or secondary management intervention studies<sup>4,5</sup>.

The devastating effects of osteoporotic fragility fractures on morbidity and mortality and the economic cost are well described<sup>6</sup>. Pelvic insufficiency fractures may also increase mortality<sup>7</sup> but these data reflect an elderly population with multiple co-morbidities and the applicability to the pelvic radiotherapy population is not well defined.

Although there are no pelvic RRIF studies reporting QOL as an outcome measure; clinical experience, patient radiotherapy support group reports and anecdotal commentary in the literature describe the anxiety, pain, reduced mobility and increased morbidity associated with these, with a number of patients requiring hospital admission for assessment and pain control<sup>8</sup>. Considering pelvic radiotherapy toxicities, including but not limited to RRIFs, more formal studies of QOL and PROMs are much needed<sup>9</sup>.

Whilst a small number of studies, confirmed in a recent meta-analysis<sup>3</sup>, suggest osteoporosis as a risk factor in pelvic RRIFs, unlike the strong evidence base for bisphosphonate use in primary and secondary prevention of fragility fractures, there is no such evidence for RRIFs<sup>5</sup>. A small non-controlled study demonstrated intravenous zoledronic acid administration prior to spinal radiotherapy led to a lower prevalence of radiotherapy bone toxicity than expected<sup>10</sup> and a single randomised prospective study in patients undergoing spinal radiotherapy for

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3 metastatic disease demonstrated that intravenous zoledronic acid reduced urinary markers  
4 of collagen cross linking<sup>11</sup>.  
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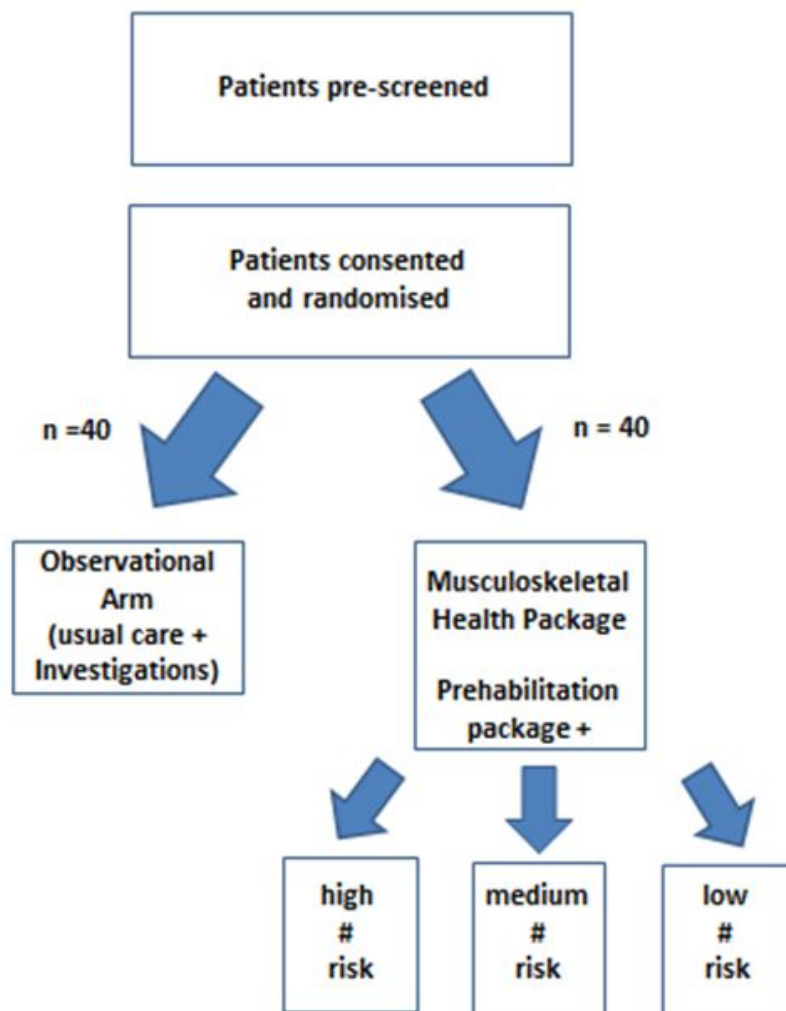
7  
8 Contradictory data from animal studies around the protective effects of bisphosphonates on  
9 RRIFs limits our understanding of the pathophysiology and therapeutics of RRIFs. Animal  
10 studies using whole mouse radiation have demonstrated an early activation of bone  
11 resorption in the 5 days following low dose (2 Gy) of radiotherapy which was reduced by  
12 subcutaneous administration of risedronate immediately following irradiation<sup>12</sup>. In contrast,  
13 a focal radiation technique in mice (using a small animal radiation research platform or  
14 SARRP), arguably a more physiological representative method of irradiation, demonstrated  
15 that alendronic acid did not prevent the radiation induced trabecular bone loss but that this  
16 was prevented by blocking osteoblast apoptosis with PTH 1-34<sup>13</sup>.  
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22 The RadBone is the first open-label prospective randomised controlled trial (RCT) to  
23 determine the feasibility and acceptability of a musculoskeletal health package (MHP)  
24 intervention in women undergoing pelvic radiotherapy for gynaecological malignancies and  
25 inform power calculations for a definitive RCT. Moreover, this feasibility trial will also explore  
26 potential implications on the incidence of RRIFs, quality of life and other clinical effectiveness  
27 and safety outcomes, as well as providing indicative estimates of the intervention's cost-  
28 effectiveness.  
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## Methods and analysis:

### Study Design



### Study setting

The planned study is a prospective randomised controlled feasibility trial of eighty patients with gynaecological malignancy (cervical and endometrial) undergoing pelvic radiotherapy at the Christie Hospital NHS Foundation Trust in Manchester, UK (a tertiary referral Oncology centre).

## Eligibility Criteria

Individuals aged over 18 years, with a histologically confirmed endometrial or cervical cancer undergoing potentially curative or adjuvant radiotherapy will be eligible, provided they are able and willing to provide an informed consent to participate.

The exclusion criteria are (i) age less than 18 years or greater than 85 years; (ii) pre-existing bone conditions such as osteoporosis treated with bisphosphonates in the previous 5 years, fibrous dysplasia, osteogenesis imperfecta, or other metabolic bone conditions; (iii) home address outside Greater Manchester; (iv) contraindication or intolerance of Magnetic Resonance scanning.

## Interventions

Women undergoing radiotherapy for a gynaecological malignancy will be randomised to an observation (Ob) group and will receive standard assessment and care, following the current local clinical pathway, or an intervention group that will receive a “musculoskeletal health package” (MHP), in addition to standard assessment and care and will be followed for 18 months.

Patients randomised to the MHP arm will receive (i) a physical assessment of musculoskeletal health and a 3-month prehabilitation personalised exercise package as part of the Greater Manchester prehab4cancer program<sup>14</sup>, (ii) a fracture risk assessment (FRAX) based on baseline dual-energy x-ray absorptiometry (DXA) bone mineral density (BMD), and (iii) treatment for bone health according to national UK recommendations i.e., standard of care for prevention of fragility fractures, by being subdivided into 3 groups (low risk, medium risk and high risk).

Patients with a normal BMD and a FRAX score below the National Osteoporosis Guideline Group (NOGG) recommended treatment line will be considered low risk. Medium risk is defined as osteopenia on the DXA, with FRAX score below the NOGG treatment line. Finally, those with osteopenia and a previous vertebral or hip fracture, or a FRAX score above the NOGG recommended treatment line will be considered high risk.

Low risk patients will be provided with a copy of the Royal Osteoporosis Society (ROS) “Healthy living for strong bones” leaflet. In addition to the leaflet, medium risk patients will receive calcium (1000 mg once daily) and vitamin D (800 IU per day) supplementation. The same interventions will be offered to high-risk patients, who will also undergo secondary osteoporosis screening (blood tests) and will receive oral alendronate 70mg once weekly, in

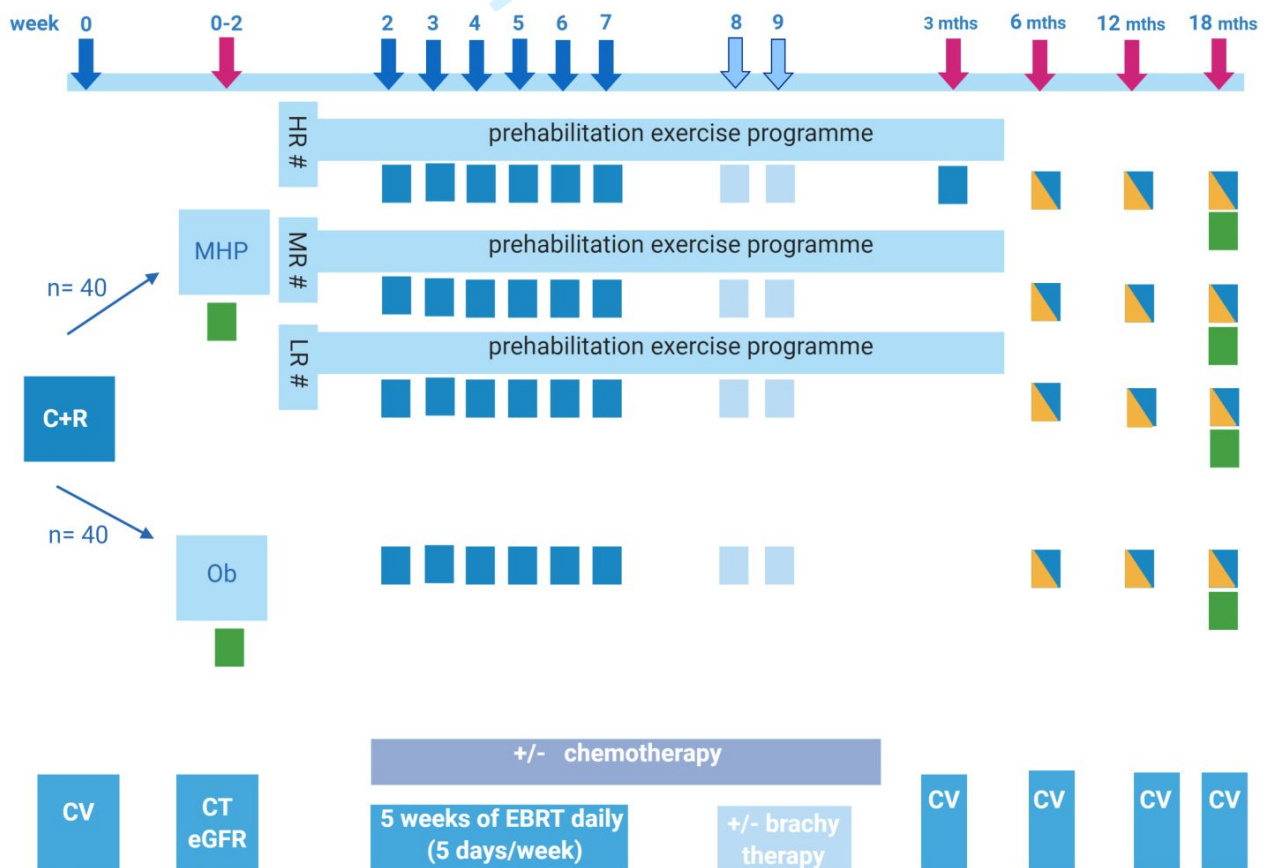
the absence of contraindications. Annual intravenous zoledronic acid infusion will be considered as an alternative where appropriate.

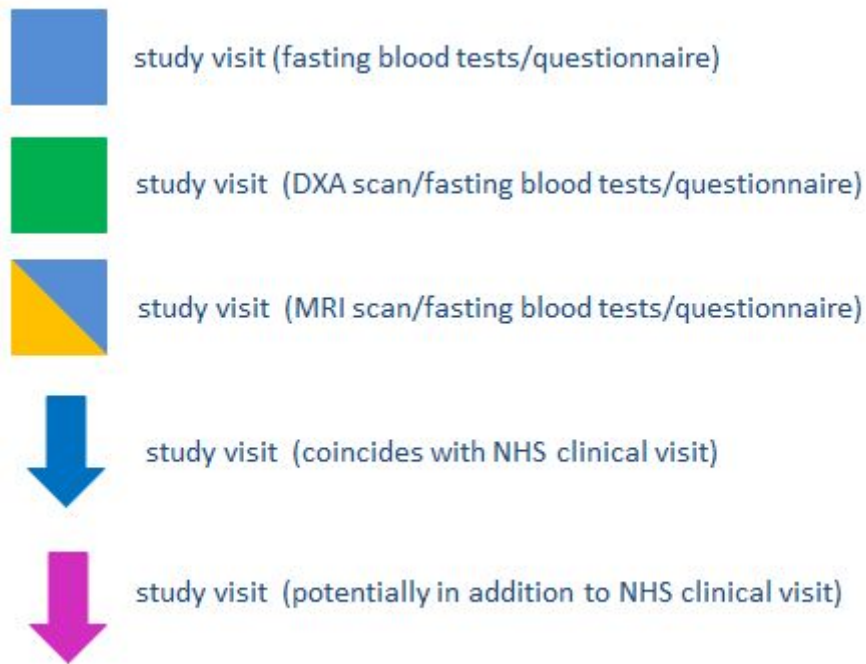
Those randomised to the observation arm will remain blinded to the results of the evaluations until the end of the study unless a fragility fracture or RRIF develops during the study.

**Prehabilitation Exercise Programme (Prehab4cancer)**

All patients randomised to the MHP arm of the study will be offered a bespoke prehabilitation exercise programme via the Prehab4cancer programme in Greater Manchester (<http://www.prehab4cancer.co.uk/>). The MHP arm patients will be referred to the Prehab4cancer team via electronic referral immediately following randomisation. Allocated patients will be individually assessed by the Prehab4cancer team according to their usual protocols and assigned an appropriate prehabilitation program. Duration of the programme is 12 weeks from the first assessment and participation will be encouraged, as tolerated.

**Baseline and Follow-up Evaluation**





27 C+R = Consent and Randomisation, MHP= Musculoskeletal Health Package arm, Ob = observational  
28 arm HR = high risk, MR = medium risk, LR = low risk, CV = clinic visit, EBRT= External Beam  
29 Radiotherapy. NHS: National Health System  
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34 Baseline evaluations will include a bone health assessment with DXA BMD measurement and  
35 completion of a bone health questionnaire. PROMs will also be captured. Finally, fasting  
36 serum and plasma blood samples will also be collected.  
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39 At 6, 12 and 18 months post radiotherapy all patients will undergo a pelvic MRI assessment  
40 for RRIFs, PROMs assessment and fasting blood sampling. During the final visit, at 18 months,  
41 all patients will have a DXA BMD scan and physical assessment of their musculoskeletal  
42 health. If signs or symptoms compatible with a RRIF are described outside the study visits  
43 study participants will be assessed and managed following the current clinical pathways.  
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### 47 **Imaging studies**

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50 DXA scans of the total hip, femoral neck, L1-L4 spine and TBS assessments will be performed  
51 on a single DXA scanner (Hologic Horizon A SN 300792M version 5.6.07 with TBS v.3.0.2  
52 calibrated to the above scanner) at the Christie NHS Foundation Trust as per local protocol.  
53 These will be undertaken by two technicians trained in conducting DXA. Images will be  
54 reviewed, validated and interpreted by the lead investigator (CEH). The femoral neck BMD  
55 ( $\text{g}/\text{cm}^2$ ) will be used in conjunction with a standardised DXA questionnaire to complete FRAX  
56 calculation.  
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3 Pelvic Magnetic Resonance Imaging (MRI) scans will be performed at 6, 12 and 18 months on  
4 a 1.5T MRI scanner at the Christie Hospital by trained radiographers in accordance with the  
5 study imaging protocol. Four pelvic sequences will be performed per patient (5mm slice  
6 thickness, field of view 400mm; coronal T1, coronal STIR (inversion time 150ms), axial T1 and  
7 axial STIR (inversion time 165 ms). These will correspond to routine follow-up scans where  
8 possible. All bone sequence scans will be dual reported by 2 consultant radiologists who will  
9 document the presence of fracture and their confidence in its presence, fracture location,  
10 fracture line, bone marrow oedema and other abnormalities.  
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### 15 ***Biochemical studies***

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18 Fasting blood tests will be performed at baseline, weekly during radiotherapy (visits 2 to 10,  
19 one day prior to chemotherapy if receiving) and at 6, 12 and 18 months in all patients. Patients  
20 allocated to the MHP High risk arm and started on oral bisphosphonate therapy will have an  
21 additional bone turnover marker blood test at 3 months to assess bisphosphonate efficacy.  
22 All samples will be taken simultaneously with routinely collected clinical blood samples where  
23 appropriate.  
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28 As part of the MHP intervention arm, blood will be sampled, analysed, and assessed at  
29 baseline, 6, 12 and 18 months for the measurement of full blood count, urea and electrolytes,  
30 liver function tests, parathyroid hormone, vitamin D, thyroid function test, oestradiol, HbA1c,  
31 procollagen type 1 amino-terminal propeptide (P1NP), and the beta-C-terminal telopeptide  
32 (CTX). Moreover, in the observation arm, serum samples will be collected, processed and  
33 stored at -80°C for batch analysis at the end of the study.  
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38 Additional fasting blood samples will be collected at all timepoints mentioned for longitudinal  
39 analysis of bone turnover markers and for proteomic analysis. These samples will be  
40 processed and stored at -80°C, following local standard operating procedures (SOPs), for  
41 batch analysis at the end of the study. Bone turnover markers will be evaluated using ELISA  
42 techniques and will include CTX, NTX, P1NP, osteocalcin, TRAcP5b and bone ALP.  
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### 46 ***Sequential Window Acquisition of all Theoretical Mass Spectra (SWATH-MS)***

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48 Proteomic analysis will be conducted at the Stoller Biomarker Discovery Centre, following  
49 local SOPs<sup>15</sup>. Samples will be analysed by a Data Independent Acquisition method known as  
50 SWATH-MS with a micro-flow LC-MS system comprising an Eksigent nanoLC 400 autosampler  
51 and an Eksigent nanoLC pump coupled to a SCIEX 6600 Triple-TOF mass spectrometer (68 min  
52 run-time). When SWATH maps are generated, the presence and abundance of plasma  
53 proteins will be quantified using published plasma reference libraries. Differential expression  
54 analysis will be used to identify candidate biomarkers using artificial intelligence approaches.  
55 Linear regression will be used to detect correlations with the presence of RRIFs and BMD.  
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3 Few longitudinal studies have tracked proteins of interest over the whole course of  
4 radiotherapy from pre-treatment baseline through to follow-up. We have undertaken one  
5 pilot that shows the potential value of this work<sup>16</sup>. Other studies that have investigated this  
6 have demonstrated distinguishing profiles with groups of approximately n=30. Two pre-  
7 radiotherapy baseline samples will be used to assess natural variation and comparison with  
8 the variance of measurements following radiotherapy and further comparison between the  
9 MHP and observation arm (n=40 per group).  
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14 Electronic data will be pseudoanonymised (coded) to protect the identity of the participants.  
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### 17 18 **PROMS and Health Utilisation Proforma**

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21 PROMs will be collected either as electronic PROMS (using the myChristie, myHealth  
22 application) or paper-based PROMS at baseline, 6, 12, and 18 months.  
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25 The evaluated PROMs will include the adapted pelvic patient-reported outcome version of  
26 the common terminology criteria for adverse events (PRO-CTCAE) assessment, the Short  
27 Musculoskeletal Function Assessment (SMFA) modified for lower limb, the 5-level version of  
28 the EuroQol tool (EQ-5D-5L) and a tailored Health Utilisation Proforma.  
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### 31 32 **Criteria for discontinuing**

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34 Participants may decide to withdraw from the study at any time. Discontinuation of the study  
35 participants may occur as a result of investigator decision, safety concerns, and significant  
36 non-compliance to the protocol or incorrect enrolment. Reasons for discontinuation will be  
37 captured.  
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41 As this is a feasibility study, participants may decide to discontinue their participation in  
42 certain aspects of the study (for example declining the prehabilitation programme or deciding  
43 not to take recommended medications). The participants can continue with the study and the  
44 details will be captured in the case report form (CRF).  
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### 48 49 **Outcomes**

50 The primary outcomes for this feasibility study will inform the design and power calculations  
51 for a definitive UK multi-centre RCT. These are:  
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- 53 1) Eligibility and screening rate: proportion of patients eligible for the study from patient  
54 population
- 55 2) Recruitment and study group allocation rate: number and proportion of eligible  
56 patients recruited, randomised and allocated to appropriate study populations.  
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- 3) Intervention fidelity rate: number and proportion of patients completing the elements of the study (assessment visits, prehab exercise programme, prescribed medications, QOL questionnaire)
- 4) Attrition rate: number of patients lost to follow-up.
- 5) Patient and physician acceptability assessed with electronic questionnaires.
- 6) Health Economic Analysis: within-trial cost-effectiveness analysis to demonstrate feasibility of health economic data collection and analysis in a multi-centre RCT.

The secondary outcomes are:

- 1) Incidence of pelvic insufficiency fracture
- 2) Longitudinal change in BMD and fracture risk
- 3) Longitudinal change in biochemical markers of bone turnover
- 4) Longitudinal change in measured musculoskeletal health markers
- 5) Quality of Life
- 6) Incremental cost-effectiveness ratios: cost-per-QALY (quality-adjusted life-year) and cost-per-change in SMFA score

Exploratory Endpoints include identification of predictive markers of RRIFs (radiomic, proteomic, BMD) and exploratory measurement of proteomic biomarkers of bone turnover during pelvic radiotherapy.

### Sample Size

No formal power calculation has been performed as this is a feasibility study. The study will collect initial data such as measures of location and variability for key outcome measures. It is recognised that in general, 30 patients are required in order to estimate such parameters<sup>17</sup>. For this study a total of 80 patients will be recruited and randomised with equal probability to either the MHP or observation arms (i.e. 40 per group). Assuming attrition rates of 15% per group, at least 30 should remain in each arm. This should be sufficient to assess the feasibility of a larger RCT study and estimate group means, standard deviations and percentages for key outcomes.

### Recruitment

80 patients will be recruited over an 18-month period, approximately 4 patients per month. As this is a feasibility study there will be no interim analysis of study results.

### Assignment of interventions

Consenting, eligible participants will be randomised to the MHP or observation group using a validated online service; sealedenvelope™ (<https://www.sealedenvelope.com>). A permuted

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3 block (block size:4) randomisation protocol will be utilised with a 1:1 allocation (MHP to  
4 observation arm).  
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## 6 7 **Data Collection, management and analysis** 8

### 9 10 *Statistical and Health Economic Analysis*

11 As this is a feasibility study, it will not involve hypothesis testing to identify whether the  
12 intervention has had an impact. Instead, data analysis will be descriptive, focusing on the  
13 percentage of patients in each group developing RRIFs and risk factors for this. Means and a  
14 measure of variation will be calculated for each secondary outcome. These data, along with  
15 estimates of recruitment and attrition rates, will help inform a power calculation for the  
16 definitive trial.  
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21 A within-trial cost-effectiveness analysis<sup>18</sup> will be undertaken from the perspective of the UK  
22 National Health Service (NHS). Cost data for the intervention arm will reflect resource use  
23 associated with the musculoskeletal health package and treatment costs for both the control  
24 and intervention arm will be taken into account. Resource use will be extracted from patient  
25 records and the health care utilisation proforma. Relevant sources (e.g., NHS reference costs)  
26 will be used to identify unit costs. Health related quality of life (HRQL) scores will be generated  
27 using the EQ-5D-5L at baseline and at each of the three follow-up time points (6, 12, 18  
28 months).  
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33 A descriptive analysis of the costs and outcomes data will be completed focusing on: a.  
34 whether the EQ-5D-5L and SMFA are able to adequately capture differences in health status  
35 before and after implementation of the musculoskeletal health package and across both  
36 treatment arms of the study; b. whether the resource-use survey is able to record data  
37 necessary to enable a full cost-effectiveness analysis; c. the nature of missing data for the EQ-  
38 5D-5L, SMFA and resource-use survey to assess responses, sensitivity, and any patterns within  
39 the missing data.  
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45 A within-trial cost-effectiveness analysis will be conducted to provide an indicative estimate  
46 of cost-effectiveness. Between-arm differences in costs and outcomes will be expressed as an  
47 incremental cost-effectiveness ratio (ICERs): the cost per QALY gained from the intervention  
48 compared to usual care. ICERs will also be calculated using the SMFA in an additional scenario  
49 analysis.  
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## 53 54 **Trial oversight** 55

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57 An internal trial management group will be convened for the study, consisting of the chief  
58 investigator, project manager, Clinical Trials administrator, research nurse and a  
59 representative of the research and innovation division (R+I) as core members. The group will  
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3 meet monthly. The study sponsor (Christie Hospital NHS Foundation Trust) will monitor the  
4 conduct of the trial.  
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### 7 **Patient and Public Involvement**

8 This protocol was developed with the participation of the Christie pelvic radiotherapy user  
9 group and supported by the Pelvic Radiation Disease Association (PRDA).  
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### 13 **Ethics and Dissemination**

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15 This study has been approved by GM East Research Ethics Committee in November 2020 (REC  
16 reference 20/NW/0410) and is registered at clinicaltrials.gov (ClinicalTrials.gov Identifier:  
17 NCT04555317). The study opened for recruitment in May 2021. The results of this study will  
18 be published in peer reviewed journals, will be presented in national and international  
19 conferences, and will be communicated to relevant stakeholders. Moreover, a plain English  
20 report will be shared with the study participants, patients' organizations, and media.  
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25 **Authors' contributions:** CEH developed the protocol, MRC application and ethics application  
26 for the study. RB is the MRC-CARP academic partner to CEH and contributed to the study  
27 design and protocol.  
28  
29

30 KJ, LHB, KH contributed to the development of the gynae-oncology aspects  
31  
32

33 RK, SO'C, TW contributed to the development of the MRI radiology aspects  
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35

36 ZM, JM contributed to the development of the Prehab4Cancer aspects  
37  
38

39 ST, JY contributed to the PROMS development  
40  
41

42 ME contributed to the Health Economic Analysis  
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44

45 ADW, IBJ contributed to the proteomic and data analysis  
46  
47

48 VCG and CEH prepared the manuscript  
49  
50

51 All authors: critically reviewed and commented on the manuscript.  
52  
53

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55 Research Partnership) award: grant number MR/T024887/1. Funding is being sought for  
56 Health Economic Analysis, QOL and PROMS development and longitudinal proteomic analysis.  
57 Equipment used in the Stoller Biomarker Discovery Centre is funded by a donation received  
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59 Council (MR/M008959/1). MRC/EPSC Molecular Pathology Node provided additional  
60

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2  
3 financial support by a grant from the Medical Research Council and Engineering & Physical  
4 Sciences Research Council (MR/N00583X/1).  
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7 **Competing interests statement.** No competing interests  
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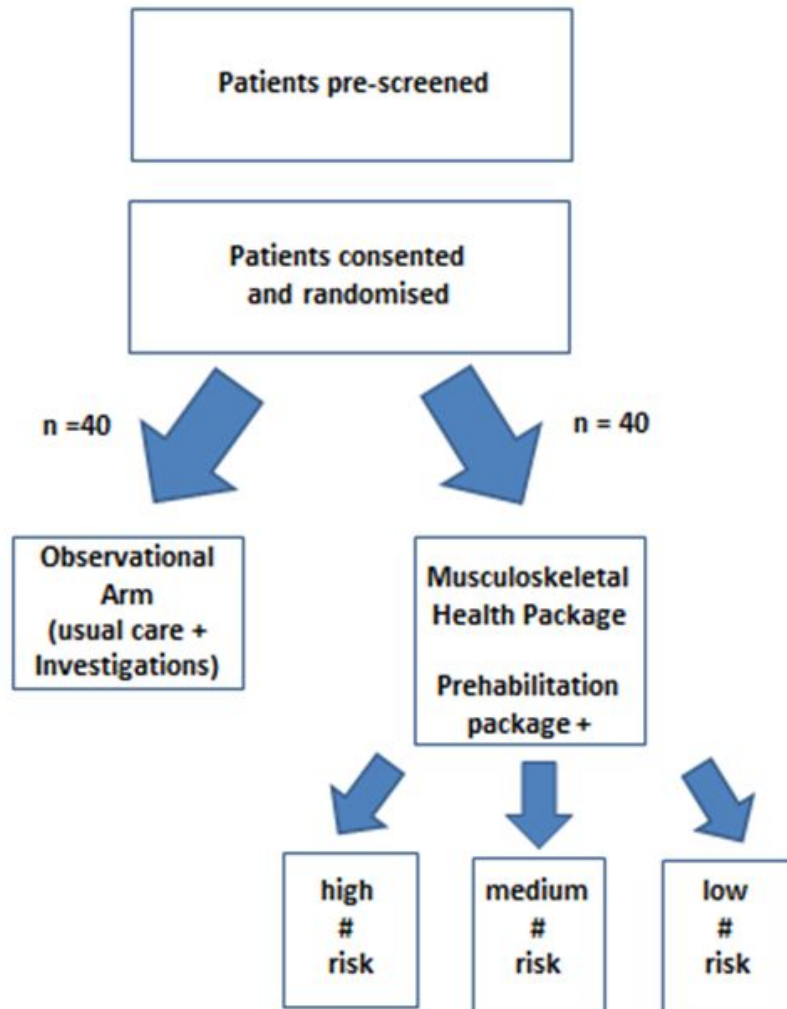
## 10 11 12 13 14 15 **Full references** 16

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19 1. Available from: [https://www.macmillan.org.uk/\\_images/cancer-statistics-factsheet\\_tcm9-260514.pdf](https://www.macmillan.org.uk/_images/cancer-statistics-factsheet_tcm9-260514.pdf)  
20 [Accessed June 2021]  
21 2. Higham CE, Faithfull S. Bone Health and Pelvic Radiotherapy. *Clin Oncol (R Coll Radiol)*. 2015;27(11):668-678.  
22 doi:10.1016/j.clon.2015.07.006  
23 3. Sapienza LG, Salcedo MP, Ning MS, et al. Pelvic Insufficiency Fractures After External Beam Radiation  
24 Therapy for Gynecologic Cancers: A Meta-analysis and Meta-regression of 3929 Patients. *Int J Radiat Oncol Biol*  
25 *Phys*. 2020;106(3):475-484. doi:10.1016/j.ijrobp.2019.09.012  
26 4. Gebauer J, Higham C, Langer T, Denzer C, Brabant G. Long-Term Endocrine and Metabolic Consequences of  
27 Cancer Treatment: A Systematic Review. *Endocr Rev*. 2019;40(3):711-767. doi:10.1210/er.2018-00092  
28 5. van den Blink QU, Garcez K, Henson CC, Davidson SE, Higham CE. Pharmacological interventions for the  
29 prevention of insufficiency fractures and avascular necrosis associated with pelvic radiotherapy in adults.  
30 *Cochrane Database Syst Rev*. 2018;4(4):CD010604. Published 2018 Apr 23. doi:10.1002/14651858.CD010604.  
31 pub2.  
32 6. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic  
33 fracture in men and women: an observational study. *Lancet*. 1999;353(9156):878-882. doi:10.1016/S0140-  
34 6736(98)09075-8  
35 7. Taillandier J, Langue F, Alemanni M, Taillandier-Heriche E. Mortality and functional outcomes of pelvic  
36 insufficiency fractures in older patients. *Joint Bone Spine*. 2003;70(4):287-289. doi:10.1016/s1297-  
37 319x(03)00015-0  
38 8. Oh D, Huh SJ, Nam H, et al. Pelvic insufficiency fracture after pelvic radiotherapy for cervical cancer: analysis  
39 of risk factors. *Int J Radiat Oncol Biol Phys*. 2008;70(4):1183-1188. doi:10.1016/j.ijrobp.2007.08.005  
40 9. Holch P, Pini S, Henry AM, et al. eRAPID electronic patient self-Reporting of Adverse-events: Patient  
41 Information and aDvice: a pilot study protocol in pelvic radiotherapy. *Pilot Feasibility Stud*. 2018;4:110.  
42 Published 2018 Jun 5. doi:10.1186/s40814-018-0304-6  
43 10. Pichon B, Campion L, Delpon G, et al. High-Dose Hypofractionated Radiation Therapy for Noncompressive  
44 Vertebral Metastases in Combination With Zoledronate: A Phase 1 Study. *Int J Radiat Oncol Biol Phys*.  
45 2016;96(4):840-847. doi:10.1016/j.ijrobp.2016.07.027  
46 11. Gierloff M, Reutemann M, Gülses A, Niehoff P, Wiltfang J, Açil Y. Effects of zoledronate on the radiation-  
47 induced collagen breakdown: a prospective randomized clinical trial. *Clin Transl Oncol*. 2015;17(6):454-461.  
48 doi:10.1007/s12094-014-1257-8  
49 12. Willey JS, Livingston EW, Robbins ME, et al. Risedronate prevents early radiation-induced osteoporosis in  
50 mice at multiple skeletal locations. *Bone*. 2010;46(1):101-111. doi:10.1016/j.bone.2009.09.002  
51 13. Chandra A, Lin T, Tribble MB, et al. PTH1-34 alleviates radiotherapy-induced local bone loss by improving  
52 osteoblast and osteocyte survival. *Bone*. 2014;67:33-40. doi:10.1016/j.bone.2014.06.030  
53 14. Moore J, Merchant Z, Rowlinson K, et al. Implementing a system-wide cancer prehabilitation programme:  
54 The journey of Greater Manchester's 'Prehab4cancer'. *Eur J Surg Oncol*. 2021;47(3 Pt A):524-532.  
55 doi:10.1016/j.ejso.2020.04.042  
56 15. Geary B, Walker MJ, Snow JT, et al. Identification of a Biomarker Panel for Early Detection of Lung Cancer  
57 Patients. *J Proteome Res*. 2019;18(9):3369-3382. doi:10.1021/acs.jproteome.9b00287  
58 16. Walker MJ, Zhou C, Backen A, et al. Discovery and Validation of Predictive Biomarkers of Survival for Non-  
59 small Cell Lung Cancer Patients Undergoing Radical Radiotherapy: Two Proteins With Predictive Value.  
60 *EBioMedicine*. 2015;2(8):841-850. Published 2015 Jun 19. doi:10.1016/j.ebiom.2015.06.013

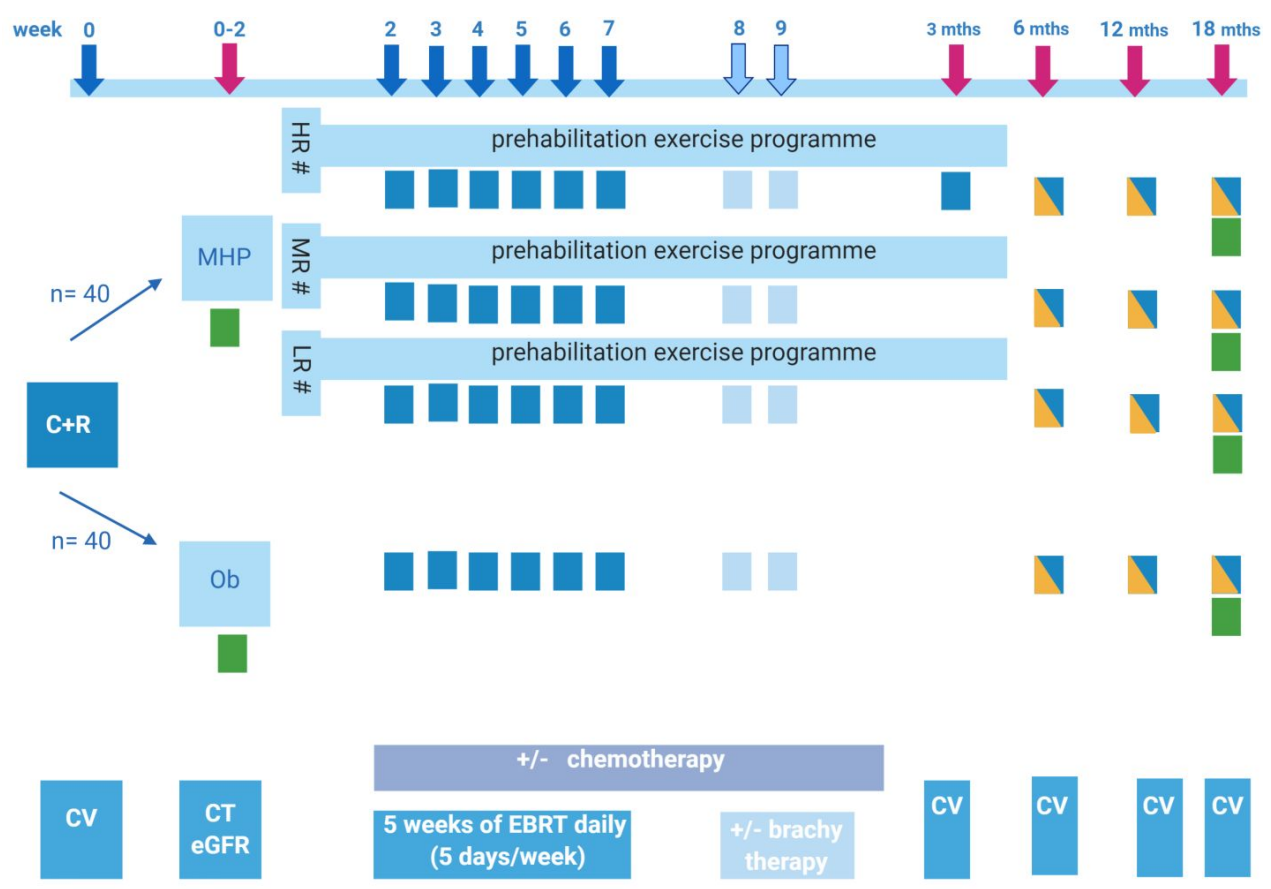
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17. Billingham SA, Whitehead AL, Julious SA. An audit of sample sizes for pilot and feasibility trials being undertaken in the United Kingdom registered in the United Kingdom Clinical Research Network database. *BMC Med Res Methodol.* 2013;13:104. Published 2013 Aug 20. doi:10.1186/1471-2288-13-104
18. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes.* 4th ed. Oxford: Oxford University Press, Oxford.  
<<https://books.google.co.uk/books?id=lvWACgAAQBAJ>>






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Study Design



### Baseline and Follow-up Evaluation



-  study visit (fasting blood tests/questionnaire)
-  study visit (DXA scan/fasting blood tests/questionnaire)
-  study visit (MRI scan/fasting blood tests/questionnaire)
-  study visit (coincides with NHS clinical visit)
-  study visit (potentially in addition to NHS clinical visit)

1  
2  
3 C+R = Consent and Randomisation, MHP= Musculoskeletal Health Package arm, Ob = observational  
4 arm HR = high risk, MR = medium risk, LR = low risk, CV = clinic visit, EBRT= External Beam  
5 Radiotherapy. NHS: National Health System  
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For peer review only

# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586

			Page
		Reporting Item	Number
<b>Administrative information</b>			
Title	<a href="#">#1</a>	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	<a href="#">#2a</a>	Trial identifier and registry name. If not yet registered,	2

1		name of intended registry	
2			
3			
4	Trial registration: data	<a href="#">#2b</a> All items from the World Health Organization Trial	6-14
5			
6	set	Registration Data Set	
7			
8			
9	Protocol version	<a href="#">#3</a> Date and version identifier	N/A
10			
11			
12	Funding	<a href="#">#4</a> Sources and types of financial, material, and other support	14,15
13			
14			
15	Roles and	<a href="#">#5a</a> Names, affiliations, and roles of protocol contributors	14
16			
17	responsibilities:		
18			
19	contributorship		
20			
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22			
23	Roles and	<a href="#">#5b</a> Name and contact information for the trial sponsor	13,14
24			
25	responsibilities:		
26			
27	sponsor contact		
28			
29	information		
30			
31			
32			
33	Roles and	<a href="#">#5c</a> Role of study sponsor and funders, if any, in study design;	13,14
34			
35	responsibilities:	collection, management, analysis, and interpretation of	
36			
37	sponsor and funder	data; writing of the report; and the decision to submit the	
38			
39		report for publication, including whether they will have	
40			
41		ultimate authority over any of these activities	
42			
43			
44			
45	Roles and	<a href="#">#5d</a> Composition, roles, and responsibilities of the coordinating	13,14
46			
47	responsibilities:	centre, steering committee, endpoint adjudication	
48			
49	committees	committee, data management team, and other individuals	
50			
51		or groups overseeing the trial, if applicable (see Item 21a	
52			
53		for data monitoring committee)	
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56			
57	<b>Introduction</b>		
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60			



1	Background and	<a href="#">#6a</a>	Description of research question and justification for	5
2				
3	rationale		undertaking the trial, including summary of relevant studies	
4			(published and unpublished) examining benefits and harms	
5			for each intervention	
6				
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11	Background and	<a href="#">#6b</a>	Explanation for choice of comparators	5
12				
13	rationale: choice of			
14				
15	comparators			
16				
17				
18	Objectives	<a href="#">#7</a>	Specific objectives or hypotheses	4,5
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20				
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22	Trial design	<a href="#">#8</a>	Description of trial design including type of trial (eg, parallel	5
23			group, crossover, factorial, single group), allocation ratio,	
24			and framework (eg, superiority, equivalence, non-inferiority,	
25			exploratory)	
26				
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31	<b>Methods:</b>			
32				
33	<b>Participants,</b>			
34				
35	<b>interventions, and</b>			
36				
37	<b>outcomes</b>			
38				
39				
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41	Study setting	<a href="#">#9</a>	Description of study settings (eg, community clinic,	6
42			academic hospital) and list of countries where data will be	
43			collected. Reference to where list of study sites can be	
44			obtained	
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51	Eligibility criteria	<a href="#">#10</a>	Inclusion and exclusion criteria for participants. If	7
52			applicable, eligibility criteria for study centres and	
53			individuals who will perform the interventions (eg,	
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		surgeons, psychotherapists)	
Interventions:	<a href="#">#11a</a>	Interventions for each group with sufficient detail to allow	7,8
description		replication, including how and when they will be	
		administered	
Interventions:	<a href="#">#11b</a>	Criteria for discontinuing or modifying allocated	11
modifications		interventions for a given trial participant (eg, drug dose	
		change in response to harms, participant request, or	
		improving / worsening disease)	
Interventions:	<a href="#">#11c</a>	Strategies to improve adherence to intervention protocols,	N/A
adherence		and any procedures for monitoring adherence (eg, drug	
		tablet return; laboratory tests)	
Interventions:	<a href="#">#11d</a>	Relevant concomitant care and interventions that are	7,8
concomitant care		permitted or prohibited during the trial	
Outcomes	<a href="#">#12</a>	Primary, secondary, and other outcomes, including the	11,12
		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	
Participant timeline	<a href="#">#13</a>	Time schedule of enrolment, interventions (including any	8-11
		run-ins and washouts), assessments, and visits for	
		participants. A schematic diagram is highly recommended	
		(see Figure)	

1	Sample size	<a href="#">#14</a>	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
2				
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11	Recruitment	<a href="#">#15</a>	Strategies for achieving adequate participant enrolment to reach target sample size	12
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16	<b>Methods: Assignment</b>			
17	<b>of interventions (for</b>			
18	<b>controlled trials)</b>			
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24	Allocation: sequence generation	<a href="#">#16a</a>	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	12,13
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41	Allocation concealment mechanism	<a href="#">#16b</a>	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	12,13
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51	Allocation: implementation	<a href="#">#16c</a>	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12,13
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1	Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions (eg,	5
2			trial participants, care providers, outcome assessors, data	
3			analysts), and how	
4				
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8	Blinding (masking):	<a href="#">#17b</a>	If blinded, circumstances under which unblinding is	N/a
9	emergency		permissible, and procedure for revealing a participant's	
10			allocated intervention during the trial	
11	unblinding			
12				
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16	<b>Methods: Data</b>			
17	<b>collection,</b>			
18	<b>management, and</b>			
19	<b>analysis</b>			
20				
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26	Data collection plan	<a href="#">#18a</a>	Plans for assessment and collection of outcome, baseline,	9-11
27			and other trial data, including any related processes to	
28			promote data quality (eg, duplicate measurements, training	
29			of assessors) and a description of study instruments (eg,	
30			questionnaires, laboratory tests) along with their reliability	
31			and validity, if known. Reference to where data collection	
32			forms can be found, if not in the protocol	
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43	Data collection plan:	<a href="#">#18b</a>	Plans to promote participant retention and complete follow-	11
44	retention		up, including list of any outcome data to be collected for	
45			participants who discontinue or deviate from intervention	
46			protocols	
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53	Data management	<a href="#">#19</a>	Plans for data entry, coding, security, and storage,	13
54			including any related processes to promote data quality	
55			(eg, double data entry; range checks for data values).	
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1		Reference to where details of data management	
2			
3		procedures can be found, if not in the protocol	
4			
5			
6	Statistics: outcomes	<a href="#">#20a</a> Statistical methods for analysing primary and secondary	13
7			
8		outcomes. Reference to where other details of the	
9			
10		statistical analysis plan can be found, if not in the protocol	
11			
12			
13	Statistics: additional	<a href="#">#20b</a> Methods for any additional analyses (eg, subgroup and	13
14			
15	analyses	adjusted analyses)	
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19	Statistics: analysis	<a href="#">#20c</a> Definition of analysis population relating to protocol non-	13
20			
21	population and	adherence (eg, as randomised analysis), and any statistical	
22			
23	missing data	methods to handle missing data (eg, multiple imputation)	
24			
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26	<b>Methods: Monitoring</b>		
27			
28			
29	Data monitoring:	<a href="#">#21a</a> Composition of data monitoring committee (DMC);	13,14
30			
31	formal committee	summary of its role and reporting structure; statement of	
32			
33		whether it is independent from the sponsor and competing	
34			
35		interests; and reference to where further details about its	
36			
37		charter can be found, if not in the protocol. Alternatively, an	
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39		explanation of why a DMC is not needed	
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44	Data monitoring:	<a href="#">#21b</a> Description of any interim analyses and stopping	12
45			
46	interim analysis	guidelines, including who will have access to these interim	
47			
48		results and make the final decision to terminate the trial	
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51	Harms	<a href="#">#22</a> Plans for collecting, assessing, reporting, and managing	11
52			
53		solicited and spontaneously reported adverse events and	
54			
55		other unintended effects of trial interventions or trial	
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1		conduct	
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4	Auditing	<a href="#">#23</a> Frequency and procedures for auditing trial conduct, if any,	14
5		and whether the process will be independent from	
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8		investigators and the sponsor	
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11	<b>Ethics and</b>		
12			
13	<b>dissemination</b>		
14			
15			
16	Research ethics	<a href="#">#24</a> Plans for seeking research ethics committee / institutional	2
17		review board (REC / IRB) approval	
18	approval		
19			
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22	Protocol	<a href="#">#25</a> Plans for communicating important protocol modifications	13,14
23		(eg, changes to eligibility criteria, outcomes, analyses) to	
24	amendments	relevant parties (eg, investigators, REC / IRBs, trial	
25		participants, trial registries, journals, regulators)	
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32	Consent or assent	<a href="#">#26a</a> Who will obtain informed consent or assent from potential	7
33		trial participants or authorised surrogates, and how (see	
34		Item 32)	
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39	Consent or assent:	<a href="#">#26b</a> Additional consent provisions for collection and use of	N/A
40		participant data and biological specimens in ancillary	
41	ancillary studies	studies, if applicable	
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47	Confidentiality	<a href="#">#27</a> How personal information about potential and enrolled	13
48		participants will be collected, shared, and maintained in	
49		order to protect confidentiality before, during, and after the	
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51			
52		trial	
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57	Declaration of	<a href="#">#28</a> Financial and other competing interests for principal	14,15
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1	interests		investigators for the overall trial and each study site	
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3				
4	Data access	<a href="#">#29</a>	Statement of who will have access to the final trial dataset,	TBC
5			and disclosure of contractual agreements that limit such	
6			access for investigators	
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11	Ancillary and post	<a href="#">#30</a>	Provisions, if any, for ancillary and post-trial care, and for	N/A
12			compensation to those who suffer harm from trial	
13	trial care		participation	
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19	Dissemination policy:	<a href="#">#31a</a>	Plans for investigators and sponsor to communicate trial	14
20			results to participants, healthcare professionals, the public,	
21	trial results		and other relevant groups (eg, via publication, reporting in	
22			results databases, or other data sharing arrangements),	
23			including any publication restrictions	
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31	Dissemination policy:	<a href="#">#31b</a>	Authorship eligibility guidelines and any intended use of	14
32			professional writers	
33	authorship			
34				
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36	Dissemination policy:	<a href="#">#31c</a>	Plans, if any, for granting public access to the full protocol,	14
37			participant-level dataset, and statistical code	
38	reproducible research			
39				
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42	<b>Appendices</b>			
43				
44				
45	Informed consent	<a href="#">#32</a>	Model consent form and other related documentation given	TBC
46			to participants and authorised surrogates	
47	materials			
48				
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50	Biological specimens	<a href="#">#33</a>	Plans for collection, laboratory evaluation, and storage of	N/A
51			biological specimens for genetic or molecular analysis in	
52			the current trial and for future use in ancillary studies, if	
53			applicable	
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2 Commons Attribution License CC-BY-NC. This checklist can be completed online using  
3 <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with  
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# BMJ Open

**RadBone: Bone Toxicity following Pelvic Radiotherapy. A prospective randomised controlled feasibility study evaluating a musculoskeletal health package in women with gynaecological cancers undergoing pelvic radiotherapy.**

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4 2 controlled feasibility study evaluating a musculoskeletal health package in women with  
5 3 gynaecological cancers undergoing pelvic radiotherapy.  
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20 41 **Abstract:**  
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22 42 **Introduction:** Patients receiving radiotherapy are at risk of developing Radiotherapy Related  
23 43 Insufficiency Fractures (RRIFs), which are associated with increased morbidity and pose a  
24 44 significant burden to patients' quality of life and to the health system. Therefore, effective  
25 45 preventive techniques are urgently required. The RadBone randomized controlled trial (RCT)  
26 46 aims to determine the feasibility and acceptability of a musculoskeletal health package  
27 47 (MHP) intervention in women undergoing pelvic radiotherapy for gynaecological  
28 48 malignancies and to preliminary explore clinical effectiveness of the intervention.  
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33 49 **Methods and Analysis:** The RadBone RCT will evaluate the addition to standard care of a  
34 50 MHP consisting of a physical assessment of the musculoskeletal health, a three-month  
35 51 prehabilitation personalised exercise package, as well as an evaluation of the fracture risk  
36 52 and if required the prescription of appropriate bone treatment including calcium, vitamin D  
37 53 and -for high-risk individuals- bisphosphonates. Forty participants will be randomized in  
38 54 each group (MHP or observation) and will be followed for 18 months. The primary outcome  
39 55 of this RCT will be feasibility, including the eligibility, screening and recruitment rate,  
40 56 intervention fidelity and attrition rates; acceptability; and health economics. Clinical  
41 57 effectiveness and bone turnover markers will be evaluated as secondary outcomes.  
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47 58 **Ethics and dissemination:** This study has been approved by the Greater Manchester East  
48 59 Research Ethics Committee (Reference: 20/NW/0410, November 2020). The results will be  
49 60 published in peer reviewed journals, will be presented in national and international  
50 61 conferences, and will be communicated to relevant stakeholders. Moreover, a plain English  
51 62 report will be shared with the study participants, patients' organizations, and media.  
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55 63 **Clinical trial registration:** NCT04555317.  
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3 65 **Keywords:** radiotherapy, insufficiency fractures, musculoskeletal health, gynaecological  
4 66 cancer, randomised control trial.  
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10 68 **Strengths and Limitations of this study**  
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- 12 69 • The RadBone is the first randomized controlled trial to assess a musculoskeletal  
13 70 health package aimed to prevent radiotherapy related insufficiency fractures (RRIFs).  
14 71 • A feasibility economic evaluation will allow future assessment of this complex  
15 72 intervention's cost-effectiveness.  
16 73 • Planned longitudinal proteomic analyses may reveal mechanistic insights and  
17 74 promising treatment targets.  
18 75 • A prospectively published detailed protocol increases the transparency and allows  
19 76 for peer review of the methodology used.  
20 77 • This study is not blinded and lacks an active comparator, hence, it is susceptible to  
21 78 performance and detection bias.  
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29 80 **Word count: 3,740**  
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## 103 Introduction

104 In 2015 there were 2.5 million people in the UK with a diagnosis of cancer and this number  
105 is expected to rise to 4 million by 2030<sup>1</sup>. As a result of the continuing improvement in early  
106 detection of disease and improved treatment efficacy, a significant proportion are living  
107 long beyond their cancer diagnosis. However, estimates suggest that currently over 500,000  
108 people living with and beyond cancer have one or more physical or psychosocial  
109 consequences of their cancer or its treatment that affect their lives on a long-term basis.  
110 These consequences also have a substantial implication in terms of NHS resources.

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112 Patients receiving radiotherapy are at risk of developing radiotherapy related bone toxicity,  
113 in particular radiotherapy related insufficiency fractures (RRIFs). Incidence of RRIFs following  
114 pelvic radiotherapy has been reported as between 1.7 and 89% and occurring between 3 to  
115 20 months post radiotherapy. The wide variation in reported incidence depends on imaging  
116 modality and radiological reporting standards, symptomatic versus asymptomatic fractures,  
117 radiotherapy dose and underlying tumour type (reviewed in<sup>2</sup>). A recent meta-analysis of  
118 over 400 patients with RRIFs following pelvic radiotherapy for gynaecological cancers  
119 suggested an overall incidence of 14%<sup>3</sup>. Over 30 studies have been published since the  
120 1990's describing more than 1000 patients with pelvic RRIFs. This literature is notable for  
121 being almost exclusively retrospective in nature, a sparsity of baseline assessment of bone  
122 density and fracture risk, the absence of Patient Reported Outcome Measures (PROMs)  
123 used to assess Quality of Life (QOL) and no primary preventative or secondary management  
124 intervention studies<sup>4,5</sup>.

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126 The devastating effects of osteoporotic fragility fractures on morbidity and mortality and  
127 the economic cost are well described<sup>6</sup>. Pelvic insufficiency fractures may also increase  
128 mortality<sup>7</sup> but these data reflect an elderly population with multiple co-morbidities and the  
129 applicability to the pelvic radiotherapy population is not well defined. In addition, there are  
130 no pelvic RRIF studies reporting QOL as an outcome measure. However, the anxiety, pain,  
131 reduced mobility and increased morbidity associated with these has been described, with a  
132 number of patients requiring hospital admission for assessment and pain control<sup>8</sup>.  
133 Therefore, formal studies of QOL and PROMs are much needed, considering the wide range  
134 of pelvic radiotherapy toxicities<sup>9</sup>.

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136 Whilst a small number of studies, confirmed in a recent meta-analysis<sup>3</sup>, suggest  
137 osteoporosis as a risk factor in pelvic RRIFs, unlike the strong evidence base for  
138 bisphosphonate use in primary and secondary prevention of fragility fractures, there is no  
139 such evidence for RRIFs<sup>5</sup>. A small non-controlled study demonstrated intravenous  
140 zolendronic acid administration prior to spinal radiotherapy led to a lower prevalence of  
141 radiotherapy bone toxicity than expected<sup>10</sup> and a single randomised prospective study in

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3 142 patients undergoing spinal radiotherapy for metastatic disease demonstrated that  
4 143 intravenous zoledronic acid reduced urinary markers of collagen cross linking<sup>11</sup>.  
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7 145 Contradictory data from animal studies around the protective effects of bisphosphonates on  
8 146 RRIFs limits our understanding of the pathophysiology and therapeutics of RRIFs. Animal  
9 147 studies using whole mouse radiation have demonstrated an early activation of bone  
10 148 resorption in the 5 days following low dose (2 Gy) of radiotherapy which was reduced by  
11 149 subcutaneous administration of risedronate immediately following irradiation<sup>12</sup>. In contrast,  
12 150 a focal radiation technique in mice (using a small animal radiation research platform or  
13 151 SARRP), arguably a more physiological representative method of irradiation, demonstrated  
14 152 that alendronic acid did not prevent the radiation induced trabecular bone loss but that this  
15 153 was prevented by blocking osteoblast apoptosis with PTH 1-34<sup>13</sup>.  
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18 155 The RadBone is the first open-label prospective randomised controlled trial (RCT) to  
19 156 determine the feasibility and acceptability of a musculoskeletal health package (MHP)  
20 157 intervention in women undergoing pelvic radiotherapy for gynaecological malignancies and  
21 158 inform power calculations for a definitive RCT. Moreover, this feasibility trial will also  
22 159 explore potential implications on the incidence of RRIFs, quality of life and other clinical  
23 160 effectiveness and safety outcomes, as well as providing indicative estimates of the  
24 161 intervention's cost-effectiveness.  
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3 173 **Methods and analysis:**  
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6 174 **Study Design** (Figure 1)  
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11 176 **Study setting**  
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13 177 The planned study is a prospective randomised controlled feasibility trial of eighty patients  
14 178 with gynaecological malignancy (cervical and endometrial) undergoing pelvic radiotherapy  
15 179 at the Christie Hospital NHS Foundation Trust in Manchester, UK (a tertiary referral  
16 180 Oncology centre). The study opened for recruitment in May 2021, and the estimated  
17 181 primary completion date is in November 2022 and study completion date in June 2023.  
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24 183 **Eligibility Criteria**  
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27 184 Individuals aged over 18 years, with a histologically confirmed endometrial or cervical  
28 185 cancer undergoing potentially curative or adjuvant radiotherapy will be eligible, provided  
29 186 they are able and willing to provide an informed consent to participate.  
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32 187 The exclusion criteria are (i) age less than 18 years or greater than 85 years; (ii) pre-existing  
33 188 bone conditions such as osteoporosis treated with bisphosphonates in the previous 5 years,  
34 189 fibrous dysplasia, osteogenesis imperfecta, or other metabolic bone conditions; (iii) home  
35 190 address outside Greater Manchester; (iv) contraindication or intolerance of Magnetic  
36 191 Resonance scanning.  
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42 193 **Interventions**  
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44 194 Women undergoing radiotherapy for a gynaecological malignancy will be randomised to an  
45 195 observation (Ob) group and will receive standard assessment and care, following the current  
46 196 local clinical pathway, or an intervention group that will receive a “musculoskeletal health  
47 197 package” (MHP), in addition to standard assessment and care and will be followed for 18  
48 198 months.  
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53 199 Patients randomised to the MHP arm will receive (i) a physical assessment of  
54 200 musculoskeletal health and a 3-month prehabilitation personalised exercise package as part  
55 201 of the Greater Manchester prehab4cancer program<sup>14</sup>, (ii) a fracture risk assessment (FRAX)  
56 202 based on baseline dual-energy x-ray absorptiometry (DXA) bone mineral density (BMD), and  
57 203 (iii) treatment for bone health according to national UK recommendations i.e., standard of  
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204 care for prevention of fragility fractures, by being subdivided into 3 groups (low risk,  
205 medium risk and high risk).

206 Patients with a normal BMD and a FRAX score below the National Osteoporosis Guideline  
207 Group (NOGG) recommended treatment line will be considered low risk. Medium risk is  
208 defined as osteopenia on the DXA, with FRAX score below the NOGG treatment line. Finally,  
209 those with osteopenia and a previous vertebral or hip fracture, or a FRAX score above the  
210 NOGG recommended treatment line will be considered high risk.

211 Low risk patients will be provided with a copy of the Royal Osteoporosis Society (ROS)  
212 "Healthy living for strong bones" leaflet. In addition to the leaflet, medium risk patients will  
213 receive calcium (1000 mg once daily) and vitamin D (800 IU per day) supplementation. The  
214 same interventions will be offered to high-risk patients, who will also undergo secondary  
215 osteoporosis screening (blood tests) and will receive oral alendronate 70mg once weekly, in  
216 the absence of contraindications. Annual intravenous zoledronic acid infusion will be  
217 considered as an alternative where appropriate.

218 Those randomised to the observation arm will remain blinded to the results of the  
219 evaluations until the end of the study unless a fragility fracture or RRIF develops during the  
220 study.

### 221 ***Prehabilitation Exercise Programme (Prehab4cancer)***

222 All patients randomised to the MHP arm of the study will be offered a bespoke  
223 prehabilitation exercise programme via the Prehab4cancer programme in Greater  
224 Manchester. The MHP arm patients will be referred to the Prehab4cancer team via  
225 electronic referral immediately following randomisation. Allocated patients will be  
226 individually assessed by the Prehab4cancer team according to their usual protocols and  
227 assigned an appropriate prehabilitation program. Duration of the programme is 12 weeks  
228 from the first assessment and participation will be encouraged, as tolerated. The  
229 Prehab4Cancer and recovery programme is community-based, which incorporates exercise  
230 (cardiovascular and muscle strengthening/resistance training), nutritional screening, and  
231 advice and wellbeing support. Further details of programmes' assessment tools and the  
232 stratification of interventions are described by Moore et al<sup>14</sup> and can be found here:  
233 [www.prehab4cancer.co.uk](http://www.prehab4cancer.co.uk). The current scope of this protocol is to evaluate feasibility of  
234 participants' engagement in this face to face and remote prehabilitation service both pre-  
235 and during treatment.

236

### 237 **Baseline and Follow-up Evaluation (Figure 2)**

238 As described in figure 2, baseline evaluations will include a bone health assessment with  
239 DXA BMD measurement and completion of a bone health questionnaire. PROMs will also be  
240 captured. Finally, fasting serum and plasma blood samples will also be collected.

241 At 6, 12 and 18 months post radiotherapy all patients will undergo a pelvic MRI assessment  
242 for RRIFs, PROMs assessment and fasting blood sampling. During the final visit, at 18  
243 months, all patients will have a DXA BMD scan and physical assessment of their  
244 musculoskeletal health. If signs or symptoms compatible with a RRIF are described outside  
245 the study visits study participants will be assessed and managed following the current  
246 clinical pathways.

### 247 ***Imaging studies***

248 DXA scans of the total hip, femoral neck, L1-L4 spine and TBS assessments will be performed  
249 on a single DXA scanner (Hologic Horizon A SN 300792M version 5.6.07 with TBS v.3.0.2  
250 calibrated to the above scanner) at the Christie NHS Foundation Trust as per local protocol.  
251 These will be undertaken by two technicians trained in conducting DXA. Images will be  
252 reviewed, validated and interpreted by the lead investigator (CEH). The femoral neck BMD  
253 ( $\text{g}/\text{cm}^2$ ) will be used in conjunction with a standardised DXA questionnaire to complete FRAX  
254 calculation.

255 Pelvic Magnetic Resonance Imaging (MRI) scans will be performed at 6, 12 and 18 months  
256 on a 1.5T MRI scanner at the Christie Hospital by trained radiographers in accordance with  
257 the study imaging protocol. Four pelvic sequences will be performed per patient (5mm slice  
258 thickness, field of view 400mm; coronal T1, coronal STIR (inversion time 150ms), axial T1  
259 and axial STIR (inversion time 165 ms). These will correspond to routine follow-up scans  
260 where possible. All bone sequence scans will be dual reported by 2 consultant radiologists  
261 who will document the presence of fracture and their confidence in its presence, fracture  
262 location, fracture line, bone marrow oedema and other abnormalities.

### 263 ***Biochemical studies***

264 Fasting blood tests will be performed at baseline, weekly during radiotherapy (visits 2 to 10,  
265 one day prior to chemotherapy if receiving) and at 6, 12 and 18 months in all patients.  
266 Patients allocated to the MHP High risk arm and started on oral bisphosphonate therapy will  
267 have an additional bone turnover marker blood test at 3 months to assess bisphosphonate  
268 efficacy. All samples will be taken simultaneously with routinely collected clinical blood  
269 samples where appropriate.

270 As part of the MHP intervention arm, blood will be sampled, analysed, and assessed at  
271 baseline, 6, 12 and 18 months for the measurement of full blood count, urea and  
272 electrolytes, liver function tests, parathyroid hormone, vitamin D, thyroid function test,

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3 273 oestradiol, HbA1c, procollagen type 1 amino-terminal propeptide (P1NP), and the beta-C-  
4 274 terminal telopeptide (CTx). Moreover, in the observation arm, serum samples will be  
5 275 collected, processed and stored at -80°C for batch analysis at the end of the study.  
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9 276 Additional fasting blood samples will be collected at all timepoints mentioned for  
10 277 longitudinal analysis of bone turnover markers and for proteomic analysis. These samples  
11 278 will be processed and stored at -80°C, following local standard operating procedures (SOPs),  
12 279 for batch analysis at the end of the study. Bone turnover markers will be evaluated using  
13 280 ELISA techniques and will include CTX, NTX, P1NP, osteocalcin, TRAcP5b and bone ALP.  
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### 16 17 281 ***Sequential Window Acquisition of all Theoretical Mass Spectra (SWATH-MS)***

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19 282 Proteomic analysis will be conducted at the Stoller Biomarker Discovery Centre, following  
20 283 local SOPs<sup>15</sup>. Samples will be analysed by a Data Independent Acquisition method known as  
21 284 SWATH-MS with a micro-flow LC-MS system comprising an Eksigent nanoLC 400  
22 285 autosampler and an Eksigent nanoLC pump coupled to a SCIEX 6600 Triple-TOF mass  
23 286 spectrometer (68 min run-time). When SWATH maps are generated, the presence and  
24 287 abundance of plasma proteins will be quantified using published plasma reference libraries.  
25 288 Differential expression analysis will be used to identify candidate biomarkers using artificial  
26 289 intelligence approaches. Linear regression will be used to detect correlations with the  
27 290 presence of RRIFs and BMD.  
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33 291 Few longitudinal studies have tracked proteins of interest over the whole course of  
34 292 radiotherapy from pre-treatment baseline through to follow-up. We have undertaken one  
35 293 pilot that shows the potential value of this work<sup>16</sup>. Other studies that have investigated this  
36 294 have demonstrated distinguishing profiles with groups of approximately n=30. Two pre-  
37 295 radiotherapy baseline samples will be used to assess natural variation and comparison with  
38 296 the variance of measurements following radiotherapy and further comparison between the  
39 297 MHP and observation arm (n=40 per group).  
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44 299 Electronic data will be pseudoanonymised (coded) to protect the identity of the  
45 300 participants.  
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### 50 302 ***PROMS and Health Utilisation Proforma***

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52 303 PROMs will be collected either as electronic PROMS (using the myChristie, myHealth  
53 304 application) or paper-based PROMS at baseline 6, 12, and 18 months.  
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56 305 The evaluated PROMs will include the adapted pelvic patient-reported outcome version of  
57 306 the common terminology criteria for adverse events (PRO-CTCAE) assessment, the Short  
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307 Musculoskeletal Function Assessment (SMFA) modified for lower limb, the 5-level version of  
308 the EuroQol tool (EQ-5D-5L) and a tailored Health Utilisation Proforma.

309 The CTCAE pelvic questionnaire will include as measures bowel questions scored out of 22,  
310 urinary questions out of 19 and sexual questions out of 8, with a total out of 49; a higher  
311 score indicates worse quality of life. The adapted SMFA questionnaire includes 39 questions,  
312 with a minimum possible score of 39 and maximum of 195; scores are standardised with  
313 high scores indicating poor function.

#### 314 **Criteria for discontinuing**

315 Participants may decide to withdraw from the study at any time. Discontinuation of the  
316 study participants may occur as a result of investigator decision, safety concerns, and  
317 significant non-compliance to the protocol or incorrect enrolment. Reasons for  
318 discontinuation will be captured.

319 As this is a feasibility study, participants may decide to discontinue their participation in  
320 certain aspects of the study (for example declining the prehabilitation programme or  
321 deciding not to take recommended medications). The participants can continue with the  
322 study and the details will be captured in the case report form (CRF).

#### 323 **Outcomes**

324 The primary outcomes for this feasibility study will inform the design and power calculations  
325 for a definitive UK multi-centre RCT. These are:

- 326 1) Eligibility and screening rate: proportion of patients eligible for the study from  
327 patient population. [Assessed at baseline]
- 328 2) Recruitment and study group allocation rate: number and proportion of eligible  
329 patients recruited, randomised and allocated to appropriate study populations.  
330 [Assessed 2 weeks post consent]
- 331 3) Intervention fidelity rate: number and proportion of patients completing the  
332 elements of the study (assessment visits, prehab exercise programme, prescribed  
333 medications, QOL questionnaire). [Assessed at the end of study, at 18 months]
- 334 4) Attrition rate: number of patients lost to follow-up. [Assessed at the end of study, at  
335 18 months]
- 336 5) Patient and physician acceptability assessed with electronic questionnaires. [Change  
337 from baseline assessed at 6,12 and 18 months]
- 338 6) Health Economic Analysis: within-trial cost-effectiveness analysis to demonstrate  
339 feasibility of health economic data collection and analysis in a multi-centre RCT.  
340 [Change from baseline assessed at 6,12 and 18 months]

342 The secondary outcomes are:

- 343 1) Incidence of pelvic Radiotherapy Related Insufficiency Fracture (RRIF). [Assessed at  
344 6, 12 and 18 months post radiotherapy]

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3 345 2) Longitudinal change in BMD and fracture risk using FRAX. [Assessed at baseline and  
4 346 18 months]  
5  
6 347 3) Longitudinal change in biochemical markers of bone turnover. [Change from baseline  
7 348 assessed at 2, 3, 4, 5, 6, 7, 8 and 9 weeks and at 6, 12 and 18 months]  
8 349 4) Quality of Life assessment: adapted CTCAE pelvic questionnaire and SMFA adapted  
9 350 to lower limbs. [Change from baseline assessed at 6, 12 and 18 months]  
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11  
12 352 Exploratory Endpoints include identification of predictive markers of RRIFs (radiomic,  
13 353 proteomic, BMD) and exploratory measurement of proteomic biomarkers of bone turnover  
14 354 during pelvic radiotherapy.  
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## 18 19 20 356 **Sample Size**

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22 357 No formal power calculation has been performed as this is a feasibility study. The study will  
23 358 collect initial data such as measures of location and variability for key outcome measures. It  
24 359 is recognised that in general, 30 patients are required in order to estimate such  
25 360 parameters<sup>17</sup>. For this study a total of 80 patients will be recruited and randomised with  
26 361 equal probability to either the MHP or observation arms (i.e. 40 per group). Assuming  
27 362 attrition rates of 15% per group, at least 30 should remain in each arm. This should be  
28 363 sufficient to assess the feasibility of a larger RCT study and estimate group means, standard  
29 364 deviations and percentages for key outcomes.  
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## 34 35 365 **Recruitment**

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37 366 80 patients will be recruited over an 18-month period, approximately 4 patients per month.  
38 367 As this is a feasibility study there will be no interim analysis of study results.  
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## 41 368 **Assignment of interventions**

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44 369 Consenting, eligible participants will be randomised to the MHP or observation group using  
45 370 a validated online service; sealedenvelope™ (<https://www.sealedenvelope.com>). A  
46 371 permuted block (block size:4) randomisation protocol will be utilised with a 1:1 allocation  
47 372 (MHP to observation arm).  
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## 50 373 **Data Collection, management and analysis**

### 51 52 374 *Statistical and Health Economic Analysis*

53 375 As this is a feasibility study, it will not involve hypothesis testing to identify whether the  
54 376 intervention has had an impact. Instead, data analysis will be descriptive, focusing on the  
55 377 percentage of patients in each group developing RRIFs and risk factors for this. Means and a  
56 378 measure of variation will be calculated for each secondary outcome. These data, along with  
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2  
3 379 estimates of recruitment and attrition rates, will help inform a power calculation for the  
4 380 definitive trial.

5 381  
6  
7 382 A within-trial cost-effectiveness analysis<sup>18</sup> will be undertaken from the perspective of the UK  
8 383 National Health Service (NHS). Cost data for the intervention arm will reflect resource use  
9 384 associated with the musculoskeletal health package and treatment costs for both the  
10 385 control and intervention arm will be taken into account. Resource use will be extracted from  
11 386 patient records and the health care utilisation proforma. Relevant sources (e.g., NHS  
12 387 reference costs) will be used to identify unit costs. Health related quality of life (HRQL)  
13 388 scores will be generated using the EQ-5D-5L at baseline and at each of the three follow-up  
14 389 time points (6, 12, 18 months).

15 390  
16 391 A descriptive analysis of the costs and outcomes data will be completed focusing on: a.  
17 392 whether the EQ-5D-5L and SMFA are able to adequately capture differences in health status  
18 393 before and after implementation of the musculoskeletal health package and across both  
19 394 treatment arms of the study; b. whether the resource-use survey is able to record data  
20 395 necessary to enable a full cost-effectiveness analysis; c. the nature of missing data for the  
21 396 EQ-5D-5L, SMFA and resource-use survey to assess responses, sensitivity, and any patterns  
22 397 within the missing data.

23 398  
24 399 A within-trial cost-effectiveness analysis will be conducted to provide an indicative estimate  
25 400 of cost-effectiveness. Between-arm differences in costs and outcomes will be expressed as  
26 401 an incremental cost-effectiveness ratio (ICERs): the cost per QALY gained from the  
27 402 intervention compared to usual care. ICERs will also be calculated using the SMFA in an  
28 403 additional scenario analysis.

29 404

30 405

#### 31 406 **Trial oversight**

32 407 An internal trial management group will be convened for the study, consisting of the chief  
33 408 investigator, project manager, Clinical Trials administrator, research nurse and a  
34 409 representative of the research and innovation division (R+I) as core members. The group will  
35 410 meet monthly. The study sponsor (Christie Hospital NHS Foundation Trust) will monitor the  
36 411 conduct of the trial.

#### 37 412 **Patient and Public Involvement**

38 413 This protocol was developed with the participation of the Christie pelvic radiotherapy user  
39 414 group and supported by the Pelvic Radiation Disease Association (PRDA).

40 415

#### 41 416 **Ethics and Dissemination**

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3 417 This study has been approved by GM East Research Ethics Committee in November 2020  
4 418 (REC reference 20/NW/0410) and is registered at clinicaltrials.gov (ClinicalTrials.gov  
5 419 Identifier: NCT04555317). The study opened for recruitment in May 2021. The results of this  
6 420 study will be published in peer reviewed journals, will be presented in national and  
7 421 international conferences, and will be communicated to relevant stakeholders. Moreover, a  
8 422 plain English report will be shared with the study participants, patients' organizations, and  
9 423 media.

#### 14 424 **Data sharing statement**

16 425 Consent to share data from this study for future research is voluntary. To ensure compliance  
17 426 with regulatory and governance requirements, approval from the sponsor team is required  
18 427 prior to the release of any data generated by this Christie sponsored study, to a third party.  
19 428 Any requests are to be directed towards the-christie.sponsoredresearch@nhs.net for  
20 429 consideration and must follow all local Policies and review procedures. If a proposal is  
21 430 accepted, then the sponsor will work with the requestor to develop any necessary data  
22 431 transfer plans/agreements.

27 432 **Authors' contributions:** CEH developed the protocol, MRC application and ethics application  
28 433 for the study. RB is the MRC-CARP academic partner to CEH and contributed to the study  
29 434 design and protocol.

32 435 KJ, LHB, KH contributed to the development of the gynae-oncology aspects

34 436 RK, SO'C, TW contributed to the development of the MRI radiology aspects

36 437 ZM, JM contributed to the development of the Prehab4Cancer aspects

38 438 ST, JY contributed to the PROMS development

40 439 ME contributed to the Health Economic Analysis

42 440 ADW, IBJ contributed to the proteomic and data analysis

44 441 VCG and CEH prepared the manuscript

46 442 All authors: critically reviewed and commented on the manuscript.

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52 444 Research Partnership) award: grant number MR/T024887/1. Funding is being sought for  
53 445 Health Economic Analysis, QOL and PROMS development and longitudinal proteomic  
54 446 analysis. Equipment used in the Stoller Biomarker Discovery Centre is funded by a donation  
55 447 received from the Stoller Charitable Trust and a research grant awarded by the Medical  
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4 449 additional financial support by a grant from the Medical Research Council and Engineering &  
5 450 Physical Sciences Research Council (MR/N00583X/1).  
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8 451 **Competing interests statement.** No competing interests  
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3 453 **Figures legends**  
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8 455 **Figure 1:** Recruitment, randomisation process and description of the stratified interventions.  
9 (#: fracture)  
10 456

11  
12 457 **Figure 2:** Study flow chart; assessments and outcome time-points.  
13

14 458 C+R = Consent and Randomisation, MHP= Musculoskeletal Health Package arm, Ob =  
15 459 observational arm, HR = high risk, CV = clinic visit, EBRT= External Beam Radiotherapy. NHS:  
16 460 National Health System  
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## 462 Full references

1. Available from: [https://www.macmillan.org.uk/\\_images/cancer-statistics-factsheet\\_tcm9-260514.pdf](https://www.macmillan.org.uk/_images/cancer-statistics-factsheet_tcm9-260514.pdf) [Accessed February 2022]
2. Higham CE, Faithfull S. Bone Health and Pelvic Radiotherapy. *Clin Oncol (R Coll Radiol)*. 2015;27(11):668-678. doi:10.1016/j.clon.2015.07.006
3. Sapienza LG, Salcedo MP, Ning MS, et al. Pelvic Insufficiency Fractures After External Beam Radiation Therapy for Gynecologic Cancers: A Meta-analysis and Meta-regression of 3929 Patients. *Int J Radiat Oncol Biol Phys*. 2020;106(3):475-484. doi:10.1016/j.ijrobp.2019.09.012
4. Gebauer J, Higham C, Langer T, Denzer C, Brabant G. Long-Term Endocrine and Metabolic Consequences of Cancer Treatment: A Systematic Review. *Endocr Rev*. 2019;40(3):711-767. doi:10.1210/er.2018-00092
5. van den Blink QU, Garcez K, Henson CC, Davidson SE, Higham CE. Pharmacological interventions for the prevention of insufficiency fractures and avascular necrosis associated with pelvic radiotherapy in adults. *Cochrane Database Syst Rev*. 2018;4(4):CD010604. Published 2018 Apr 23. doi:10.1002/14651858.CD010604.pub2.
6. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. *Lancet*. 1999;353(9156):878-882. doi:10.1016/S0140-6736(98)09075-8
7. Taillandier J, Languet F, Alemanni M, Taillandier-Herich E. Mortality and functional outcomes of pelvic insufficiency fractures in older patients. *Joint Bone Spine*. 2003;70(4):287-289. doi:10.1016/s1297-319x(03)00015-0
8. Oh D, Huh SJ, Nam H, et al. Pelvic insufficiency fracture after pelvic radiotherapy for cervical cancer: analysis of risk factors. *Int J Radiat Oncol Biol Phys*. 2008;70(4):1183-1188. doi:10.1016/j.ijrobp.2007.08.005
9. Holch P, Pini S, Henry AM, et al. eRAPID electronic patient self-Reporting of Adverse-events: Patient Information and aDvice: a pilot study protocol in pelvic radiotherapy. *Pilot Feasibility Stud*. 2018;4:110. Published 2018 Jun 5. doi:10.1186/s40814-018-0304-6
10. Pichon B, Campion L, Delpon G, et al. High-Dose Hypofractionated Radiation Therapy for Noncompressive Vertebral Metastases in Combination With Zoledronate: A Phase 1 Study. *Int J Radiat Oncol Biol Phys*. 2016;96(4):840-847. doi:10.1016/j.ijrobp.2016.07.027
11. Gierloff M, Reutemann M, Gülses A, Niehoff P, Wiltfang J, Açil Y. Effects of zoledronate on the radiation-induced collagen breakdown: a prospective randomized clinical trial. *Clin Transl Oncol*. 2015;17(6):454-461. doi:10.1007/s12094-014-1257-8
12. Willey JS, Livingston EW, Robbins ME, et al. Risedronate prevents early radiation-induced osteoporosis in mice at multiple skeletal locations. *Bone*. 2010;46(1):101-111. doi:10.1016/j.bone.2009.09.002
13. Chandra A, Lin T, Tribble MB, et al. PTH1-34 alleviates radiotherapy-induced local bone loss by improving osteoblast and osteocyte survival. *Bone*. 2014;67:33-40. doi:10.1016/j.bone.2014.06.030
14. Moore J, Merchant Z, Rowlinson K, et al. Implementing a system-wide cancer prehabilitation programme: The journey of Greater Manchester's 'Prehab4cancer'. *Eur J Surg Oncol*. 2021;47(3 Pt A):524-532. doi:10.1016/j.ejso.2020.04.042
15. Geary B, Walker MJ, Snow JT, et al. Identification of a Biomarker Panel for Early Detection of Lung Cancer Patients. *J Proteome Res*. 2019;18(9):3369-3382. doi:10.1021/acs.jproteome.9b00287
16. Walker MJ, Zhou C, Backen A, et al. Discovery and Validation of Predictive Biomarkers of Survival for Non-small Cell Lung Cancer Patients Undergoing Radical Radiotherapy: Two Proteins With Predictive Value. *EBioMedicine*. 2015;2(8):841-850. Published 2015 Jun 19. doi:10.1016/j.ebiom.2015.06.013
17. Billingham SA, Whitehead AL, Julious SA. An audit of sample sizes for pilot and feasibility trials being undertaken in the United Kingdom registered in the United Kingdom Clinical Research Network database. *BMC Med Res Methodol*. 2013;13:104. Published 2013 Aug 20. doi:10.1186/1471-2288-13-104
18. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes*. 4th ed. Oxford: Oxford University Press, Oxford. <<https://books.google.co.uk/books?id=lvWACgAAQBAJ>>

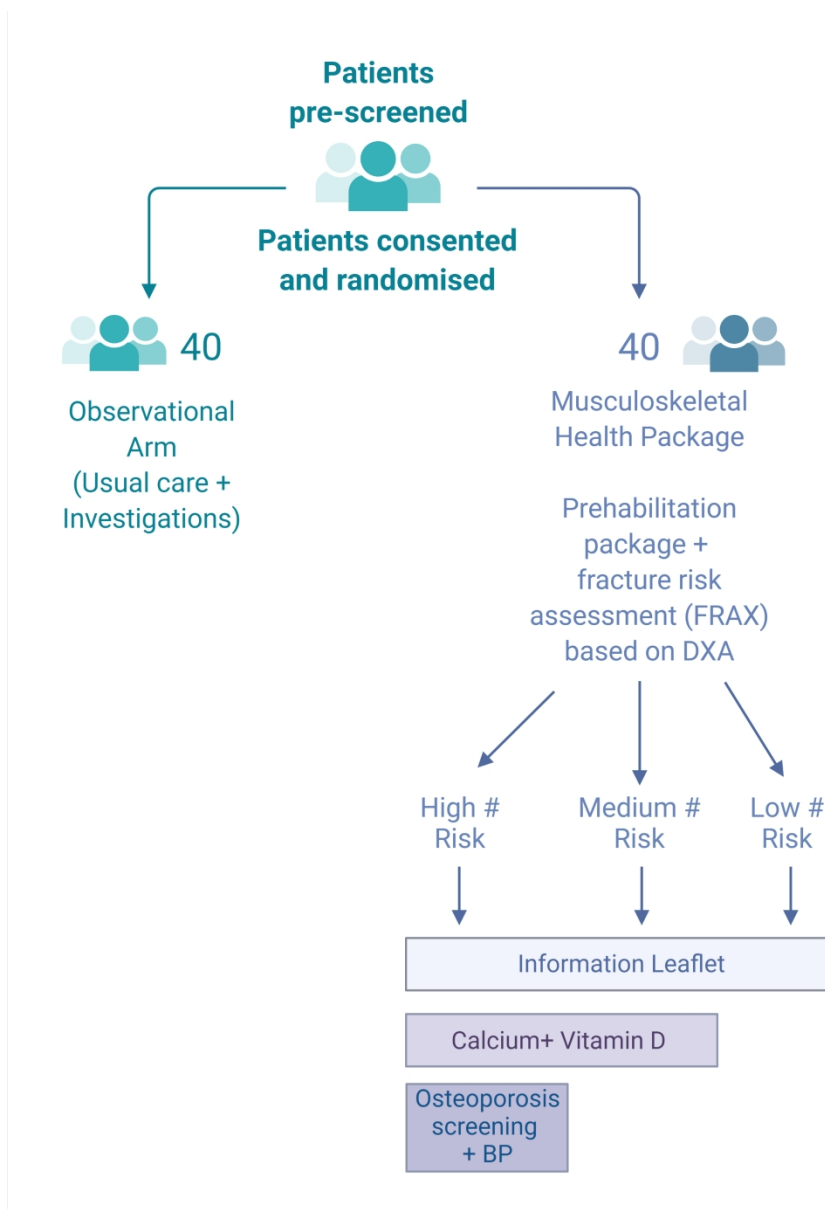


Figure 1: Recruitment, randomisation process and description of the stratified interventions. (# : fracture)

218x310mm (300 x 300 DPI)

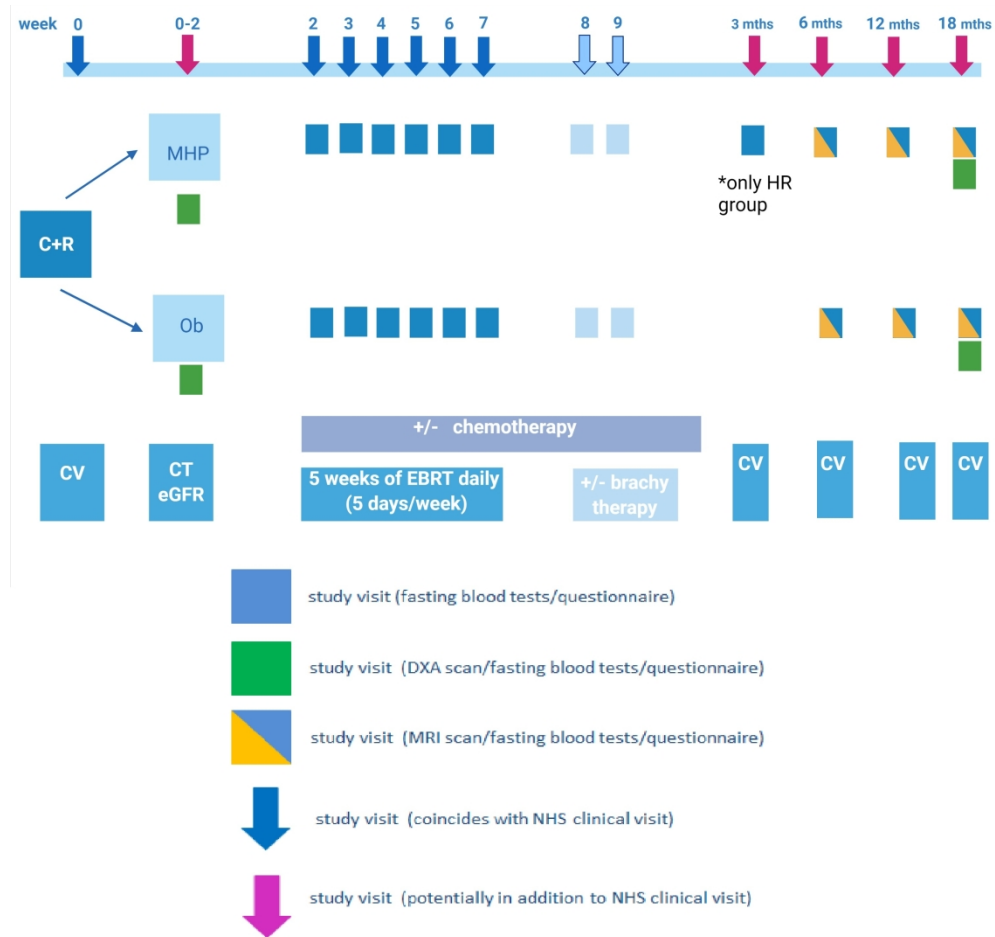


Figure 2: Study flow chart; assessments and outcome time-points.  
 C+R = Consent and Randomisation, MHP= Musculoskeletal Health Package arm, Ob = observational arm,  
 HR = high risk, CV = clinic visit, EBRT= External Beam Radiotherapy. NHS: National Health System

257x246mm (300 x 300 DPI)

# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

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			Page
		Reporting Item	Number
<b>Administrative information</b>			
Title	<a href="#">#1</a>	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	<a href="#">#2a</a>	Trial identifier and registry name. If not yet registered,	2

1		name of intended registry	
2			
3			
4	Trial registration: data	<a href="#">#2b</a> All items from the World Health Organization Trial	6-14
5			
6	set	Registration Data Set	
7			
8			
9	Protocol version	<a href="#">#3</a> Date and version identifier	N/A
10			
11			
12	Funding	<a href="#">#4</a> Sources and types of financial, material, and other support	14,15
13			
14			
15	Roles and	<a href="#">#5a</a> Names, affiliations, and roles of protocol contributors	14
16			
17	responsibilities:		
18			
19	contributorship		
20			
21			
22			
23	Roles and	<a href="#">#5b</a> Name and contact information for the trial sponsor	13,14
24			
25	responsibilities:		
26			
27	sponsor contact		
28			
29	information		
30			
31			
32			
33	Roles and	<a href="#">#5c</a> Role of study sponsor and funders, if any, in study design;	13,14
34			
35	responsibilities:	collection, management, analysis, and interpretation of	
36			
37	sponsor and funder	data; writing of the report; and the decision to submit the	
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45	Roles and	<a href="#">#5d</a> Composition, roles, and responsibilities of the coordinating	13,14
46			
47	responsibilities:	centre, steering committee, endpoint adjudication	
48			
49	committees	committee, data management team, and other individuals	
50			
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57	<b>Introduction</b>		
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60			

1	Background and	<a href="#">#6a</a>	Description of research question and justification for	5
2				
3	rationale		undertaking the trial, including summary of relevant studies	
4			(published and unpublished) examining benefits and harms	
5			for each intervention	
6				
7				
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11	Background and	<a href="#">#6b</a>	Explanation for choice of comparators	5
12				
13	rationale: choice of			
14				
15	comparators			
16				
17				
18	Objectives	<a href="#">#7</a>	Specific objectives or hypotheses	4,5
19				
20				
21				
22	Trial design	<a href="#">#8</a>	Description of trial design including type of trial (eg, parallel	5
23			group, crossover, factorial, single group), allocation ratio,	
24			and framework (eg, superiority, equivalence, non-inferiority,	
25			exploratory)	
26				
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28				
29				
30				
31	<b>Methods:</b>			
32				
33	<b>Participants,</b>			
34				
35	<b>interventions, and</b>			
36				
37	<b>outcomes</b>			
38				
39				
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41	Study setting	<a href="#">#9</a>	Description of study settings (eg, community clinic,	6
42			academic hospital) and list of countries where data will be	
43			collected. Reference to where list of study sites can be	
44			obtained	
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51	Eligibility criteria	<a href="#">#10</a>	Inclusion and exclusion criteria for participants. If	7
52			applicable, eligibility criteria for study centres and	
53			individuals who will perform the interventions (eg,	
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1		surgeons, psychotherapists)	
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3			
4	Interventions:	<a href="#">#11a</a> Interventions for each group with sufficient detail to allow	7,8
5			
6	description	replication, including how and when they will be	
7			
8		administered	
9			
10			
11	Interventions:	<a href="#">#11b</a> Criteria for discontinuing or modifying allocated	11
12			
13	modifications	interventions for a given trial participant (eg, drug dose	
14			
15		change in response to harms, participant request, or	
16			
17		improving / worsening disease)	
18			
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20			
21	Interventions:	<a href="#">#11c</a> Strategies to improve adherence to intervention protocols,	N/A
22			
23	adherence	and any procedures for monitoring adherence (eg, drug	
24			
25		tablet return; laboratory tests)	
26			
27			
28			
29	Interventions:	<a href="#">#11d</a> Relevant concomitant care and interventions that are	7,8
30			
31	concomitant care	permitted or prohibited during the trial	
32			
33			
34	Outcomes	<a href="#">#12</a> Primary, secondary, and other outcomes, including the	11,12
35			
36		specific measurement variable (eg, systolic blood	
37			
38		pressure), analysis metric (eg, change from baseline, final	
39			
40		value, time to event), method of aggregation (eg, median,	
41			
42		proportion), and time point for each outcome. Explanation	
43			
44		of the clinical relevance of chosen efficacy and harm	
45			
46		outcomes is strongly recommended	
47			
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50			
51	Participant timeline	<a href="#">#13</a> Time schedule of enrolment, interventions (including any	8-11
52			
53		run-ins and washouts), assessments, and visits for	
54			
55		participants. A schematic diagram is highly recommended	
56			
57		(see Figure)	
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1	Sample size	<a href="#">#14</a>	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
2				
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11	Recruitment	<a href="#">#15</a>	Strategies for achieving adequate participant enrolment to reach target sample size	12
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16	<b>Methods: Assignment</b>			
17	<b>of interventions (for</b>			
18	<b>controlled trials)</b>			
19				
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24	Allocation: sequence generation	<a href="#">#16a</a>	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	12,13
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41	Allocation concealment mechanism	<a href="#">#16b</a>	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	12,13
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51	Allocation: implementation	<a href="#">#16c</a>	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12,13
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1	Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions (eg,	5
2			trial participants, care providers, outcome assessors, data	
3			analysts), and how	
4				
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9	Blinding (masking):	<a href="#">#17b</a>	If blinded, circumstances under which unblinding is	N/a
10	emergency		permissible, and procedure for revealing a participant's	
11	unblinding		allocated intervention during the trial	
12				
13				
14				
15				
16	<b>Methods: Data</b>			
17	<b>collection,</b>			
18	<b>management, and</b>			
19	<b>analysis</b>			
20				
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26	Data collection plan	<a href="#">#18a</a>	Plans for assessment and collection of outcome, baseline,	9-11
27			and other trial data, including any related processes to	
28			promote data quality (eg, duplicate measurements, training	
29			of assessors) and a description of study instruments (eg,	
30			questionnaires, laboratory tests) along with their reliability	
31			and validity, if known. Reference to where data collection	
32			forms can be found, if not in the protocol	
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43	Data collection plan:	<a href="#">#18b</a>	Plans to promote participant retention and complete follow-	11
44	retention		up, including list of any outcome data to be collected for	
45			participants who discontinue or deviate from intervention	
46			protocols	
47				
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53	Data management	<a href="#">#19</a>	Plans for data entry, coding, security, and storage,	13
54			including any related processes to promote data quality	
55			(eg, double data entry; range checks for data values).	
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1		Reference to where details of data management	
2			
3		procedures can be found, if not in the protocol	
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5			
6	Statistics: outcomes	<a href="#">#20a</a> Statistical methods for analysing primary and secondary	13
7			
8		outcomes. Reference to where other details of the	
9			
10		statistical analysis plan can be found, if not in the protocol	
11			
12			
13	Statistics: additional	<a href="#">#20b</a> Methods for any additional analyses (eg, subgroup and	13
14			
15	analyses	adjusted analyses)	
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18			
19	Statistics: analysis	<a href="#">#20c</a> Definition of analysis population relating to protocol non-	13
20			
21	population and	adherence (eg, as randomised analysis), and any statistical	
22			
23	missing data	methods to handle missing data (eg, multiple imputation)	
24			
25			
26	<b>Methods: Monitoring</b>		
27			
28			
29	Data monitoring:	<a href="#">#21a</a> Composition of data monitoring committee (DMC);	13,14
30			
31	formal committee	summary of its role and reporting structure; statement of	
32			
33		whether it is independent from the sponsor and competing	
34			
35		interests; and reference to where further details about its	
36			
37		charter can be found, if not in the protocol. Alternatively, an	
38			
39		explanation of why a DMC is not needed	
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44	Data monitoring:	<a href="#">#21b</a> Description of any interim analyses and stopping	12
45			
46	interim analysis	guidelines, including who will have access to these interim	
47			
48		results and make the final decision to terminate the trial	
49			
50			
51	Harms	<a href="#">#22</a> Plans for collecting, assessing, reporting, and managing	11
52			
53		solicited and spontaneously reported adverse events and	
54			
55		other unintended effects of trial interventions or trial	
56			
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1		conduct	
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4	Auditing	<a href="#">#23</a> Frequency and procedures for auditing trial conduct, if any,	14
5		and whether the process will be independent from	
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8		investigators and the sponsor	
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11	<b>Ethics and</b>		
12			
13	<b>dissemination</b>		
14			
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16	Research ethics	<a href="#">#24</a> Plans for seeking research ethics committee / institutional	2
17		review board (REC / IRB) approval	
18	approval		
19			
20			
21			
22	Protocol	<a href="#">#25</a> Plans for communicating important protocol modifications	13,14
23		(eg, changes to eligibility criteria, outcomes, analyses) to	
24	amendments	relevant parties (eg, investigators, REC / IRBs, trial	
25		participants, trial registries, journals, regulators)	
26			
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31			
32	Consent or assent	<a href="#">#26a</a> Who will obtain informed consent or assent from potential	7
33		trial participants or authorised surrogates, and how (see	
34		Item 32)	
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36			
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38			
39	Consent or assent:	<a href="#">#26b</a> Additional consent provisions for collection and use of	N/A
40		participant data and biological specimens in ancillary	
41	ancillary studies	studies, if applicable	
42			
43			
44			
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46			
47	Confidentiality	<a href="#">#27</a> How personal information about potential and enrolled	13
48		participants will be collected, shared, and maintained in	
49		order to protect confidentiality before, during, and after the	
50		trial	
51			
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57	Declaration of	<a href="#">#28</a> Financial and other competing interests for principal	14,15
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1	interests		investigators for the overall trial and each study site	
2				
3				
4	Data access	<a href="#">#29</a>	Statement of who will have access to the final trial dataset,	TBC
5			and disclosure of contractual agreements that limit such	
6			access for investigators	
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11	Ancillary and post	<a href="#">#30</a>	Provisions, if any, for ancillary and post-trial care, and for	N/A
12			compensation to those who suffer harm from trial	
13	trial care		participation	
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19	Dissemination policy:	<a href="#">#31a</a>	Plans for investigators and sponsor to communicate trial	14
20			results to participants, healthcare professionals, the public,	
21	trial results		and other relevant groups (eg, via publication, reporting in	
22			results databases, or other data sharing arrangements),	
23			including any publication restrictions	
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31	Dissemination policy:	<a href="#">#31b</a>	Authorship eligibility guidelines and any intended use of	14
32			professional writers	
33	authorship			
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36	Dissemination policy:	<a href="#">#31c</a>	Plans, if any, for granting public access to the full protocol,	14
37			participant-level dataset, and statistical code	
38	reproducible research			
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42	<b>Appendices</b>			
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45	Informed consent	<a href="#">#32</a>	Model consent form and other related documentation given	TBC
46			to participants and authorised surrogates	
47	materials			
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50	Biological specimens	<a href="#">#33</a>	Plans for collection, laboratory evaluation, and storage of	N/A
51			biological specimens for genetic or molecular analysis in	
52			the current trial and for future use in ancillary studies, if	
53			applicable	
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# BMJ Open

## **RadBone: Bone Toxicity following Pelvic Radiotherapy. A prospective randomised controlled feasibility study evaluating a musculoskeletal health package in women with gynaecological cancers undergoing pelvic radiotherapy.**

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Keywords:	RADIOTHERAPY, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, Gynaecological oncology < GYNAECOLOGY, Clinical trials < THERAPEUTICS

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Manuscripts



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3 1 **Title:** RadBone: Bone Toxicity following Pelvic Radiotherapy. A prospective randomised  
4 2 controlled feasibility study evaluating a musculoskeletal health package in women with  
5 3 gynaecological cancers undergoing pelvic radiotherapy.  
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20 41 **Abstract:**  
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22 42 **Introduction:** Patients receiving radiotherapy are at risk of developing Radiotherapy Related  
23 43 Insufficiency Fractures (RRIFs), which are associated with increased morbidity and pose a  
24 44 significant burden to patients' quality of life and to the health system. Therefore, effective  
25 45 preventive techniques are urgently required. The RadBone randomized controlled trial (RCT)  
26 46 aims to determine the feasibility and acceptability of a musculoskeletal health package  
27 47 (MHP) intervention in women undergoing pelvic radiotherapy for gynaecological  
28 48 malignancies and to preliminary explore clinical effectiveness of the intervention.  
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33 49 **Methods and Analysis:** The RadBone RCT will evaluate the addition to standard care of a  
34 50 MHP consisting of a physical assessment of the musculoskeletal health, a three-month  
35 51 prehabilitation personalised exercise package, as well as an evaluation of the fracture risk  
36 52 and if required the prescription of appropriate bone treatment including calcium, vitamin D  
37 53 and -for high-risk individuals- bisphosphonates. Forty participants will be randomized in  
38 54 each group (MHP or observation) and will be followed for 18 months. The primary outcome  
39 55 of this RCT will be feasibility, including the eligibility, screening and recruitment rate,  
40 56 intervention fidelity and attrition rates; acceptability; and health economics. Clinical  
41 57 effectiveness and bone turnover markers will be evaluated as secondary outcomes.  
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47 58 **Ethics and dissemination:** This study has been approved by the Greater Manchester East  
48 59 Research Ethics Committee (Reference: 20/NW/0410, November 2020). The results will be  
49 60 published in peer reviewed journals, will be presented in national and international  
50 61 conferences, and will be communicated to relevant stakeholders. Moreover, a plain English  
51 62 report will be shared with the study participants, patients' organizations, and media.  
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55 63 **Clinical trial registration:** NCT04555317.  
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3 65 **Keywords:** radiotherapy, insufficiency fractures, musculoskeletal health, gynaecological  
4 66 cancer, randomised control trial.  
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10 68 **Strengths and Limitations of this study**

- 11  
12 69 • The RadBone is the first randomized controlled trial to assess a musculoskeletal  
13 70 health package aimed to prevent radiotherapy related insufficiency fractures (RRIFs).  
14 71 • A feasibility economic evaluation will allow future assessment of this complex  
15 72 intervention's cost-effectiveness.  
16 73 • Planned longitudinal proteomic analyses may reveal mechanistic insights and  
17 74 promising treatment targets.  
18 75 • A prospectively published detailed protocol increases the transparency and allows  
19 76 for peer review of the methodology used.  
20 77 • This study is not blinded and lacks an active comparator, hence, it is susceptible to  
21 78 performance and detection bias.  
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28 79  
29 80 **Word count: 3,740**  
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## 103 Introduction

104 In 2015 there were 2.5 million people in the UK with a diagnosis of cancer and this number  
105 is expected to rise to 4 million by 2030<sup>1</sup>. As a result of the continuing improvement in early  
106 detection of disease and improved treatment efficacy, a significant proportion are living  
107 long beyond their cancer diagnosis. However, estimates suggest that currently over 500,000  
108 people living with and beyond cancer have one or more physical or psychosocial  
109 consequences of their cancer or its treatment that affect their lives on a long-term basis.  
110 These consequences also have a substantial implication in terms of NHS resources.

111  
112 Patients receiving radiotherapy are at risk of developing radiotherapy related bone toxicity,  
113 in particular radiotherapy related insufficiency fractures (RRIFs). Incidence of RRIFs following  
114 pelvic radiotherapy has been reported as between 1.7 and 89% and occurring between 3 to  
115 20 months post radiotherapy. The wide variation in reported incidence depends on imaging  
116 modality and radiological reporting standards, symptomatic versus asymptomatic fractures,  
117 radiotherapy dose and underlying tumour type (reviewed in<sup>2</sup>). A recent meta-analysis of  
118 over 400 patients with RRIFs following pelvic radiotherapy for gynaecological cancers  
119 suggested an overall incidence of 14%<sup>3</sup>. Over 30 studies have been published since the  
120 1990's describing more than 1000 patients with pelvic RRIFs. This literature is notable for  
121 being almost exclusively retrospective in nature, a sparsity of baseline assessment of bone  
122 density and fracture risk, the absence of Patient Reported Outcome Measures (PROMs)  
123 used to assess Quality of Life (QOL) and no primary preventative or secondary management  
124 intervention studies<sup>4,5</sup>.

125  
126 The devastating effects of osteoporotic fragility fractures on morbidity and mortality and  
127 the economic cost are well described<sup>6</sup>. Pelvic insufficiency fractures may also increase  
128 mortality<sup>7</sup> but these data reflect an elderly population with multiple co-morbidities and the  
129 applicability to the pelvic radiotherapy population is not well defined. In addition, there are  
130 no pelvic RRIF studies reporting QOL as an outcome measure. However, the anxiety, pain,  
131 reduced mobility and increased morbidity associated with these has been described, with a  
132 number of patients requiring hospital admission for assessment and pain control<sup>8</sup>.  
133 Therefore, formal studies of QOL and PROMs are much needed, considering the wide range  
134 of pelvic radiotherapy toxicities<sup>9</sup>.

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136 Whilst a small number of studies, confirmed in a recent meta-analysis<sup>3</sup>, suggest  
137 osteoporosis as a risk factor in pelvic RRIFs, unlike the strong evidence base for  
138 bisphosphonate use in primary and secondary prevention of fragility fractures, there is no  
139 such evidence for RRIFs<sup>5</sup>. A small non-controlled study demonstrated intravenous  
140 zolendronic acid administration prior to spinal radiotherapy led to a lower prevalence of  
141 radiotherapy bone toxicity than expected<sup>10</sup> and a single randomised prospective study in

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3 142 patients undergoing spinal radiotherapy for metastatic disease demonstrated that  
4 143 intravenous zoledronic acid reduced urinary markers of collagen cross linking<sup>11</sup>.  
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7 145 Contradictory data from animal studies around the protective effects of bisphosphonates on  
8 146 RRIFs limits our understanding of the pathophysiology and therapeutics of RRIFs. Animal  
9 147 studies using whole mouse radiation have demonstrated an early activation of bone  
10 148 resorption in the 5 days following low dose (2 Gy) of radiotherapy which was reduced by  
11 149 subcutaneous administration of risedronate immediately following irradiation<sup>12</sup>. In contrast,  
12 150 a focal radiation technique in mice (using a small animal radiation research platform or  
13 151 SARRP), arguably a more physiological representative method of irradiation, demonstrated  
14 152 that alendronic acid did not prevent the radiation induced trabecular bone loss but that this  
15 153 was prevented by blocking osteoblast apoptosis with PTH 1-34<sup>13</sup>.  
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18 155 The RadBone is the first open-label prospective randomised controlled trial (RCT) to  
19 156 determine the feasibility and acceptability of a musculoskeletal health package (MHP)  
20 157 intervention in women undergoing pelvic radiotherapy for gynaecological malignancies and  
21 158 inform power calculations for a definitive RCT. Moreover, this feasibility trial will also  
22 159 explore potential implications on the incidence of RRIFs, quality of life and other clinical  
23 160 effectiveness and safety outcomes, as well as providing indicative estimates of the  
24 161 intervention's cost-effectiveness.  
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3 173 **Methods and analysis:**  
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6 174 **Study Design** (Figure 1)  
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11 176 **Study setting**  
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13 177 The planned study is a prospective randomised controlled feasibility trial of eighty patients  
14 178 with gynaecological malignancy (cervical and endometrial) undergoing pelvic radiotherapy  
15 179 at the Christie Hospital NHS Foundation Trust in Manchester, UK (a tertiary referral  
16 180 Oncology centre). The study opened for recruitment in May 2021, and the estimated  
17 181 primary completion date is in November 2022 and study completion date in June 2023.  
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24 183 **Eligibility Criteria**  
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27 184 Individuals aged over 18 years, with a histologically confirmed endometrial or cervical  
28 185 cancer undergoing potentially curative or adjuvant radiotherapy will be eligible, provided  
29 186 they are able and willing to provide an informed consent to participate.  
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32 187 The exclusion criteria are (i) age less than 18 years or greater than 85 years; (ii) pre-existing  
33 188 bone conditions such as osteoporosis treated with bisphosphonates in the previous 5 years,  
34 189 fibrous dysplasia, osteogenesis imperfecta, or other metabolic bone conditions; (iii) home  
35 190 address outside Greater Manchester; (iv) contraindication or intolerance of Magnetic  
36 191 Resonance scanning.  
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42 193 **Interventions**  
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44 194 Women undergoing radiotherapy for a gynaecological malignancy will be randomised to an  
45 195 observation (Ob) group and will receive standard assessment and care, following the current  
46 196 local clinical pathway, or an intervention group that will receive a “musculoskeletal health  
47 197 package” (MHP), in addition to standard assessment and care and will be followed for 18  
48 198 months.  
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53 199 Patients randomised to the MHP arm will receive (i) a physical assessment of  
54 200 musculoskeletal health and a 3-month prehabilitation personalised exercise package as part  
55 201 of the Greater Manchester prehab4cancer program<sup>14</sup>, (ii) a fracture risk assessment (FRAX)  
56 202 based on baseline dual-energy x-ray absorptiometry (DXA) bone mineral density (BMD), and  
57 203 (iii) treatment for bone health according to national UK recommendations i.e., standard of  
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204 care for prevention of fragility fractures, by being subdivided into 3 groups (low risk,  
205 medium risk and high risk).

206 Patients with a normal BMD and a FRAX score below the National Osteoporosis Guideline  
207 Group (NOGG) recommended treatment line will be considered low risk. Medium risk is  
208 defined as osteopenia on the DXA, with FRAX score below the NOGG treatment line. Finally,  
209 those with osteopenia and a previous vertebral or hip fracture, or a FRAX score above the  
210 NOGG recommended treatment line will be considered high risk.

211 Low risk patients will be provided with a copy of the Royal Osteoporosis Society (ROS)  
212 "Healthy living for strong bones" leaflet. In addition to the leaflet, medium risk patients will  
213 receive calcium (1000 mg once daily) and vitamin D (800 IU per day) supplementation. The  
214 same interventions will be offered to high-risk patients, who will also undergo secondary  
215 osteoporosis screening (blood tests) and will receive oral alendronate 70mg once weekly, in  
216 the absence of contraindications. Annual intravenous zoledronic acid infusion will be  
217 considered as an alternative where appropriate.

218 Those randomised to the observation arm will remain blinded to the results of the  
219 evaluations until the end of the study unless a fragility fracture or RRIF develops during the  
220 study.

### 221 ***Prehabilitation Exercise Programme (Prehab4cancer)***

222 All patients randomised to the MHP arm of the study will be offered a bespoke  
223 prehabilitation exercise programme via the Prehab4cancer programme in Greater  
224 Manchester. The MHP arm patients will be referred to the Prehab4cancer team via  
225 electronic referral immediately following randomisation. Allocated patients will be  
226 individually assessed by the Prehab4cancer team according to their usual protocols and  
227 assigned an appropriate prehabilitation program. Duration of the programme is 12 weeks  
228 from the first assessment and participation will be encouraged, as tolerated. The  
229 Prehab4Cancer and recovery programme is community-based, which incorporates exercise  
230 (cardiovascular and muscle strengthening/resistance training), nutritional screening, and  
231 advice and wellbeing support. Further details of programmes' assessment tools and the  
232 stratification of interventions are described by Moore et al<sup>14</sup> and can be found here:  
233 [www.prehab4cancer.co.uk](http://www.prehab4cancer.co.uk). The current scope of this protocol is to evaluate feasibility of  
234 participants' engagement in this face to face and remote prehabilitation service both pre-  
235 and during treatment.

236

### 237 **Baseline and Follow-up Evaluation (Figure 2)**

238 As described in figure 2, baseline evaluations will include a bone health assessment with  
239 DXA BMD measurement and completion of a bone health questionnaire. PROMs will also be  
240 captured. Finally, fasting serum and plasma blood samples will also be collected.

241 At 6, 12 and 18 months post radiotherapy all patients will undergo a pelvic MRI assessment  
242 for RRIFs, PROMs assessment and fasting blood sampling. During the final visit, at 18  
243 months, all patients will have a DXA BMD scan and physical assessment of their  
244 musculoskeletal health. If signs or symptoms compatible with a RRIF are described outside  
245 the study visits study participants will be assessed and managed following the current  
246 clinical pathways.

### 247 ***Imaging studies***

248 DXA scans of the total hip, femoral neck, L1-L4 spine and TBS assessments will be performed  
249 on a single DXA scanner (Hologic Horizon A SN 300792M version 5.6.07 with TBS v.3.0.2  
250 calibrated to the above scanner) at the Christie NHS Foundation Trust as per local protocol.  
251 These will be undertaken by two technicians trained in conducting DXA. Images will be  
252 reviewed, validated and interpreted by the lead investigator (CEH). The femoral neck BMD  
253 ( $\text{g}/\text{cm}^2$ ) will be used in conjunction with a standardised DXA questionnaire to complete FRAX  
254 calculation.

255 Pelvic Magnetic Resonance Imaging (MRI) scans will be performed at 6, 12 and 18 months  
256 on a 1.5T MRI scanner at the Christie Hospital by trained radiographers in accordance with  
257 the study imaging protocol. Four pelvic sequences will be performed per patient (5mm slice  
258 thickness, field of view 400mm; coronal T1, coronal STIR (inversion time 150ms), axial T1  
259 and axial STIR (inversion time 165 ms). These will correspond to routine follow-up scans  
260 where possible. All bone sequence scans will be dual reported by 2 consultant radiologists  
261 who will document the presence of fracture and their confidence in its presence, fracture  
262 location, fracture line, bone marrow oedema and other abnormalities.

### 263 ***Biochemical studies***

264 Fasting blood tests will be performed at baseline, weekly during radiotherapy (visits 2 to 10,  
265 one day prior to chemotherapy if receiving) and at 6, 12 and 18 months in all patients.  
266 Patients allocated to the MHP High risk arm and started on oral bisphosphonate therapy will  
267 have an additional bone turnover marker blood test at 3 months to assess bisphosphonate  
268 efficacy. All samples will be taken simultaneously with routinely collected clinical blood  
269 samples where appropriate.

270 As part of the MHP intervention arm, blood will be sampled, analysed, and assessed at  
271 baseline, 6, 12 and 18 months for the measurement of full blood count, urea and  
272 electrolytes, liver function tests, parathyroid hormone, vitamin D, thyroid function test,



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3 273 oestradiol, HbA1c, procollagen type 1 amino-terminal propeptide (P1NP), and the beta-C-  
4 274 terminal telopeptide (CTx). Moreover, in the observation arm, serum samples will be  
5 275 collected, processed and stored at -80°C for batch analysis at the end of the study.  
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9 276 Additional fasting blood samples will be collected at all timepoints mentioned for  
10 277 longitudinal analysis of bone turnover markers and for proteomic analysis. These samples  
11 278 will be processed and stored at -80°C, following local standard operating procedures (SOPs),  
12 279 for batch analysis at the end of the study. Bone turnover markers will be evaluated using  
13 280 ELISA techniques and will include CTX, NTX, P1NP, osteocalcin, TRAcP5b and bone ALP.  
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### 16 17 281 ***Sequential Window Acquisition of all Theoretical Mass Spectra (SWATH-MS)***

18  
19 282 Proteomic analysis will be conducted at the Stoller Biomarker Discovery Centre, following  
20 283 local SOPs<sup>15</sup>. Samples will be analysed by a Data Independent Acquisition method known as  
21 284 SWATH-MS with a micro-flow LC-MS system comprising an Eksigent nanoLC 400  
22 285 autosampler and an Eksigent nanoLC pump coupled to a SCIEX 6600 Triple-TOF mass  
23 286 spectrometer (68 min run-time). When SWATH maps are generated, the presence and  
24 287 abundance of plasma proteins will be quantified using published plasma reference libraries.  
25 288 Differential expression analysis will be used to identify candidate biomarkers using artificial  
26 289 intelligence approaches. Linear regression will be used to detect correlations with the  
27 290 presence of RRIFs and BMD.  
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33 291 Few longitudinal studies have tracked proteins of interest over the whole course of  
34 292 radiotherapy from pre-treatment baseline through to follow-up. We have undertaken one  
35 293 pilot that shows the potential value of this work<sup>16</sup>. Other studies that have investigated this  
36 294 have demonstrated distinguishing profiles with groups of approximately n=30. Two pre-  
37 295 radiotherapy baseline samples will be used to assess natural variation and comparison with  
38 296 the variance of measurements following radiotherapy and further comparison between the  
39 297 MHP and observation arm (n=40 per group).  
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44 299 Electronic data will be pseudoanonymised (coded) to protect the identity of the  
45 300 participants.  
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### 50 302 ***PROMS and Health Utilisation Proforma***

51  
52 303 PROMs will be collected either as electronic PROMS (using the myChristie, myHealth  
53 304 application) or paper-based PROMS at baseline 6, 12, and 18 months.  
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56 305 The evaluated PROMs will include the adapted pelvic patient-reported outcome version of  
57 306 the common terminology criteria for adverse events (PRO-CTCAE) assessment, the Short  
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3 307 Musculoskeletal Function Assessment (SMFA) modified for lower limb, the 5-level version of  
4 308 the EuroQol tool (EQ-5D-5L) and a tailored Health Utilisation Proforma.

6  
7 309 The CTCAE pelvic questionnaire will include as measures bowel questions scored out of 22,  
8 310 urinary questions out of 19 and sexual questions out of 8, with a total out of 49; a higher  
9 311 score indicates worse quality of life. The adapted SMFA questionnaire includes 39 questions,  
10 312 with a minimum possible score of 39 and maximum of 195; scores are standardised with  
11 313 high scores indicating poor function.

#### 15 314 **Criteria for discontinuing**

17  
18 315 Participants may decide to withdraw from the study at any time. Discontinuation of the  
19 316 study participants may occur as a result of investigator decision, safety concerns, and  
20 317 significant non-compliance to the protocol or incorrect enrolment. Reasons for  
21 318 discontinuation will be captured.

23  
24 319 As this is a feasibility study, participants may decide to discontinue their participation in  
25 320 certain aspects of the study (for example declining the prehabilitation programme or  
26 321 deciding not to take recommended medications). The participants can continue with the  
27 322 study and the details will be captured in the case report form (CRF).

#### 31 323 **Outcomes**

33  
34 324 The primary outcomes for this feasibility study will inform the design and power calculations  
35 325 for a definitive UK multi-centre RCT. These are:

- 36 326 1) Eligibility and screening rate: proportion of patients eligible for the study from  
37 327 patient population. [Assessed at baseline]
- 38 328 2) Recruitment and study group allocation rate: number and proportion of eligible  
39 329 patients recruited, randomised and allocated to appropriate study populations.  
40 330 [Assessed 2 weeks post consent]
- 41 331 3) Intervention fidelity rate: number and proportion of patients completing the  
42 332 elements of the study (assessment visits, prehab exercise programme, prescribed  
43 333 medications, QOL questionnaire). [Assessed at the end of study, at 18 months]
- 44 334 4) Attrition rate: number of patients lost to follow-up. [Assessed at the end of study, at  
45 335 18 months]
- 46 336 5) Patient and physician acceptability assessed with electronic questionnaires. [Change  
47 337 from baseline assessed at 6,12 and 18 months]
- 48 338 6) Health Economic Analysis: within-trial cost-effectiveness analysis to demonstrate  
49 339 feasibility of health economic data collection and analysis in a multi-centre RCT.  
50 340 [Change from baseline assessed at 6,12 and 18 months]

51 341  
52 342 The secondary outcomes are:

- 53 343 1) Incidence of pelvic Radiotherapy Related Insufficiency Fracture (RRIF). [Assessed at  
54 344 6, 12 and 18 months post radiotherapy]

- 1  
2  
3 345 2) Longitudinal change in BMD and fracture risk using FRAX. [Assessed at baseline and  
4 346 18 months]  
5  
6 347 3) Longitudinal change in biochemical markers of bone turnover. [Change from baseline  
7 348 assessed at 2, 3, 4, 5, 6, 7, 8 and 9 weeks and at 6, 12 and 18 months]  
8 349 4) Quality of Life assessment: adapted CTCAE pelvic questionnaire and SMFA adapted  
9 350 to lower limbs. [Change from baseline assessed at 6, 12 and 18 months]  
10 351

11  
12 352 Exploratory Endpoints include identification of predictive markers of RRIFs (radiomic,  
13 353 proteomic, BMD) and exploratory measurement of proteomic biomarkers of bone turnover  
14 354 during pelvic radiotherapy.  
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17 355

## 18 19 20 356 **Sample Size**

21  
22 357 No formal power calculation has been performed as this is a feasibility study. The study will  
23 358 collect initial data such as measures of location and variability for key outcome measures. It  
24 359 is recognised that in general, 30 patients are required in order to estimate such  
25 360 parameters<sup>17</sup>. For this study a total of 80 patients will be recruited and randomised with  
26 361 equal probability to either the MHP or observation arms (i.e. 40 per group). Assuming  
27 362 attrition rates of 15% per group, at least 30 should remain in each arm. This should be  
28 363 sufficient to assess the feasibility of a larger RCT study and estimate group means, standard  
29 364 deviations and percentages for key outcomes.  
30  
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## 34 35 365 **Recruitment**

36  
37 366 80 patients will be recruited over an 18-month period, approximately 4 patients per month.  
38 367 As this is a feasibility study there will be no interim analysis of study results.  
39  
40

## 41 368 **Assignment of interventions**

42  
43 369 Consenting, eligible participants will be randomised to the MHP or observation group using  
44 370 a validated online service; sealedenvelope™ (<https://www.sealedenvelope.com>). A  
45 371 permuted block (block size:4) randomisation protocol will be utilised with a 1:1 allocation  
46 372 (MHP to observation arm).  
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## 50 373 **Data Collection, management and analysis**

### 51 52 374 *Statistical and Health Economic Analysis*

53 375 As this is a feasibility study, it will not involve hypothesis testing to identify whether the  
54 376 intervention has had an impact. Instead, data analysis will be descriptive, focusing on the  
55 377 percentage of patients in each group developing RRIFs and risk factors for this. Means and a  
56 378 measure of variation will be calculated for each secondary outcome. These data, along with  
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2  
3 379 estimates of recruitment and attrition rates, will help inform a power calculation for the  
4 380 definitive trial.

5 381  
6  
7 382 A within-trial cost-effectiveness analysis<sup>18</sup> will be undertaken from the perspective of the UK  
8 383 National Health Service (NHS). Cost data for the intervention arm will reflect resource use  
9 384 associated with the musculoskeletal health package and treatment costs for both the  
10 385 control and intervention arm will be taken into account. Resource use will be extracted from  
11 386 patient records and the health care utilisation proforma. Relevant sources (e.g., NHS  
12 387 reference costs) will be used to identify unit costs. Health related quality of life (HRQL)  
13 388 scores will be generated using the EQ-5D-5L at baseline and at each of the three follow-up  
14 389 time points (6, 12, 18 months).

15 390  
16 391 A descriptive analysis of the costs and outcomes data will be completed focusing on: a.  
17 392 whether the EQ-5D-5L and SMFA are able to adequately capture differences in health status  
18 393 before and after implementation of the musculoskeletal health package and across both  
19 394 treatment arms of the study; b. whether the resource-use survey is able to record data  
20 395 necessary to enable a full cost-effectiveness analysis; c. the nature of missing data for the  
21 396 EQ-5D-5L, SMFA and resource-use survey to assess responses, sensitivity, and any patterns  
22 397 within the missing data.

23 398  
24 399 A within-trial cost-effectiveness analysis will be conducted to provide an indicative estimate  
25 400 of cost-effectiveness. Between-arm differences in costs and outcomes will be expressed as  
26 401 an incremental cost-effectiveness ratio (ICERs): the cost per QALY gained from the  
27 402 intervention compared to usual care. ICERs will also be calculated using the SMFA in an  
28 403 additional scenario analysis.

29 404

30 405

#### 31 406 **Trial oversight**

32  
33 407 An internal trial management group will be convened for the study, consisting of the chief  
34 408 investigator, project manager, Clinical Trials administrator, research nurse and a  
35 409 representative of the research and innovation division (R+I) as core members. The group will  
36 410 meet monthly. The study sponsor (Christie Hospital NHS Foundation Trust) will monitor the  
37 411 conduct of the trial.

#### 38 412 **Patient and Public Involvement**

39 413 This protocol was developed with the participation of the Christie pelvic radiotherapy user  
40 414 group and supported by the Pelvic Radiation Disease Association (PRDA).

41 415

#### 42 416 **Ethics and Dissemination**

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2  
3 417 This study has been approved by GM East Research Ethics Committee in November 2020  
4 418 (REC reference 20/NW/0410) and is registered at [clinicaltrials.gov](https://clinicaltrials.gov) (ClinicalTrials.gov  
5 419 Identifier: NCT04555317). The study opened for recruitment in May 2021. The results of this  
6 420 study will be published in peer reviewed journals, will be presented in national and  
7 421 international conferences, and will be communicated to relevant stakeholders. Moreover, a  
8 422 plain English report will be shared with the study participants, patients' organizations, and  
9 423 media.

#### 14 424 **Data sharing statement**

16  
17 425 Consent to share data from this study for future research is voluntary. To ensure compliance  
18 426 with regulatory and governance requirements, approval from the sponsor team is required  
19 427 prior to the release of any data generated by this Christie sponsored study, to a third party.  
20 428 Any requests are to be directed towards [the-christie.sponsoredresearch@nhs.net](mailto:the-christie.sponsoredresearch@nhs.net) for  
21 429 consideration and must follow all local Policies and review procedures. If a proposal is  
22 430 accepted, then the sponsor will work with the requestor to develop any necessary data  
23 431 transfer plans/agreements.

27  
28 432 **Authors' contributions:** CEH developed the protocol, MRC application and ethics application  
29 433 for the study. RB is the MRC-CARP academic partner to CEH and contributed to the study  
30 434 design and protocol.

32  
33 435 KJ, LHB, KH contributed to the development of the gynae-oncology aspects

34  
35 436 RK, SO'C, TW contributed to the development of the MRI radiology aspects

36  
37 437 ZM, JM contributed to the development of the Prehab4Cancer aspects

38  
39 438 ST, JY contributed to the PROMS development

40  
41 439 ME contributed to the Health Economic Analysis

42  
43 440 ADW, IBJ contributed to the proteomic and data analysis

44  
45 441 VCG and CEH prepared the manuscript

46  
47 442 All authors: critically reviewed and commented on the manuscript.

48  
49 443 **Funding statement:** This work is partially supported by an MRC-NIHR Clinical Academic  
50 444 Research Partnership) award: grant number MR/T024887/1. Funding is being sought for  
51 445 Health Economic Analysis, QOL and PROMS development and longitudinal proteomic  
52 446 analysis. Equipment used in the Stoller Biomarker Discovery Centre is funded by a donation  
53 447 received from the Stoller Charitable Trust and a research grant awarded by the Medical

1  
2  
3 448 Research Council (MR/M008959/1). MRC/EPSRC Molecular Pathology Node provided  
4 449 additional financial support by a grant from the Medical Research Council and Engineering &  
5 450 Physical Sciences Research Council (MR/N00583X/1).  
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8 451 **Competing interests statement.** No competing interests  
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3 453 **Figures legends**  
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7  
8 455 **Figure 1:** Recruitment, randomisation process and description of the stratified interventions.  
9 (#: fracture)  
10 456

11  
12 457 **Figure 2:** Study flow chart; assessments and outcome time-points.  
13

14 458 C+R = Consent and Randomisation, MHP= Musculoskeletal Health Package arm, Ob =  
15 459 observational arm, HR = high risk, CV = clinic visit, EBRT= External Beam Radiotherapy. NHS:  
16 460 National Health System  
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For peer review only

## 462 Full references

1. Available from: [https://www.macmillan.org.uk/\\_images/cancer-statistics-factsheet\\_tcm9-260514.pdf](https://www.macmillan.org.uk/_images/cancer-statistics-factsheet_tcm9-260514.pdf) [Accessed February 2022]
2. Higham CE, Faithfull S. Bone Health and Pelvic Radiotherapy. *Clin Oncol (R Coll Radiol)*. 2015;27(11):668-678. doi:10.1016/j.clon.2015.07.006
3. Sapienza LG, Salcedo MP, Ning MS, et al. Pelvic Insufficiency Fractures After External Beam Radiation Therapy for Gynecologic Cancers: A Meta-analysis and Meta-regression of 3929 Patients. *Int J Radiat Oncol Biol Phys*. 2020;106(3):475-484. doi:10.1016/j.ijrobp.2019.09.012
4. Gebauer J, Higham C, Langer T, Denzer C, Brabant G. Long-Term Endocrine and Metabolic Consequences of Cancer Treatment: A Systematic Review. *Endocr Rev*. 2019;40(3):711-767. doi:10.1210/er.2018-00092
5. van den Blink QU, Garcez K, Henson CC, Davidson SE, Higham CE. Pharmacological interventions for the prevention of insufficiency fractures and avascular necrosis associated with pelvic radiotherapy in adults. *Cochrane Database Syst Rev*. 2018;4(4):CD010604. Published 2018 Apr 23. doi:10.1002/14651858.CD010604.pub2.
6. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. *Lancet*. 1999;353(9156):878-882. doi:10.1016/S0140-6736(98)09075-8
7. Taillandier J, Languet F, Alemanni M, Taillandier-Herich E. Mortality and functional outcomes of pelvic insufficiency fractures in older patients. *Joint Bone Spine*. 2003;70(4):287-289. doi:10.1016/s1297-319x(03)00015-0
8. Oh D, Huh SJ, Nam H, et al. Pelvic insufficiency fracture after pelvic radiotherapy for cervical cancer: analysis of risk factors. *Int J Radiat Oncol Biol Phys*. 2008;70(4):1183-1188. doi:10.1016/j.ijrobp.2007.08.005
9. Holch P, Pini S, Henry AM, et al. eRAPID electronic patient self-Reporting of Adverse-events: Patient Information and aDvice: a pilot study protocol in pelvic radiotherapy. *Pilot Feasibility Stud*. 2018;4:110. Published 2018 Jun 5. doi:10.1186/s40814-018-0304-6
10. Pichon B, Campion L, Delpon G, et al. High-Dose Hypofractionated Radiation Therapy for Noncompressive Vertebral Metastases in Combination With Zoledronate: A Phase 1 Study. *Int J Radiat Oncol Biol Phys*. 2016;96(4):840-847. doi:10.1016/j.ijrobp.2016.07.027
11. Gierloff M, Reutemann M, Gülses A, Niehoff P, Wiltfang J, Açil Y. Effects of zoledronate on the radiation-induced collagen breakdown: a prospective randomized clinical trial. *Clin Transl Oncol*. 2015;17(6):454-461. doi:10.1007/s12094-014-1257-8
12. Willey JS, Livingston EW, Robbins ME, et al. Risedronate prevents early radiation-induced osteoporosis in mice at multiple skeletal locations. *Bone*. 2010;46(1):101-111. doi:10.1016/j.bone.2009.09.002
13. Chandra A, Lin T, Tribble MB, et al. PTH1-34 alleviates radiotherapy-induced local bone loss by improving osteoblast and osteocyte survival. *Bone*. 2014;67:33-40. doi:10.1016/j.bone.2014.06.030
14. Moore J, Merchant Z, Rowlinson K, et al. Implementing a system-wide cancer prehabilitation programme: The journey of Greater Manchester's 'Prehab4cancer'. *Eur J Surg Oncol*. 2021;47(3 Pt A):524-532. doi:10.1016/j.ejso.2020.04.042
15. Geary B, Walker MJ, Snow JT, et al. Identification of a Biomarker Panel for Early Detection of Lung Cancer Patients. *J Proteome Res*. 2019;18(9):3369-3382. doi:10.1021/acs.jproteome.9b00287
16. Walker MJ, Zhou C, Backen A, et al. Discovery and Validation of Predictive Biomarkers of Survival for Non-small Cell Lung Cancer Patients Undergoing Radical Radiotherapy: Two Proteins With Predictive Value. *EBioMedicine*. 2015;2(8):841-850. Published 2015 Jun 19. doi:10.1016/j.ebiom.2015.06.013
17. Billingham SA, Whitehead AL, Julious SA. An audit of sample sizes for pilot and feasibility trials being undertaken in the United Kingdom registered in the United Kingdom Clinical Research Network database. *BMC Med Res Methodol*. 2013;13:104. Published 2013 Aug 20. doi:10.1186/1471-2288-13-104
18. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes*. 4th ed. Oxford: Oxford University Press, Oxford. <<https://books.google.co.uk/books?id=lvWACgAAQBAJ>>



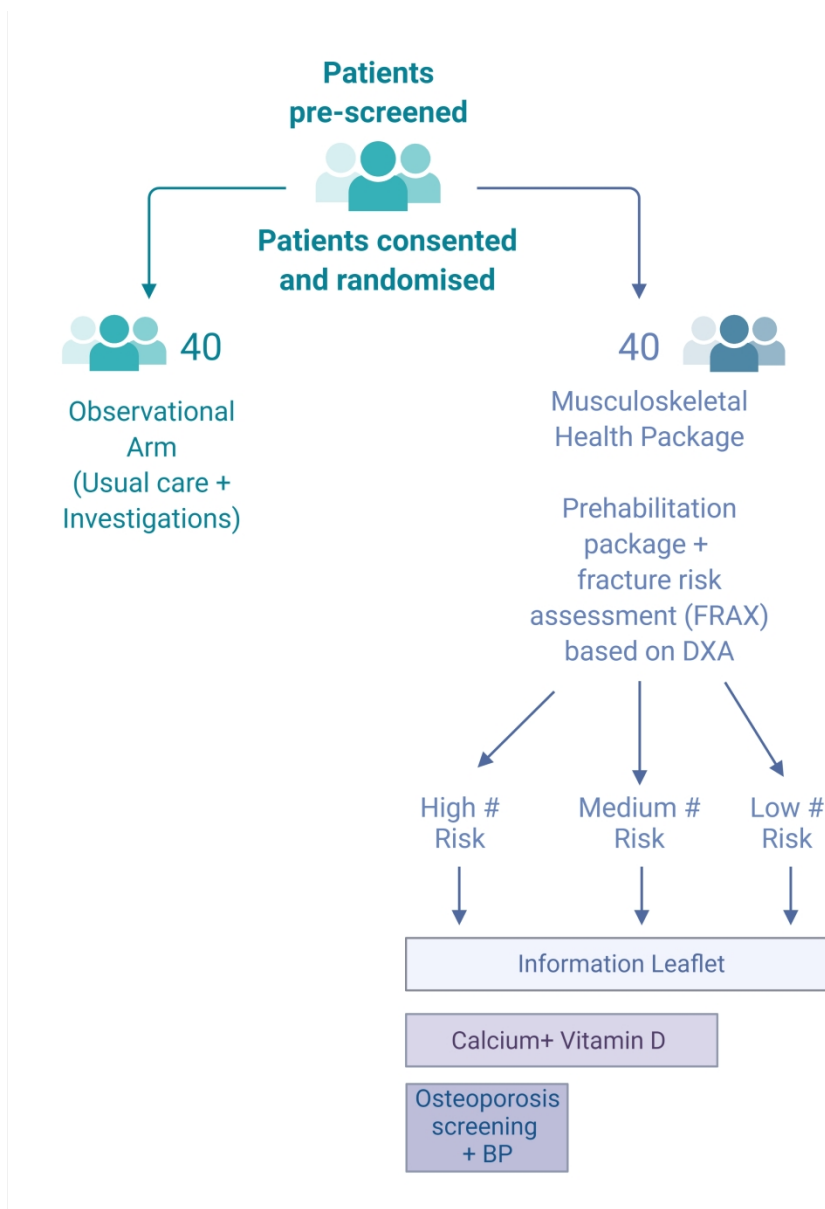


Figure 1: Recruitment, randomisation process and description of the stratified interventions. (# : fracture)

218x310mm (300 x 300 DPI)

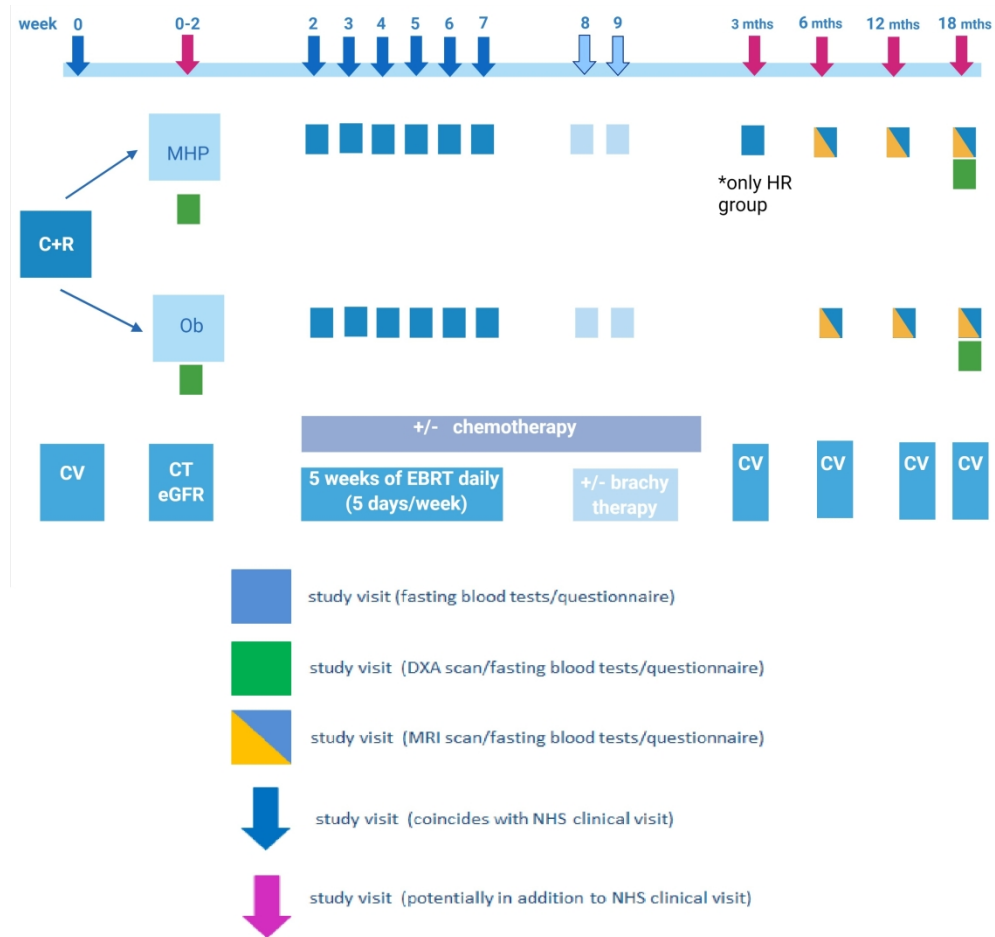


Figure 2: Study flow chart; assessments and outcome time-points. C+R = Consent and Randomisation, MHP= Musculoskeletal Health Package arm, Ob = observational arm, HR = high risk, CV = clinic visit, EBRT= External Beam Radiotherapy. NHS: National Health System

257x246mm (300 x 300 DPI)

# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586

			Page
		Reporting Item	Number
<b>Administrative information</b>			
Title	<a href="#">#1</a>	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	<a href="#">#2a</a>	Trial identifier and registry name. If not yet registered,	2

1		name of intended registry	
2			
3			
4	Trial registration: data	<a href="#">#2b</a> All items from the World Health Organization Trial	6-14
5			
6	set	Registration Data Set	
7			
8			
9	Protocol version	<a href="#">#3</a> Date and version identifier	N/A
10			
11			
12	Funding	<a href="#">#4</a> Sources and types of financial, material, and other support	14,15
13			
14			
15	Roles and	<a href="#">#5a</a> Names, affiliations, and roles of protocol contributors	14
16			
17	responsibilities:		
18			
19	contributorship		
20			
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22			
23	Roles and	<a href="#">#5b</a> Name and contact information for the trial sponsor	13,14
24			
25	responsibilities:		
26			
27	sponsor contact		
28			
29	information		
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32			
33	Roles and	<a href="#">#5c</a> Role of study sponsor and funders, if any, in study design;	13,14
34			
35	responsibilities:	collection, management, analysis, and interpretation of	
36			
37	sponsor and funder	data; writing of the report; and the decision to submit the	
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45	Roles and	<a href="#">#5d</a> Composition, roles, and responsibilities of the coordinating	13,14
46			
47	responsibilities:	centre, steering committee, endpoint adjudication	
48			
49	committees	committee, data management team, and other individuals	
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57	<b>Introduction</b>		
58			
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60			

1	Background and	<a href="#">#6a</a>	Description of research question and justification for	5
2				
3	rationale		undertaking the trial, including summary of relevant studies	
4			(published and unpublished) examining benefits and harms	
5			for each intervention	
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11	Background and	<a href="#">#6b</a>	Explanation for choice of comparators	5
12				
13	rationale: choice of			
14				
15	comparators			
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18	Objectives	<a href="#">#7</a>	Specific objectives or hypotheses	4,5
19				
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21				
22	Trial design	<a href="#">#8</a>	Description of trial design including type of trial (eg, parallel	5
23			group, crossover, factorial, single group), allocation ratio,	
24			and framework (eg, superiority, equivalence, non-inferiority,	
25			exploratory)	
26				
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30				
31	<b>Methods:</b>			
32				
33	<b>Participants,</b>			
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35	<b>interventions, and</b>			
36				
37	<b>outcomes</b>			
38				
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41	Study setting	<a href="#">#9</a>	Description of study settings (eg, community clinic,	6
42			academic hospital) and list of countries where data will be	
43			collected. Reference to where list of study sites can be	
44			obtained	
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51	Eligibility criteria	<a href="#">#10</a>	Inclusion and exclusion criteria for participants. If	7
52			applicable, eligibility criteria for study centres and	
53			individuals who will perform the interventions (eg,	
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		surgeons, psychotherapists)	
Interventions:	<a href="#">#11a</a>	Interventions for each group with sufficient detail to allow	7,8
description		replication, including how and when they will be	
		administered	
Interventions:	<a href="#">#11b</a>	Criteria for discontinuing or modifying allocated	11
modifications		interventions for a given trial participant (eg, drug dose	
		change in response to harms, participant request, or	
		improving / worsening disease)	
Interventions:	<a href="#">#11c</a>	Strategies to improve adherence to intervention protocols,	N/A
adherence		and any procedures for monitoring adherence (eg, drug	
		tablet return; laboratory tests)	
Interventions:	<a href="#">#11d</a>	Relevant concomitant care and interventions that are	7,8
concomitant care		permitted or prohibited during the trial	
Outcomes	<a href="#">#12</a>	Primary, secondary, and other outcomes, including the	11,12
		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	
Participant timeline	<a href="#">#13</a>	Time schedule of enrolment, interventions (including any	8-11
		run-ins and washouts), assessments, and visits for	
		participants. A schematic diagram is highly recommended	
		(see Figure)	

1	Sample size	<a href="#">#14</a>	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
2				
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11	Recruitment	<a href="#">#15</a>	Strategies for achieving adequate participant enrolment to reach target sample size	12
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15				
16	<b>Methods: Assignment</b>			
17	<b>of interventions (for</b>			
18	<b>controlled trials)</b>			
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24	Allocation: sequence generation	<a href="#">#16a</a>	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	12,13
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41	Allocation concealment mechanism	<a href="#">#16b</a>	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	12,13
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51	Allocation: implementation	<a href="#">#16c</a>	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12,13
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1	Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions (eg,	5
2			trial participants, care providers, outcome assessors, data	
3			analysts), and how	
4				
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9	Blinding (masking):	<a href="#">#17b</a>	If blinded, circumstances under which unblinding is	N/a
10	emergency		permissible, and procedure for revealing a participant's	
11			allocated intervention during the trial	
12	unblinding			
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16	<b>Methods: Data</b>			
17	<b>collection,</b>			
18	<b>management, and</b>			
19	<b>analysis</b>			
20				
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25				
26	Data collection plan	<a href="#">#18a</a>	Plans for assessment and collection of outcome, baseline,	9-11
27			and other trial data, including any related processes to	
28			promote data quality (eg, duplicate measurements, training	
29			of assessors) and a description of study instruments (eg,	
30			questionnaires, laboratory tests) along with their reliability	
31			and validity, if known. Reference to where data collection	
32			forms can be found, if not in the protocol	
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43	Data collection plan:	<a href="#">#18b</a>	Plans to promote participant retention and complete follow-	11
44	retention		up, including list of any outcome data to be collected for	
45			participants who discontinue or deviate from intervention	
46			protocols	
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53	Data management	<a href="#">#19</a>	Plans for data entry, coding, security, and storage,	13
54			including any related processes to promote data quality	
55			(eg, double data entry; range checks for data values).	
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1		Reference to where details of data management	
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3		procedures can be found, if not in the protocol	
4			
5			
6	Statistics: outcomes	<a href="#">#20a</a> Statistical methods for analysing primary and secondary	13
7			
8		outcomes. Reference to where other details of the	
9			
10		statistical analysis plan can be found, if not in the protocol	
11			
12			
13	Statistics: additional	<a href="#">#20b</a> Methods for any additional analyses (eg, subgroup and	13
14			
15	analyses	adjusted analyses)	
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19	Statistics: analysis	<a href="#">#20c</a> Definition of analysis population relating to protocol non-	13
20			
21	population and	adherence (eg, as randomised analysis), and any statistical	
22			
23	missing data	methods to handle missing data (eg, multiple imputation)	
24			
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26	<b>Methods: Monitoring</b>		
27			
28			
29	Data monitoring:	<a href="#">#21a</a> Composition of data monitoring committee (DMC);	13,14
30			
31	formal committee	summary of its role and reporting structure; statement of	
32			
33		whether it is independent from the sponsor and competing	
34			
35		interests; and reference to where further details about its	
36			
37		charter can be found, if not in the protocol. Alternatively, an	
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39		explanation of why a DMC is not needed	
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44	Data monitoring:	<a href="#">#21b</a> Description of any interim analyses and stopping	12
45			
46	interim analysis	guidelines, including who will have access to these interim	
47			
48		results and make the final decision to terminate the trial	
49			
50			
51	Harms	<a href="#">#22</a> Plans for collecting, assessing, reporting, and managing	11
52			
53		solicited and spontaneously reported adverse events and	
54			
55		other unintended effects of trial interventions or trial	
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1		conduct	
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4	Auditing	<a href="#">#23</a> Frequency and procedures for auditing trial conduct, if any,	14
5		and whether the process will be independent from	
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7			
8		investigators and the sponsor	
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10			
11	<b>Ethics and</b>		
12			
13	<b>dissemination</b>		
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16	Research ethics	<a href="#">#24</a> Plans for seeking research ethics committee / institutional	2
17		review board (REC / IRB) approval	
18	approval		
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22	Protocol	<a href="#">#25</a> Plans for communicating important protocol modifications	13,14
23		(eg, changes to eligibility criteria, outcomes, analyses) to	
24	amendments	relevant parties (eg, investigators, REC / IRBs, trial	
25		participants, trial registries, journals, regulators)	
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32	Consent or assent	<a href="#">#26a</a> Who will obtain informed consent or assent from potential	7
33		trial participants or authorised surrogates, and how (see	
34		Item 32)	
35			
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39	Consent or assent:	<a href="#">#26b</a> Additional consent provisions for collection and use of	N/A
40		participant data and biological specimens in ancillary	
41	ancillary studies	studies, if applicable	
42			
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47	Confidentiality	<a href="#">#27</a> How personal information about potential and enrolled	13
48		participants will be collected, shared, and maintained in	
49		order to protect confidentiality before, during, and after the	
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52		trial	
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57	Declaration of	<a href="#">#28</a> Financial and other competing interests for principal	14,15
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1	interests		investigators for the overall trial and each study site	
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3				
4	Data access	<a href="#">#29</a>	Statement of who will have access to the final trial dataset,	TBC
5			and disclosure of contractual agreements that limit such	
6			access for investigators	
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11	Ancillary and post	<a href="#">#30</a>	Provisions, if any, for ancillary and post-trial care, and for	N/A
12			compensation to those who suffer harm from trial	
13	trial care		participation	
14				
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19	Dissemination policy:	<a href="#">#31a</a>	Plans for investigators and sponsor to communicate trial	14
20			results to participants, healthcare professionals, the public,	
21	trial results		and other relevant groups (eg, via publication, reporting in	
22			results databases, or other data sharing arrangements),	
23			including any publication restrictions	
24				
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31	Dissemination policy:	<a href="#">#31b</a>	Authorship eligibility guidelines and any intended use of	14
32			professional writers	
33	authorship			
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36	Dissemination policy:	<a href="#">#31c</a>	Plans, if any, for granting public access to the full protocol,	14
37			participant-level dataset, and statistical code	
38	reproducible research			
39				
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41				
42	<b>Appendices</b>			
43				
44				
45	Informed consent	<a href="#">#32</a>	Model consent form and other related documentation given	TBC
46			to participants and authorised surrogates	
47	materials			
48				
49				
50	Biological specimens	<a href="#">#33</a>	Plans for collection, laboratory evaluation, and storage of	N/A
51			biological specimens for genetic or molecular analysis in	
52			the current trial and for future use in ancillary studies, if	
53			applicable	
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