

BMJ Open Protocol for PIT: a phase III trial of prophylactic irradiation of tracts in patients with malignant pleural mesothelioma following invasive chest wall intervention

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ABSTRACT

Introduction: Histological diagnosis of malignant mesothelioma requires an invasive procedure such as CT-guided needle biopsy, thoracoscopy, video-assisted thorascopic surgery (VATs) or thoracotomy. These invasive procedures encourage tumour cell seeding at the intervention site and patients can develop tumour nodules within the chest wall. In an effort to prevent nodules developing, it has been widespread practice across Europe to irradiate intervention sites postprocedure—a practice known as prophylactic irradiation of tracts (PIT). To date there has not been a suitably powered randomised trial to determine whether PIT is effective at reducing the risk of chest wall nodule development.

Methods and analysis: In this multicentre phase III randomised controlled superiority trial, 374 patients who can receive radiotherapy within 42 days of a chest wall intervention will be randomised to receive PIT or no PIT. Patients will be randomised on a 1:1 basis. Radiotherapy in the PIT arm will be 21 Gy in three fractions. Subsequent chemotherapy is given at the clinicians' discretion. A reduction in the incidence of chest wall nodules from 15% to 5% in favour of radiotherapy 6 months after randomisation would be clinically significant. All patients will be followed up for up to 2 years with monthly telephone contact and at least four outpatient visits in the first year.

Ethics and dissemination: PIT was approved by NRES Committee North West—Greater Manchester West (REC reference 12/NW/0249) and recruitment is currently on-going, the last patient is expected to be randomised by the end of 2015. The analysis of the primary end point, incidence of chest wall nodules 6 months after randomisation, is expected to be published in 2016 in a peer reviewed journal and results will also be presented at scientific meetings and summary results published online. A follow-up analysis is expected to be published in 2018.

Trial registration number: ISRCTN04240319; NCT016044005; Pre-results.

Strengths and limitations of this study

- Largest, adequately powered randomised controlled study of prophylactic radiotherapy in this population.
- Radiotherapy fields reflect current practice for thoracoscopy and drain insertion.
- Monthly telephone follow-up to supplement outpatient follow-up clinical significance of chest wall metastases measured with visual analogue scale pain score.
- Will not determine role of prophylactic radiotherapy at the site of an indwelling pleural catheter.

INTRODUCTION

Malignant pleural mesothelioma (MPM) is almost exclusively linked to asbestos exposure with a latency period that is usually more than 30 years and prognosis is poor.^{1–4} The median survival in the UK is 8.8 months and the 1-year survival 38.5%.⁵

Diagnosis of mesothelioma is usually made by pleural biopsy either via CT-guided needle biopsy, thoracoscopy, video-assisted thoracic surgery (VATs) or thoracotomy. Patients often have associated pleural effusions and require chest drains to relieve symptoms such as chest pain and difficulty breathing. These invasive procedures encourage tumour cell seeding at the site of the intervention, which can result in formation of a subcutaneous tumour. The rate of chest wall metastases ranges from 2% to 50%, and depends on the procedure performed.^{4 6–14}

In an effort to minimise tumour seeding and prevent nodule development, it has been widespread practice for more than 20 years in the UK to irradiate intervention sites

postprocedure—a practice known as prophylactic irradiation of tracts (PIT).

Only three randomised controlled trials, the largest with 61 patients, have assessed the role of PIT with conflicting results reported.^{14–19} One study reported a statistically significant reduction in the frequency of malignant seeding of tracts in the PIT arm compared to the control arm¹⁴; the other two studies did not.^{15–16} Systematic reviews of the literature have concluded that the randomised trials conducted to date were considered the best available evidence for PIT, but that there was insufficient evidence to definitively recommend PIT.^{17–20} Inconsistencies are also evident in current national recommendations on the use of PIT. The British Thoracic Society²¹ recommends the use of PIT to prevent chest wall nodule formation following an interventional procedure. In contrast, the Cancer Care Ontario Programme²² stated that a recommendation for PIT in MPM could not be made due to inconsistent evidence, reflecting a lack of high-quality data. Similarly, in 2010 the European Respiratory Society stated “The value of prophylactic radiotherapy is questionable”²³ and the European Society of Medical Oncology (ESMO) clinical recommendations for diagnosis, treatment and follow-up of MPM state that “it remains impossible to draw definitive conclusions regarding its efficacy”.²⁴

Currently in the UK the routine use of PIT in patients with MPM depends on locality. A 2008 UK survey showed that 75% of radiotherapy centres are routinely using PIT.¹⁷ In addition, the small number of patients recruited to each arm, the high death rates, and overestimation of the rate of chest wall metastasis in the control arms, question whether the three previous randomised controlled trials were adequately powered. Furthermore, recent evidence shows that portal tracts are not always perpendicular to the skin²⁵ and thus the small radiation fields centred on the chest wall scar employed by the previous negative studies may have been suboptimal.

There is now strong evidence to support the role of palliative chemotherapy in patients with MPM²⁶ which is approved in the UK by the National Institute of Clinical Excellence (NICE).²⁷ Importantly, the previous studies were conducted before palliative chemotherapy was widely used in MPM. Therefore, the role of PIT in the era of effective palliative chemotherapy remains undefined. In addition, no previous studies have used validated pain scoring tools to assess pain from tract metastases.

We believe a trial is essential for the following reasons: first an adequately powered RCT employing radiotherapy techniques ensuring adequate coverage of the entire portal tract will establish whether PIT should be offered routinely to patients with MPM after chest wall intervention in the era of palliative chemotherapy; second to establish whether chest wall metastases are symptomatic and thus, whether PIT, if effective, is clinically significant.

The hypothesis for this trial is that prophylactic irradiation of tracts will reduce the incidence of chest wall

nodules from 15% to 5%. The primary objective of the PIT study is to determine the efficacy, as assessed by the incidence of chest wall metastasis, of prophylactic irradiation of tracts following invasive chest wall intervention in malignant pleural mesothelioma compared to no prophylactic radiotherapy. Secondary objectives include: the description of the toxicity of PIT; time from randomisation to chest wall tract metastasis in patients undergoing PIT compared with the no prophylactic radiotherapy; the assessment of pain from chest wall metastasis.

METHODS AND ANALYSIS

Trial design

This is a two-arm, phase III multicentre (list of centres can be found in online supplementary appendix 1 including a mix of academic centres and community hospitals) randomised superiority trial comparing radiotherapy versus no radiotherapy in patients with a histological diagnosis of MPM following chest wall intervention (see figure 1). A total of 374 patients will be randomised on a 1:1 basis to receive PIT

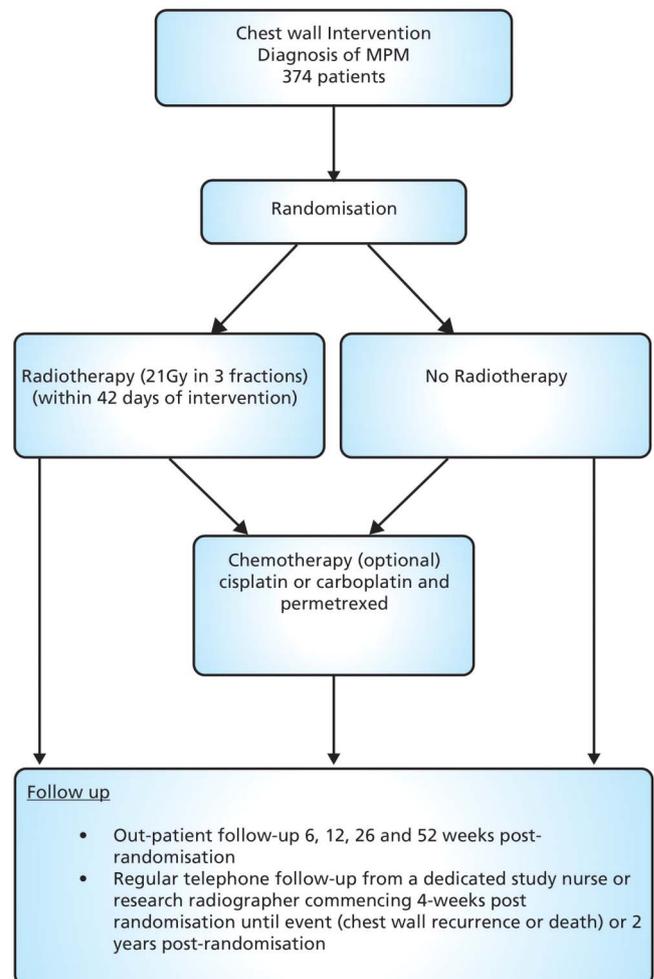


Figure 1 Trial schema/flow chart. MPM, malignant pleural mesothelioma.

(experimental arm) or no PIT (control arm). Patients can receive chemotherapy postradiotherapy/randomisation at the discretion of the treating physician.

The follow-up period for the study is up to 2 years postrandomisation which includes regular telephone follow-up and a minimum of four outpatient visits in the first year.

Patient selection

Potential participants will be identified by the principal investigator and his/her team at each centre, via the discussion of cases in a multidisciplinary team meeting (MDT). If a patient is identified as a potential participant in the PIT trial they will be approached at their next clinic visit, as part of discussions with the patient about their options for treatment. Patients who are interested in receiving further information about the trial will be given a copy of the patient information sheet (see online supplementary appendix 2) and consent form (see online supplementary appendix 3), and will have the opportunity to discuss the trial in detail before deciding whether to participate.

Inclusion criteria

- ▶ Either sex, age ≥ 18 years.
- ▶ Diagnosis of mesothelioma by MDT
- ▶ All histological subtypes. Where the histological diagnosis is unclear, a specialist thoracic pathologist should be consulted.
- ▶ Eastern Cooperative Oncology Group performance status 0–2.
- ▶ Inoperable disease or operable disease in patients unsuitable for surgery as decided by a MDT.
- ▶ Chest wall intervention with video-assisted thoracoscopy (VATS), open surgical biopsy, local anaesthetic thoracoscopy or chest drain.
- ▶ Able to start radiotherapy within 42 days (6 weeks) from most recent chest wall intervention.
- ▶ Chest wall intervention scar visible at time of randomisation.
- ▶ No indwelling pleural catheters in situ at the intervention site.
- ▶ Radiotherapy target volume acceptable by the local radiotherapist.
- ▶ No previous open thoracotomy.
- ▶ No previous radiotherapy to the region of the chest wall intervention site.
- ▶ Not currently receiving chemotherapy and not received chemotherapy for mesothelioma before randomisation.
- ▶ No other previous or concomitant illness or treatment which in the opinion of the clinician will interfere with the trial treatments or comparisons.
- ▶ Patients enrolled on other clinical trials could be considered after discussion with the chief investigators.
- ▶ Female patients must satisfy the investigator that they are not pregnant, or are not of childbearing potential, or are using adequate contraception.

- ▶ Patients must not be breastfeeding.
- ▶ Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the trial protocol and follow-up schedule; those conditions should be discussed with the patient before randomisation in the trial
- ▶ Patients can only be randomised in this trial once.

Exclusion criteria

- ▶ Patients who underwent a thoracotomy (as large thoracotomy scars may not be adequately covered by this radiotherapy technique).
- ▶ Previous radiotherapy to the region of the chest wall intervention site.
- ▶ Indwelling pleural catheter in situ at the intervention site.
- ▶ Patients currently receiving chemotherapy.

Consent

All patients will be informed of the aims of the trial, the procedures and possible adverse effects, and the mechanism of treatment allocation. Patients will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorised individuals other than their treating physician.

It will be emphasised that the participation is voluntary and that the patient is allowed to decline further participation in the protocol whenever he/she wants. This will not prejudice the patient's subsequent care. Documented informed consent will be obtained by local principal investigators or a delegated member of staff for all patients included in the trial before they are registered or randomised in the trial in accordance with the national and local regulatory requirements.

Randomisation procedure

Patients will be randomised by phone or fax on a 1:1 basis to one of two treatment arms. A variant of an adaptive biased coin randomisation method will be used to favour balance between treatment arms in the four strata formed from the following two factors:

- ▶ Histology (epithelioid or not epithelioid)
- ▶ Intention to give chemotherapy

Randomisation will be undertaken centrally by Manchester Academic Health Science Centre Clinical Trials Unit (MAHSC-CTU).

Radiotherapy

Patients are treated on a linear accelerator using a single electron field. Treatment fields can be shaped using individualised lead cut-outs of the appropriate thickness. The total dose of radiotherapy in the PIT arm is 21 Gy in three fractions, once daily over three consecutive days. The patient can be treated supine, prone or in the lateral position depending on the position of the chest wall intervention site. To ensure >90% of the prescribed dose is delivered to the skin surface, 0.5 cm

tissue-equivalent bolus can be applied to the whole treatment field. The field position for radiotherapy is recorded so that if the patient develops chest wall nodules it can be determined if the nodules are inside or outside the treatment field.

The clinical target volume (CTV) comprises the visible and palpable scar with a 1 cm margin of clinically normal tissue in the lateral, medial and inferior directions at the skin surface. The planning target volume (PTV) comprises the CTV with a 1 cm margin in all directions at the skin surface. The CTV to PTV expansion allows for set up errors, changes in the electron beam profile at depth and patient motion. The treatment field is defined by adding a further 1 cm margin in all directions to account for the beam penumbra.

The superior margin will vary and should be determined by counting three ribs superiorly. The upper border of the third rib superior to the scar will be the superior border of the treatment field. This will take into account microscopic spread but also ensure that chest wall intervention tracts (which will commonly run over the rib superior to the scar) are covered at depth (see figure 2).

No organs at risk need to be identified and if a patient has two intervention sites, and therefore two scars (eg, a VATS scar and adjacent chest drain scar) these can be treated within a single treatment field or two separate fields. A gap of >1 cm must separate two treatment fields.

Chemotherapy

Patients can be treated with palliative chemotherapy at the physician's discretion after completion of radiotherapy (experimental arm) or after randomisation (control arm). The efficacy and/or safety of chemotherapy is not being investigated as part of the study. The

chemotherapy regimen used should be cisplatin or carboplatin plus pemetrexed, although alternative chemotherapy regimens (including clinical trial agents) may be considered after discussion with the chief investigators. The number of cycles given is left to the physician's discretion. A gap of at least 1-week must separate the completion of radiotherapy and the start of palliative chemotherapy. The chemotherapy regimen, start and stop dates and total number of cycles administered should be recorded. No further data needs to be collected concerning the patients chemotherapy treatment.

Concomitant medication-not applicable for this trial.

Discontinuation or withdrawal of patients

In the case of disease progression, the patient will be treated according to each centre's policy. For patients allocated to the treatment arm, radiotherapy can be stopped at the participants request or if too unwell to continue at the discretion of the treating clinician.

Outpatient visits

The patient is reviewed in clinic 6, 12, 26 and 52 weeks following randomisation to assess for any signs of chest wall metastasis and to record any treatment-related toxicities. In addition, telephone follow-up at 4-weekly intervals following randomisation will determine if the patient has noted any chest wall nodules. If a patient is suspicious that a nodule has appeared, they will be invited to clinic for assessment.

If a chest wall metastases is confirmed, the position of the metastases is recorded in relation to the reconstructed radiotherapy treatment field.

Patients are asked to complete a visual analogue score (VAS) for pain at baseline, and at each telephone and clinic follow-up. Patients are specifically asked to only consider pain at the original site of chest wall

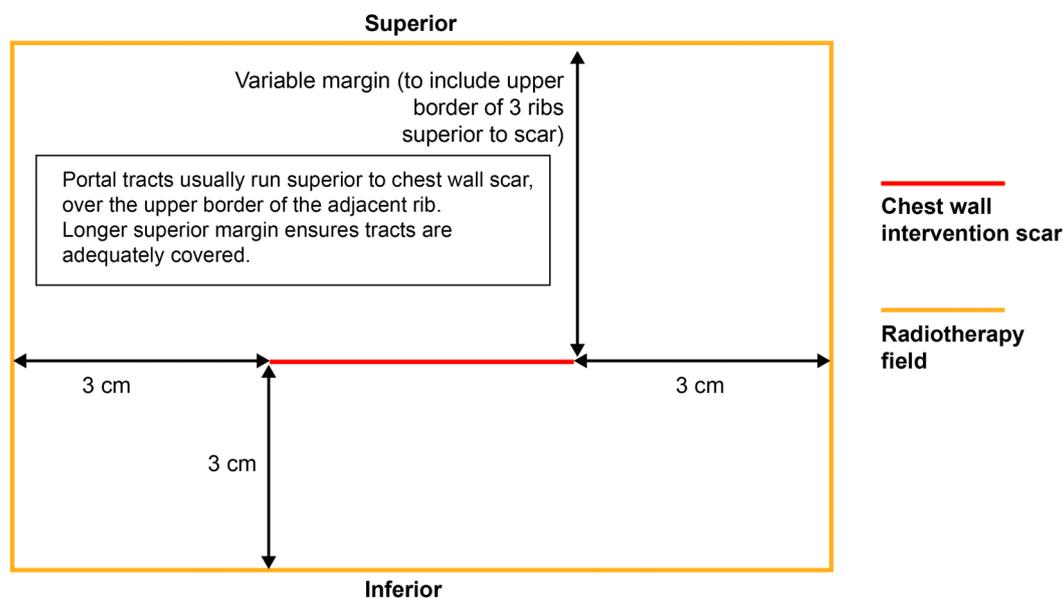


Figure 2 Prophylactic irradiation of tracts radiotherapy field margins.

intervention. If the patient develops chest wall nodules they will be asked to complete a VAS for pain at the site of the chest wall intervention at for the three nodules closest to the original intervention.

Outcome measures

The primary end point is the incidence of chest wall tract metastasis 6 months from randomisation. If a patient raises suspicion that a chest wall nodule had developed at telephone follow-up, they will be invited to attend an outpatient appointment with the investigator. If there is clinical evidence of a chest wall metastases, a chest wall metastasis cardio respiratory fitness (CRF) is completed using the clinic date as date of chest wall metastasis.

The secondary end points are:

- ▶ Time from randomisation to chest wall tract metastasis (recorded on chest wall metastasis CRF)
- ▶ Position of chest wall tract metastasis recurrence in relation to radiotherapy field in patients randomised to experimental arm (in field/out-of-field, recorded on chest wall metastasis CRF)
- ▶ Acute and late skin radiotherapy toxicity (recorded by CTCAE v4.0 at baseline and at each outpatient visit on CRF)
- ▶ Pain from chest wall tract metastasis (recorded by VAS pain scores recorded on chest wall metastasis CRF)

Sample size calculation

The crude rate of tract metastases following chest wall intervention until death, based on historical data, is expected to be 15%. It is estimated that the majority of events will occur within 6 months of the intervention. A reduction in the incidence of chest wall nodules from 15% to 5% in favour of radiotherapy would be clinically significant. Based on a two-arm trial with a 5% significance level, two-sided test and 80% power this would require 280 patients. Furthermore it is anticipated that 25% of patients will not survive for 6 months therefore an additional 94 patients will be required, making the total number of patients to be enrolled 374.

Analysis

Incidence of chest wall tract metastasis

All patients randomised will be analysed on an intention-to-treat basis. A two-sided χ^2 test of proportions of chest wall tract metastasis at 6 months between the control and experimental arms will be used with a 5% significance level. Secondary analysis using logistic regression will be used to investigate treatment after adjusting for significant baseline prognostic variables.

Time to chest wall tract metastasis

Kaplan-Meier curves will be drawn for each treatment group. Time to chest wall tract metastasis will be compared using a two-sided log rank test with a 5% level of significance. Cox-proportional hazards models will be

used to investigate the effect of treatment after adjusting for stratification factors and other significant baseline variables.

Toxicity

Skin toxicity will be assessed according to NCI Common Terminology Criteria for Adverse Events V4.0. The proportions of patients experiencing a grade of 3 or above acute toxicity, including acute radiation morbidity, or late radiation morbidity will be compared between the treatment groups using a two-sided χ^2 test with a 5% level of significance. Acute toxicity will be defined as toxicities occurring from start of treatment to 3 months after completion; late toxicity will be defined as toxicities occurring between 3 months and 2 years after completion of treatment.

Position of chest wall tract metastases

Position of the central point of a chest wall tract metastases in relation to the reconstructed radiotherapy treatment field will be recorded as in field/out-of field recurrence. Where the central point falls on the edge of the radiotherapy treatment field this will be recorded as in-field recurrence

Pain scores

Patients will be analysed using the intent-to-treat method. All tests will be two-sided and a p value of 0.05 or less will be considered statistically significant. In patients who develop tract metastasis, the VAS pain score from the assessment immediately before the occurrence of the tract metastasis will be considered baseline. Descriptive analysis will be performed to summarise change in pain score from baseline to subsequent pain score. Two-sample t tests will be used to explore difference between treatments. A 20% increase in VAS pain score is considered significant. The proportion of significant increases in pain in both arms will be analysed using a two-sided χ^2 test.

No formal interim analysis is planned.

Protocol adherence

No major problems are anticipated in terms of adherence to intervention protocols as the experimental arm only involves three fractions of standard radiotherapy delivered over approximately 5 min on three consecutive days.

Data handling and analysis

All forms will be entered in a trial defined database for which some consistency checking will be programmed in. Data managers will check for missing and invalid data using SQL queries and statistical programs. Any queries will be highlighted on trial-specific query forms and returned to the centre for correction and/or clarification. The data will be stored on a secure server access to which is restricted to MAHSC-CTU staff. The data management procedures can be found in the PIT Data

Management Manual, this is an internal document created for use by the Data Manager within the MAHSC-CTU and contains all procedures defined to ensure the data management and validation procedures are properly carried out.

ETHICS AND DISSEMINATION

Protocol and protocol amendments

The trial details documented here are consistent with PIT study protocol V.3.0 (dated: 19th April 2012, available on request from the trial manager, MAHSC-CTU).

There have been two substantial amendments for the study.

1. 25 April 2012—addition of an inclusion criterion ‘Indwelling pleural catheter in situ at the intervention site’ and several administrative updates to the protocol and patient information sheets. The amendment also included the home and outpatient VAS questionnaires.
2. 17 April 2013—introduction of the VAS chest wall nodule page which the patient is asked to complete if they develop chest wall nodules.

Trial monitoring

The trial management group (TMG) is responsible for reviewing the trial’s day-to-day activities, the overall supervision of the trial and ensure that it is being conducted in accordance with the principles of good clinical practice and relevant regulations. The group should agree any protocol amendments and provide advice to the investigators on all aspects of the trial. The TMG meets twice a year and includes patient/carer representatives, respiratory physicians, thoracic surgeons, clinical oncologists, medical oncologists and clinical nurse specialists. Three additional members who are independent of the trial have been appointed and will be available to advise the TMG should any issues arise requiring an independent viewpoint.

An Independent Data Monitoring Committee (IDMC) will not be appointed for this trial as PIT is currently widely used in clinical practice, it is not a new treatment and we not envisage that any safety issues will arise.

Trial sponsorship

The study is sponsored by The Christie NHS Foundation Trust, Research & Development Department, Wilmslow Road, Manchester, M20 4BX, UK

Trial management

The Manchester Academic Health Science Centre Clinical Trial Unit is co-ordinating the study. This includes data collection, management, monitoring, analysis and interpretation of data. The PIT TMG will write the report and will make the decision to submit the report for publication.

Safety reporting

An adverse event (AE) is defined on this trial as any untoward medical occurrence in a clinical trial subject which does not necessarily have a causal relationship with the trial-related procedures. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease.

A serious adverse event (SAE) for this trial is an adverse event only if it meets the following criteria.

- ▶ Results in death (within 90 days of last dose of radiotherapy and is considered related to trial radiotherapy);
- ▶ Is life-threatening (and is considered related to the trial radiotherapy);
- ▶ Requires hospitalisation, or prolongation of existing hospitalisation (and is considered related to trial radiotherapy);
- ▶ Results in persistent or significant disability or incapacity (and is considered related to trial radiotherapy);
- ▶ Is a congenital anomaly or birth defect;
- ▶ Other medically significant event. Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Disease progressions or events related to disease progressions are not considered to be SAEs. AEs relating to other anticancer treatments that the patient may be receiving are not considered to be SAEs.

All SAEs are reported by site teams to the MAHSC-CTU within 24 h of the investigator being made aware of the event.

End of the trial

The study will close 2 years after the 374th patient is randomised. The Chief Investigator, TMG and/or the three independent members have the right at any time to terminate the study for clinical or administrative reasons. The end of the study will be reported to the REC and Regulatory Authority (where applicable) within the required timeframes.

Investigators will inform participants of any premature termination of the trial and ensure that the appropriate follow-up is arranged for all involved.

Dissemination

Data from all centres will be analysed together and published as soon as possible. Individual participants may not publish data concerning their patients that are directly relevant to questions posed by the trial until the TMG has published its report. The TMG will have access to the final data set, form the basis of the Writing Committee and advise on the nature of publications. The trial will be publicised at regional and national meetings, and to patient groups with the support of Mesothelioma UK.

The final results will be presented at scientific meetings and published in a peer-reviewed journal (authorship will be according to the journal's guidelines). A lay summary will be disseminated via local and national mesothelioma charities. Summary results will also be published online at clinicaltrials.gov and cancerhelp.org.

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Contributors CFF and NB conceived the study. CFF, NB, DA, LA, DRB, RB, LD, JGE, LLL, JFL, MP, RCR, MS and PT initiated the study design and helped with implementation. CFF is the grant holder. LA provided statistical expertise in clinical trial. All authors contributed to refinement of the study protocol and approved the final manuscript.

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Competing interests None declared.

Ethics approval The trial has been reviewed by NRES Committee North West—Greater Manchester West which granted ethical approval for the study on 4 April 2012 (REC reference 12/NW/0249).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The trial is being coordinated by the Manchester Academic Health Science Centre, Trials Coordination Unit (MAHSC-CTU). Additional study information can be obtained from the PIT trial manager or trial statistician. Contact details included in manuscript.

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Appendix 1: Open and recruiting sites

Name	Principal Investigator
Addenbrookes - Cambridge University Hospitals	Dr David Gilligan
Alexandra Hospital	Dr Asha Siva
Basingstoke & North Hampshire Hospital	Dr Andrew Jackson
Blackpool Victoria Hospital	Dr Muthiah Sivaramalingham
Bradford	Dr Michael Snee
Calderdale & Huddersfield NHS Trust	Dr Pooja Jain
Clatterbridge Cancer Centre NHS Foundation Trust	Dr Aisha Tufail
Dorset Cancer Centre	Dr Mike Bayne
Edinburgh Cancer Centre	Prof Allan Price
George Eliot Hospital	Dr Mark Hocking
Glan Clwyd Hospital	Dr Niladri Ghosal
Harrogate District Foundation Trust	Dr Samuel Chan
Ipswich Hospital	Dr Jamey Morgan
Isle of Wight	Dr Paul Fenton
James Cook University Hospital	Dr Devadasan Shakespeare
Kent & Canterbury Hospital	Dr Mathilda Cominos
Kidderminster General Hospital	Dr Asha Siva
Kings Mill Hospital	Dr Karen Foweraker
Leighton Hospital	Dr Paul Burt
Llandough Hospital (Velindre)	Dr Jason Lester
Macclesfield District General Hospital	Dr Hamid Sheikh
Maidstone Hospital	Dr Russell Burcombe
Manor Hospital Walsall	Dr AD Chetiyawardana
Medway NHS Foundation Trust	Dr Maher Hadaki
Mount Vernon Cancer Centre	Dr Russell Moule
New Cross Hospital (Wolves)	Dr Ian Sayers
Ninewells Hospital	Dr Hannah Lord
North Middlesex Hospital	Dr Nishi Gupta
North Midlands NHS Trust	Dr Apurna Jegannathen
Northampton General Hospital	Dr Anupama Gore
Northern Ireland Cancer Centre	Dr Jonathan McAleese
Nottingham University Hospitals	Dr Sally Morgan
Peterborough and Stamford Hospitals NHS Foundation Trust	Dr Sarah Treece
Pilgrim	Dr Abhro Chaudhuri
Princess Alexandra	Dr Nishi Gupta
Queen's Hospital, Burton	Dr AD Chetiyawardana
Royal Blackburn and Burnley Hospitals	Dr Weibke Appel
Royal Bolton Hospital	Dr Neil Bayman
Royal Derby Hospital	Dr Manjusha Keni
Royal Oldham Hospital	Dr Laura Pemberton

Royal Preston Hospital	Dr Weibke Appel
Royal Surrey	Dr Veni Ezhil
Salford Royal NHS Foundation Trust	Dr Hamid Sheikh
Salisbury	Dr Adityanarayan Bhatnagar
South Warwickshire	Dr Caroline Humber
Southampton General Hospital	Dr Andrew Bates
St James Leeds	Dr Michael Snee
Tameside General Hospital	Dr Margaret Harris
The Christie NHS Foundation Trust	Dr Neil Bayman
The Queen Elizabeth hospital, Kings Lynn	Dr Kathryn Waite
United Lincolnshire Hospitals NHS Trust	Dr Abhro Chaudhuri
University Hospital Birmingham	Dr Qamar Ghafoor
University Hospital Coventry & Warwickshire	Dr Mark Hocking
University Hospital of Leicester	Dr Thiagarajan Sridhar
University Hospital of North Tees	Dr Devadasan Shakespeare
University Hospitals of Morecambe Bay NHS Foundation Trust	Dr Geraldine Skales
Weston Park, Sheffield	Dr Matthew Hatton
Writington	Dr Neil Bayman
Wythenshawe Hospital	Dr Laura Pemberton
York Teaching Hospital	Dr Samuel Chan

Appendix 2 – Patient Information Sheet (Version 4.0, 18th April 2012)

Title of the research:

A phase III study of Prophylactic Irradiation of Tracts in patients with malignant pleural mesothelioma following invasive chest wall intervention (PIT Trial)

Invitation to participate in the trial

You are being invited to take part in a research trial. Before you decide if you want to take part, it is important for you to understand why the research is being done and what it will involve. Please read the following information carefully and if you wish, discuss it with friends, relatives and your General Practitioner. Ask us if there is anything that is not clear or if you would like more information. It is important to take time to understand this information and decide whether or not you wish to take part.

Part 1 tells you the purpose of this trial and what will happen to you if you take part

Part 2 gives you more detailed information about the conduct of the trial

PART 1

What is the purpose of this research trial?

Mesothelioma is a rare form of cancer affecting the protective lining that covers many of the body's internal organs. The most commonly affected areas are the lungs and internal chest wall. In the UK over 2300 patients are diagnosed with mesothelioma each year and the numbers are increasing.

As part of the diagnosis and treatment of mesothelioma, you will undergo a procedure which involves inserting a thin tube into the chest wall enabling an internal examination and for any biopsies or samples of fluid to be taken. These procedures can result in the development of skin lumps or nodules along the tract created by inserting the tube. To try and reduce the risk of these nodules developing in the tract or at the site of the scar, some radiotherapy treatment can be given to the chest wall at the site of the tract after the procedure has been performed; this type of radiotherapy is known as prophylactic irradiation of tracts or PIT.

Although many hospitals already give patients radiotherapy treatment to the chest wall we still do not know if the treatment works. This trial has been designed to answer the question about the effectiveness of PIT. If PIT is found to be effective in preventing or delaying the development of these skin nodules then it can be offered to all patients as part of their treatment. However, if we discover that PIT is not effective this will save patients from undergoing ineffective treatment and having to spend time making unnecessary extra visits to hospital.

This radiotherapy treatment will be given in addition to other mesothelioma treatment, for example, chemotherapy.

What is the treatment that is being tested?

The treatment being tested is radiotherapy. The trial is to compare a course of radiotherapy treatment with no radiotherapy treatment. Radiotherapy treatment will be delivered once a day for 3 days. The radiotherapy treatment will take around 15 minutes each time.

Why have I been chosen?

You have recently been diagnosed with mesothelioma and had an internal examination of your chest wall and a biopsy taken and/or had fluid removed from the lining around the lung with a chest drain. Following this procedure your doctor feels that you are suitable to take part in this trial. This is a research trial, and other patients similar to you are also being asked if they would be willing to take part. In total approximately 400 patients will take part in the UK and Europe.

Do I have to take part?

Your participation in this research trial is entirely voluntary and you will be given sufficient time to decide whether or not you wish to participate. You are free to decide at all times without giving a reason that you no longer wish to participate in the trial. Withdrawal from the trial will not affect your subsequent treatment or relationship with your treating doctor or the hospital staff in any way.

What will happen to me if I take part?

If you agree to take part, you will be asked to sign a consent form and your doctor will perform a number of checks to ensure that you are eligible for this trial. These checks will include a physical examination to look at your chest wall and the skin around the chest area. The doctor will also ask you about your current levels of activity and whether you are experiencing any pain. These tests are normally done as part of the routine checks for patients who are to be treated with radiotherapy. Female patients may also require a pregnancy test.

If you are eligible and agree to take part in the trial you will be randomly allocated to receive radiotherapy treatment or no radiotherapy treatment. This is done by a computer; you or your doctor cannot choose the treatment.

Regardless of whether you are assigned to receive the PIT radiotherapy treatment or not you will be followed up in clinic after 6 weeks, 3 months, 6 months and 12 months. You will also receive telephone calls from a trial nurse or research radiographer every 4 weeks. During each telephone call you will be asked to answer a question at home in a diary given to you after you have had the radiotherapy. The research nurse or radiographer will explain to you how to answer the questions. The telephone follow-up calls will be missed out on the months when you are seen in clinic. Telephone follow-ups will continue until a skin nodule develops or for 2-years after you enrolled on the trial.

The following examinations will be performed at each follow-up visit:

a) At the clinic appointment the doctor will perform:

- ◆ a physical examination including inspecting the chest wall. If you develop a skin nodule, the position of the nodule in relation to the area in which you were treated (if you were allocated to receive the radiotherapy treatment) will be recorded at this appointment.

- ◆ an assessment of your levels of physical activity or performance status
- ◆ any reaction of the skin to the radiotherapy treatment will be assessed
- ◆ your levels of pain and use of painkillers will be recorded
- ◆ details of any other treatment for mesothelioma will be recorded

b) At the telephone follow-up the trial nurse or research radiographer will ask you if you have noticed any skin nodules developing. If you are concerned about a possible skin nodule then you will be assessed in an out-patient clinic within 1 week.

Taking part in the PIT trial will not stop you from receiving any additional treatment that you may need such as chemotherapy or radiotherapy given to control your symptoms.

Where possible any extra tests for the trial will take place during normal clinic visits. The clinical research team can advise you how much time this will add to your visit.

What are the alternatives for treatment?

If you do not wish to take part in this trial your doctor will tell you what alternatives are available in your particular situation.

What are the possible benefits of taking part?

If you are allocated to the group receiving PIT radiotherapy, this may help you but this cannot be guaranteed. The information we get from this trial will help us to treat future patients with the same disease better.

Considering that the benefit of radiotherapy cannot be guaranteed we would like you to consider the possible side effects of the treatment, which are listed below:

What are the side effects of radiotherapy to the chest wall?

Many people who have radiotherapy to their chest wall have little or no side effects. Side effects from radiotherapy are dependent on which part of your body is being treated and the number of treatments you have. People who have had similar treatments can often have different side effects. Here are some of the more common side effects:

Early side effects

These can vary according to the individual.

Tiredness - Tiredness is one of the most common side effects of cancer treatment. Although fatigue may be a symptom that you have already due to your cancer.

Skin reactions - Approximately 10 days following radiotherapy, you will probably develop redness and soreness of the skin within the treated area like a sun-burn. This will gradually fade over a few weeks. We will give you E45/aqueous cream to moisturise the area and hydrocortisone cream to use if it sensitive or sore.

Pain - There may be an ache within the treatment area lasting about one or two days and starting just after treatment. This is nothing to worry about. It is temporary and you can take simple painkillers such as paracetamol if necessary.

Shortness of breath - It is extremely uncommon for radiotherapy to cause breathlessness with this type of treatment.

Late side effects

It is possible for some types of reaction to occur months or years after the treatment has finished. These side effects are permanent. Your doctor will discuss any possible late effects with you if they are at all likely to occur.

Skin changes - With time, your skin (within the treated area only) may become paler than your normal skin. Tiny 'thread' veins may develop on the treated skin.

Bone weakness - Rarely, radiotherapy can make some of the ribs more brittle. After a severe cough or mild trauma this can result in chest pain and/or a minor rib fracture.

Pregnancy and Birth Control

If it is possible you may conceive (i.e. you are of child bearing age), you will be asked to have a pregnancy test before starting treatment. Effective birth control with one of these methods should be used during the course of treatment.

1. Tubal ligation (informally known as getting one's "tubes tied")
2. Insertion of an intra-uterine device (IUD or coil)
3. Diaphragm with spermicidal foam/gel/film/cream/pessary
4. Condom with spermicidal foam/gel/film/cream/pessary
5. Male partner who has had a vasectomy
6. Hormonal contraceptives

If you become pregnant while in this trial, you must tell the trial doctor immediately.

Contact Persons and Further information

The research nurses and doctors listed in this section are available to answer any questions you have concerning this research trial. Understand that you are free to ask any questions concerning this research trial that you wish at any time.

It is important that you contact the research nurses or trial doctor as soon as you experience any side effects which disrupt your daily life whether you think the treatment has caused them or not. In the event of any problem or emergency, the research nurses and doctors listed in this section may be reached during working hours (9am to 5pm):

[Insert name & contact details of research doctor/research nurse/radiographer here]

If you have any concerns with your treatment and need to speak to someone outside these hours (after 5pm and before 9 am), please contact [insert institution specific hotline number]

CancerHelp UK provides general information for patients about cancer and its treatment on their website, www.cancerhelp.org.uk.

Cancer Research UK has cancer information nurses who provide a confidential service, Tel: 020 7061 8355 or email: cancer.info@cancer.org.uk

Mesothelioma UK is a national resource centre dedicated to providing specialist mesothelioma information, support & improved care and treatment.

Freephone helpline Monday - Friday 8:30 am - 4:30 pm 0800 169 2409 or visit www.mesothelioma.uk.com

Macmillan Cancer Support provides support and counselling to help people living with cancer, ask Macmillan Tel: 0808 808 0000 or visit www.macmillan.org.uk

UK Clinical Research Collaboration (UKCRC) publishes a leaflet entitled 'Understanding Clinical Trials'. This leaflet gives you more information about medical research and looks at some questions you may want to ask. A copy may be viewed online at www.ukcrc.org or may be obtained by writing to UKCRC, 20 Park Crescent, London, W1B 1AL.

This completes Part 1 of the information sheet.

If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision

PART 2

What if relevant new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your trial doctor will tell you about it and discuss whether you want to or should continue in the trial. If you decide not to carry on, or if your trial doctor considers it to be in your best interests to withdraw you from the trial, your trial doctor will make arrangements for your care to continue. If you decide to continue in the trial you will be asked to sign an updated consent form. If the trial is stopped for any other reason, you will be told why and your continuing care will be arranged.

What will happen if I don't want to carry on with the trial?

You can withdraw your consent at any time. This will not affect the standard of care you receive. Information collected up to your withdrawal may still be used.

If during the study you lose the capacity to consent, you will be withdrawn from the study. Any identifiable data already collected with consent would be retained and used in the study. No further data will be collected or any other research procedures carried out on or in relation to you.

What if something goes wrong?

Any complaint about the way you are dealt with during the trial or any possible harm you might suffer will be addressed. The trial is being performed by your doctor and insurance against injury will be provided by the hospital that is looking after you [insert institution name]. If you are harmed due to someone's negligence then you will have grounds for legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this trial, the normal NHS complaints mechanisms will be available to you. By signing a consent form you are NOT waiving any of your legal rights.

Confidentiality

Information obtained from research will be protected and its handling will be compliant with the Data Protection Act of 1998. The doctor in charge of the trial will keep your original signed consent form in a secure location. Your medical records will not hold any individual results from this trial. Your unique registration number will be used to make sure you cannot be identified outside the trial. All information about you will be treated as confidential and nothing that might identify you will be revealed to any other department or organisation. Your name will not appear in any publication or report about this trial.

There will be strict control of access to the files containing clinical information. Your personal information will be accessible to the trial doctors and others involved in the trial for the purpose of the trial and your direct clinical care only. Direct access to your records may also be required by members of the independent ethics committee and/or regulatory agencies.

Will My General Practitioner Be Involved?

With your permission, your GP will be notified of your participation in this trial. By signing the consent form you are agreeing to this.

Will I be paid any costs and reimbursements?

There will be no payment to you for entering this trial, nor payment for undergoing investigations that are additional to your standard care.

Who is organising and funding the research?

The PIT trial is being funded by the UK's National Institute for Health Research as part of their Research for Patient Benefit Programme. This trial is being organised and co-ordinated by Consultant Clinical Oncologists (radiotherapy specialists) and the Trials Co-ordination Unit at The Christie NHS Foundation Trust in Manchester. Independent international researchers in the field of mesothelioma have been involved in developing the trial and have positively reviewed the trial. None of the researchers will receive any payment for your participation in the trial.

What will happen to the results of the research trial?

Independent experts will review the progress of the research, and the results will be published in a respected medical journal. The results will help to decide how to treat mesothelioma in the future. Trials like this are often used in cancer research.

Who has reviewed the trial?

The trial was given a favourable ethical opinion for conduct in the NHS by the Greater Manchester West Research Ethics Committee.

Thank you for taking time to read this information sheet.

You will be given a copy of the information sheet and a signed consent form to keep if you decide to take part in the trial.

Appendix 3 – Informed Consent Form (Version 4.0, 19th April 2012)

Patient Identification Number:

Name of Researcher: [insert local principal investigator name]

Title of the trial: **A phase III trial of Prophylactic Irradiation of Tracts in patients with malignant pleural mesothelioma following invasive chest wall intervention (PIT Trial)**

CONSENT FORM

*Please initial
in boxes*

1. I confirm that I have read and understood the information sheet Version 4.0, dated 19 April 2012 for the above trial and have had the opportunity to ask questions.
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from [insert institution name] and its authorised agents or from Regulatory Authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.
4. I also understand that if I withdraw from the trial early, the data collected whilst I was on the trial will be retained to ensure the trial has been run in accordance with all applicable rules.
5. I understand that if I lose the capacity to consent I will be withdrawn from the study. However any identifiable data already collected with consent would be retained and used in the study
6. I understand that I will not benefit financially if this research leads to the development of a new treatment or medical test
7. I understand that my General Practitioner will be informed about my participation in this trial.
8. I agree to take part in the above trial.

Name of Patient

Date

Signature

Name of Person taking consent
(If different from researcher)

Date

Signature

Researcher

Date

Signature

1 for patient; 1 for researcher; 1 for general practitioner, 1 to be kept with hospital notes

Thank you for taking part in this research trial