Protocol for the surgical and large bore procedures in malignant pleural mesothelioma and radiotherapy trial (SMART Trial): an RCT evaluating whether prophylactic radiotherapy reduces the incidence of procedure tract metastases

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ABSTRACT

Introduction: Patients with malignant pleural mesothelioma (MPM) may develop painful ‘procedure tract metastasis’ (PTM) at the site of previous pleural interventions. Prophylactic radiotherapy has been used to minimise this complication; however, three small randomised trials have shown conflicting results regarding its effectiveness. The surgical and large bore procedures in malignant pleural mesothelioma and radiotherapy trial (SMART Trial) is a suitably powered, multicentre, randomised controlled trial, designed to evaluate the efficacy of prophylactic radiotherapy within 42 days of pleural instrumentation in preventing the development of PTM in MPM.

Methods and analysis: 203 patients with a histologically proven diagnosis of MPM, who have undergone a large bore pleural intervention (thoracic surgery, large bore chest drain, indwelling pleural catheter or local anaesthetic thoracoscopy) in the previous 35 days, will be recruited from UK hospitals. Patients will be randomised (1:1) to receive immediate radiotherapy (21 Gy in 3 fractions over 3 working days within 42 days of the pleural intervention) or deferred radiotherapy (21 Gy in 3 fractions over 3 working days given if a PTM develops). Patients will be followed up for 12 months. The primary outcome measure is the rate of PTM until death or 12 months (whichever is sooner), as defined by the presence of a clinically palpable nodule of at least 1 cm diameter felt within 7 cm of the margins of the procedure site as confirmed by two assessors. Secondary outcome measures include chest pain, quality of life, analgesic requirements, healthcare utilisation and safety (including radiotherapy toxicity).

Ethics and dissemination: The trial has received ethical approval from the Southampton B Research

Strengths and limitations of this study

- Suitably powered multicentre, randomised controlled trial of prophylactic radiotherapy in malignant pleural mesothelioma.
- Robust 1 year patient follow-up.
- All large bore pleural interventions are eligible, including indwelling pleural catheters.
- Small bore chest tubes excluded.

Ethics Committee (11/SC/0408). There is a Trial Steering Committee, including independent members and a patient and public representative. The trial results will be published in a peer-reviewed journal and presented at international conferences.

Trial registration number: ISRCTN72767336.

INTRODUCTION

Malignant pleural mesothelioma (MPM) is an aggressive tumour, which is universally fatal. In 2012, there were 2535 mesothelioma deaths in the UK alone and the incidence is predicted to increase.1 2 In order to obtain a robust histological diagnosis and to manage symptomatic pleural effusions, patients commonly undergo a number of diagnostic and therapeutic pleural interventions during the disease course.3 4

As a complication of iatrogenic instrumentation of the pleural cavity, tumour can spread to the site of previous interventions,
resulting in procedure tract metastases (PTMs), which can be intensely painful.

Mesothelioma is sensitive to radiation therapy in vitro,\(^5\) but its use as a radical treatment is limited by unacceptable toxicity. However, prophylactic radiotherapy to pleural intervention sites can be given with minimal side effects and a small randomised controlled trial (RCT) was performed in 1995 by Boutin and colleagues to evaluate its efficacy. None of the 20 patients randomised to receive prophylactic radiotherapy (21 Gy in 3 fractions over 3 days within 15 days of the procedure) developed a PTM, but 8 of the 20 patients (40%) in the untreated arm did.\(^6\)

Based on this small study, prophylactic radiotherapy to procedure tracts in mesothelioma became accepted practice worldwide.\(^7\)–\(^9\) However, the very high rate of PTM in the control arm of the Boutin study was felt to be more than that seen in routine clinical practice, particularly for patients undergoing small bore pleural procedures such as image-guided biopsies or simple pleural fluid aspirations.\(^10\)–\(^12\) Additionally, as prophylactic radiotherapy can be burdensome for patients so soon after their diagnosis (requiring up to 4 hospital attendances) and may be associated with some side effects, it was felt further evidence should be obtained to validate its routine clinical use.

Two further RCTs were therefore undertaken; the results of which called into question what had become routine clinical practice.\(^13\)–\(^14\) Bydder et al.\(^15\) randomised 43 patients with MPM (who had undergone 58 recent small and large bore pleural procedures) to receive a smaller dose of prophylactic radiotherapy (10 Gy in 1 fraction) or no radiotherapy. No significant difference in the occurrence of PTM was identified (7% in the radiotherapy arm vs 10% in the control arm).

These findings were mimicked in another small UK-based RCT evaluating 21 Gy in three fractions of radiotherapy given over 3 days within 21 days of the pleural intervention. Of 61 patients recruited, 7 patients (23%) developed a PTM in the radiotherapy arm, compared with 3 patients (10%) in the control arm.

These conflicting trial results have led to clinical equipoise regarding the benefits of prophylactic radiotherapy and calls from the mesothelioma community for a suitably powered RCT to conclusively establish its role.\(^15\) In a recent UK survey, 75% of responding centres offered prophylactic radiotherapy, but treatment protocols and patient selection varied greatly between institutions.\(^15\) Additionally, the advent of chemotherapy for mesothelioma\(^16\) and the increasing use of indwelling pleural catheters (IPC) for management of malignant pleural effusion in mesothelioma has resulted in uncertainty regarding the use of prophylactic radiotherapy in these contexts.\(^17\)–\(^18\)

This study was designed to specifically address these questions with a suitably powered, randomised, controlled trial.

**METHODS AND ANALYSIS**

The surgical and large bore procedures in malignant pleural mesothelioma and radiotherapy trial (SMART Trial) is a multicentre, prospective, RCT. The trial is sponsored by North Bristol NHS Trust and coordinated by The Respiratory Research Unit at North Bristol NHS Trust. Data management is undertaken by the Oxford Respiratory Trials Unit. The trial is registered on the International Standardised Randomised Controlled Trial Registry (ISRCTN72767336) and funded by the National Institute for Health Research (NIHR), Research for Patient Benefit (RfPB) Programme. The study is included in the NIHR Clinical Research Network portfolio (ID: 11023). The trial will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP).

The primary research question is to evaluate whether prophylactic radiotherapy prevents PTM following large bore pleural procedure in MPM. The secondary research questions are:

In MPM:

1. Does prophylactic radiotherapy lead to differences in patient symptoms and quality of life indices as compared to radiotherapy given in the event a PTM develops?
2. What proportion of PTM are symptomatic (ie, painful) and to what extent is this modulated by giving prophylactic radiotherapy?
3. In a subgroup of patients with IPCs, is prophylactic radiotherapy effective in reducing PTM?
4. Does prophylactic radiotherapy cause toxicity and impact on the quality of life of patients?
5. Is deferred radiotherapy (given when a nodule develops) as effective as prophylactic radiotherapy at controlling symptoms?
6. What is the patient experience of immediate and deferred radiotherapy?
7. What are the health economic implications of giving prophylactic radiotherapy as compared to deferred radiotherapy in this patient group?

**Setting**

Two hundred and three patients with a histocytologically proven diagnosis of MPM, who have undergone a large bore pleural intervention in the preceding 35 days, will be recruited from UK hospitals (see online supplementary appendix 1 for details of recruiting centres). Patients will be randomised to receive either immediate radiotherapy (within 35 days of their pleural intervention) or deferred radiotherapy (in the event that the patient develops a PTM) and followed up until death or a year (whichever is sooner). The study flow diagram is shown in figure 1.

**Participant screening and selection**

All patients discussed at the regional mesothelioma multidisciplinary team (MDT) meetings will be identified as potential trial candidates. Consecutive, eligible patients will be invited to participate and will be provided with a patient information sheet (PIS; see online supplementary appendix 2). Patients can only be enrolled into the SMART Trial once.
**Inclusion criteria**

1. A histocytologically proven diagnosis of malignant pleural mesothelioma, as confirmed by an MDT meeting.
2. One of the following pleural interventions in the past 35 days:
   - a. Open pleural biopsy.
   - b. Surgical thoracotomy or VATS.
   - c. Local anaesthetic thoracoscopy.
   - d. Large bore chest tube insertion (≥20 French inserted by either a seldinger technique or blunt dissection).
   - e. Indwelling pleural catheter insertion.
   - f. Written informed consent.

**Exclusion criteria**

1. Age < 18 years.
2. Expected survival <4 months.
3. Pregnancy or lactation.
4. Inability to give informed consent or comply with the protocol.
5. Previous radiotherapy which would result in an unacceptable overlap with the proposed treatment field.
6. The patient does not have access to a telephone.
7. A clinically palpable nodule of at least 1cm diameter felt within 7cm of the margins of the procedure site at the initial trial visit.

**Baseline investigations**

- History: To document histology, performance status and previous pleural procedures.
- Physical examination: for evidence of chest wall disease. Also to measure pleural procedure scar and annotate a diagram to indicate position.
- Details of treatment planned.
- EQSD/QLQ-C30 quality of life questionnaires and chest wall pain Visual Analogue Scale (VAS) score.

**RANDOMISATION**

Minimising by histology, indwelling pleural catheter or other procedure and surgical procedure or not.

**Immediate Radiotherapy Arm**

First dose of prophylactic radiotherapy given within 42 days of pleural procedure. 21Gy in three fractions (over 3 working days). Radiotherapy field to encompass scar with at least a 3cm margin.

**Deferred Radiotherapy Arm**

No radiotherapy initially.

If the patient develops a procedure tract metastasis, radiotherapy is given within 35 days of it being confirmed at a clinic visit. 21Gy in 3 fractions (over 3 working days). Radiotherapy field to encompass nodule with at least a 2cm margin.

**Follow up**

- Clinic visits at 1, 3, 6, 9 and 12 months with the local clinician (standard care). At each clinic visit:
  - History and physical examination for evidence of PTM and skin toxicity from radiotherapy.
  - Documentation of other treatments received since last visit.
  - Documentation of chemotherapy response (if given and known).
  - If the patient has had radiotherapy, questionnaire regarding the experience and side effects.
  - EQSD, QLQ-C30 and chest wall pain VAS completed.
  - If PTM has developed, symptom questionnaire, measure and refer for radiotherapy (as per protocol).
- On the months that patients are not seen in clinic, a trial nurse will undertake a monthly follow up phone call consultations for 12 months. If the patient has new symptoms or signs around the biopsy site an urgent clinic appointment will be made for further assessment.
- A visual analogue scale (VAS) pain score for chest wall pain will be recorded by the patient every month and returned to the trial team in a stamped addressed envelope.
- At 6 months, patients at Bristol and Oxford offered semi-structured qualitative interview with a research nurse.

**Figure 1** Trial overview flow diagram (MDT, multidisciplinary team; VATS, video-assisted thoracoscopic surgery).
E. IPC insertion.

3. Written informed consent.

**Exclusion criteria**

1. Age <18 years;
2. Expected survival <4 months;
3. Pregnancy or lactation;
4. Inability to give informed consent or comply with the protocol;
5. Previous radiotherapy which would result in an unacceptable overlap with the proposed treatment field;
6. The patient does not have access to a telephone;
7. A clinically palpable nodule of at least 1 cm diameter felt within 7 cm of the margins of the procedure site at the initial trial visit.

**Informed consent**

A doctor will confirm patient eligibility prior to consent being taken. Patients will be given at least 24 h to consider the PIS and time to ask questions prior to written informed consent being taken by a trial doctor, nurse or radiographer. The consent form can be viewed in online supplementary appendix 3.

**Randomisation**

Following informed consent, patients will be randomly assigned (1:1) to receive either immediate prophylactic radiotherapy (within 42 days of the pleural intervention) or deferred radiotherapy (given if the patient develops a PTM).

Treatment allocation will be performed over the telephone by UKCRC Oxford Respiratory Trials Unit. The randomisation sequence will be generated using a validated, online randomisation service (Sealed Envelope, London, UK; http://www.sealedenvelope.com). Minimisation with a random component will be used to reduce the baseline between-group differences. The minimisation factors are:

- Histological tissue type of mesothelioma (epithelioid only or other);
- IPC or other pleural procedure;
- Surgical procedure (ie, open pleural biopsy, thoracotomy or VATS) or non-surgical procedure.

Patients and clinicians will not be blinded to treatment allocation; however, the data analysis will be conducted in a blinded fashion.

**Standard care**

All patients will be discussed in an MDT meeting. If appropriate, patients will be referred to the local oncologist for discussion and consideration of their treatment options. Aside from prophylactic radiotherapy, other treatments offered to patients will be guided by clinical need and are at the discretion of the patient’s clinicians.

Ongoing clinical review will either take place in oncology or respiratory clinic. Patients requiring assistance from other services, for example, the surgeons, palliative care team or hospice, will be referred when needed by the clinical team. Patients who require radiotherapy for another indication (other than prophylactic radiotherapy as part of the trial or for treatment of a PTM) can be treated at the discretion of the local oncologist.

Co-enrolment in other clinical trials will be discussed on an individual basis, but will only be considered if compliance with both protocols can be ensured. Patients can withdraw from the trial at any time without their clinical care being affected.

**Interventions**

The full trial-specific procedure for radiotherapy can be found in online supplementary appendix 4.

**Immediate radiotherapy**

For patients in the immediate (prophylactic) radiotherapy arm, radiotherapy should be given within 35 days of the pleural procedure for which the patient has been randomised. Under exceptional circumstances, the first fraction may be postponed for up to 42 days but a reason must be clearly stated.

The treatment to be given will be 21 Gy in three fractions over 3 working days. The preferred procedure is to treat the patient using electrons of appropriate energy to treat the chest wall to at least 90% (using bolus if necessary). Alternatively, kilovoltage (kV) photons (minimum 220 kV) can be used if the depth dose to the chest wall is adequate. Megavoltage photons (MV) can be used if clinically indicated. A single direct beam will be used in the majority of cases.

The volume to be treated must be acceptable to the treating clinical oncologist and the treatment area should be no less than 7 cm in any one direction.

For pleural procedures other than IPCs:
- Suggested clinical target volume (CTV): chest drain and surgical sites/ scars with at least a 3 cm margin;
- Suggested planning target volume (PTV): CTV+0.5 cm if using kV photons or CTV+1 cm if using electrons;
- The total radiotherapy field will be equivalent to the PTV.

For patients with an IPC in situ:
- Suggested CTV: pleural puncture site, the whole of the catheter tract and the skin exit site with at least a 3 cm margin;
- Suggested PTV: CTV+0.5 cm if using kV photons or CTV+1 cm if using electrons;
- The total radiotherapy field will be equivalent to the PTV.

If patients in the immediate radiotherapy arm develop a PTM, further radiotherapy treatment to the site is at the discretion of the treating oncologist. Details of the relationship of the PTM to the prophylactic radiotherapy field will be recorded.

**Deferred radiotherapy**

If patients in the deferred radiotherapy arm are diagnosed with a PTM, 21 Gy in three fractions of
Radiotherapy will be given within 35 days of the PTM being diagnosed. The dose, technique, energy and beam arrangement will be the same as for the immediate radiotherapy arm and the treatment volume must be acceptable to the treating clinical oncologist.

- Suggested CTV: palpable nodule with at least a 2 cm margin;
- Suggested PTV: CTV+0.5 cm if using kV photons or CTV+1 cm if using electrons;
- The total radiotherapy field will be equivalent to the PTV.

**Data collection and management**

**Randomisation visit**

Clinical data will be collected at the randomisation visit. This will include a history and chest wall examination and patients will be asked to complete two quality of life questionnaires (EQ5D and QLQ-C30) and visual analogue scale (VAS) scores to quantify their current degree of chest pain.

**Follow-up visits**

Follow-up visits will be undertaken at 1, 3, 6, 9 and 12 months postrandomisation. These will include a focused history (including details of radiotherapy toxicity, mesothelioma treatments received, analgesia use and healthcare utilisation) and a chest wall examination to identify PTMs and radiation toxicity. The patient will also be invited to complete quality of life questionnaires (QLQ-C30 and EQ5D), a VAS score for chest pain and patient experience questionnaires regarding radiotherapy or the development of a PTM (if applicable).

**Telephone follow-up**

When patients are not seen in clinic, they will receive a monthly phone call from a research nurse to enquire about symptoms at the intervention site. They will also be invited to complete a chest pain VAS score, which will be returned by post. Should they develop problems at the intervention site, a clinic appointment will be arranged as soon as possible (ideally within 10 days).

**Semistructured interviews**

A small, qualitative substudy will explore patients’ experiences of being in the trial, their perceptions of the treatments and risks involved, to inform the trial results. Participants at the Bristol and Oxford sites will be invited to take part in semistructured qualitative interviews by a research nurse approximately 6 months after randomisation (see online supplementary appendix 5 for interview schedule).

From those who agree to be interviewed, a purposive maximum variation sample will be selected of up to 20 patients. Patients from Bristol and Oxford who develop a tract metastasis at any point after their 6-month follow-up visit will be invited to undertake a follow-up interview.

The data will be analysed using a thematic approach and the themes produced will help to describe participants’ views of the trial and how treatment can be optimised for these patients. This will be published separately to the main trial outcomes.

**Data management**

Clinical Record Forms will be completed by the trial team at the recruiting centre and sent to the Oxford Respiratory Trials Unit. Data will then be entered onto the trial database (OpenClinica clinical trials software). Missing data and data queries will be highlighted to the trial teams on a monthly basis. The Clinical Record Forms will only identify patients using their personal trial identification number (no identifiable patient information).

**Primary outcome**

The primary outcome will be the difference in the incidence of development of PTM within 7 cm of the site of pleural intervention within 12 months from randomisation between the study arms.

A PTM will be defined as a clinically palpable nodule of at least 1 cm diameter felt within 7 cm of the margins of the procedure site as confirmed by two assessors. One of the assessors must be a doctor who feels that clinically the nodule is a tract metastasis. The assessors will be doctors, nurses or radiographers who have read the chest wall examination standard operating procedure (SOP) (see online supplementary appendix 6) and feel confident to undertake the examination. In the event of disagreement between the assessors, they will examine the patient together to reach a consensus.

The presence or absence of PTM within 12 months of randomisation will be compared using Fisher’s exact test. This was chosen in preference to ‘time-to-event’ analysis for the primary outcome analysis, as prophylactic radiotherapy is not likely to change the speed with which the events occur, but rather prevent them from occurring, thereby violating the necessary assumptions of survival models. Time-to-event data will be modelled using regression analysis, but this will form part of the secondary analysis.

**Secondary outcomes**

Specific details regarding all the secondary outcomes can be found in the statistical analysis plan in online supplementary appendix 7. The secondary outcomes will include:

- The change in chest pain VAS scores from randomisation to 12 months postrandomisation between the study arms;
- The change in quality of life (as measured by EQ5D and QLQ-C30) from randomisation to 12 months postrandomisation between the study arms;
- The difference in analgesia requirements between the study arms;
The difference in the size, symptom severity and time to development of PTM between the study arms;

- The rate and severity of radiotherapy toxicity;

- The number of serious adverse events (SAEs) related to radiotherapy or a PTM;

- The health economic implications of immediate and deferred radiotherapy;

- The identification of emergent themes from the semistructured interviews.

Sample size calculation
The sample size calculation was based on internal audit data showing a PTM rate of <2% in those treated with prophylactic radiotherapy who underwent ‘large’ bore procedures, in comparison to a rate of between 8% and 40% in the published literature of patients not undergoing prophylactic radiotherapy.

Assuming the rates of PTM to be 2% in the intervention group and 15% in the ‘control’ group, 180 patients are required to demonstrate a difference between treatment arms with 90% power at the 5% significance level. With an estimated lost to follow-up rate of 3%, this number is increased to 185 patients randomised 1:1.

Various power modelling scenarios were considered (see table 1), demonstrating adequate power with varied control and intervention event rates if 203 patients are recruited.

Statistical analysis plan
The full statistical analysis plan can be viewed in online supplementary appendix 7. The analysis will be based on intention-to-treat principles.

For continuous outcomes, analyses will adjust for the minimisation factors and the outcome measured at baseline (provided there is no substantial missing baseline data). For binary outcomes, if the number of events allows, the analysis will adjust for the minimisation factors. If major baseline imbalances between the treatment arms are identified, these may also be adjusted for in the regression models.

For missing baseline data, if the numbers are small, median imputation will be used. If the numbers with missing data are large, alternative analysis methods may be used, which do not account for baseline values.

CONSORT data will be presented including the number of patients screened for the study and the numbers randomised. Reasons for exclusions after randomisation will be given.

Analysis for all outcomes will be presented as:

1. The number of participants included in the analysis, by treatment group;

2. A summary statistic for the outcome, by treatment group (eg, mean (SD) or median (2.5th–97.5th centile) for continuous outcomes; number (%) for binary outcomes);

3. A treatment effect, with a 95% CI and p value (2 sided; the significance level set at 5%).

The primary outcome, incidence of PTM within 12 months, will be analysed on an intention-to-treat basis. The proportion of patients developing a PTM (as defined above) within 12 months from randomisation or until death or loss to follow-up (whichever is sooner) will be calculated for both trial arms and compared using Fisher’s exact test. Alternatively, if the number of events allows, logistic regression will be performed, adjusting for the minimisation variables and any substantial baseline imbalances.

A secondary, per protocol analysis will be performed for the primary outcome, excluding patients with major protocol violations.

If numbers allow, the following subgroup analyses will be performed for the primary outcomes:

- By the type of pleural intervention randomised (large bore chest drain, local anaesthetic thoracoscopy, IPC or thoracic surgery);

- By tumour subtype (epithelioid only or other);

- Patients who were alive and in trial follow-up for at least 6 months (yes/no);

- Patients who received chemotherapy for mesothelioma within 12 months from trial entry (yes/no). Full details of the analysis of the secondary outcomes can be found in statistical analysis plan (see online supplementary appendix 7).

Changes to the protocol after start of the trial
The trial details documented here are consistent with SMART Trial protocol V.7 (date: 21 August 2013). A summary of the trial amendments can be found in online supplementary appendix 8.

In July 2012, the inclusion criteria were extended to include patients up to 35 days after their large bore pleural intervention (from 28 days) and to lengthen the maximum timeframe within which immediate radiotherapy should be performed to 42 days after the pleural intervention (from 35 days).
End of the trial
The trial will end once 203 patients have been recruited and all patients have died or completed 1 year of trial follow-up (whichever is sooner).

ETHICS AND DISSEMINATION
All substantial amendments will be submitted to the ethics committee for their approval prior to implementation (see online supplementary appendix 8).

Monitoring
As advised by the NCRI Radiotherapy Trials Quality Assurance Group (RTTQA), departments involved in delivering radiotherapy for the trial will be required to provide evidence of an independent audit measurement within the past 5 years for the radiotherapy modalities being used in the trial.

There will be no formal data monitoring committee for this study, as the risk profile of prophylactic radiotherapy is already well established. No interim analysis is planned.

Safety reporting
Data will be collected at each trial visit regarding any SAEs (as defined by GCP). All SAEs causally related to radiotherapy or a PTM will be reported to the sponsor and followed until they resolve or stabilise.

Radiotherapy toxicities will be recorded at each follow-up visit (according to the Radiation Therapy Oncology Group (RTOG) grading system).

IPC complications will also be recorded at each clinic visit.

Trial monitoring and oversight
The Trial Steering Committee (TSC) will be responsible for overseeing the progress of the trial and will meet at approximately six monthly intervals. The TSC will include an independent chairperson, independent members, statistician, patient and public representative and members of the trial team from all the main disciplines (respiratory medicine, oncology, palliative care and thoracic surgery).

Dissemination
The trial will be publicised at regional and national conferences. 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). In addition, a lay summary of the study results will be circulated to potentially interested parties (eg, local and national mesothelioma charities and the trial participants).

Trial status
The trial is currently in follow-up. The first patient was recruited in December 2011 and the final patient was enrolled in August 2014.

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Contributors NAM and PW conceived the initial trial concept. AOC, PW, NAM, EIW, NP, NR, JP, TH, TJPB, YCGL and LD developed the trial design and protocol. AOC, NU and AJM designed the semistructured interviews. HT and NR carried out the sample size calculations. AOC, HT, YCGL, NR, JP, LD and NAM wrote the statistical analysis plan. NAM is the chief investigator and takes overall responsibility for all aspects of trial design, the protocol and trial conduct. All authors have read and approved this manuscript.

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Competing interests None.

Ethics approval The trial has been reviewed by South Central—Southampton B National Research Ethics Service (NRES) Committee which granted ethical approval for the study (REC: 11/SC/0408).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Additional study information can be obtained from The Respiratory Research Unit, North Bristol NHS Trust (e mail: respiratoryresearch@nbt.nhs.uk).

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## SMART Trial Recruiting Centres

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<tr>
<th>Centre</th>
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<tr>
<td>North Bristol NHS Trust</td>
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<td>Gloucestershire Hospitals NHS Trust</td>
<td>Dr P Jenkins</td>
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<td>Royal United Hospital Bath NHS Trust</td>
<td>Dr E de Winton</td>
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<td>Portsmouth Hospitals NHS Trust</td>
<td>Dr L Bishop</td>
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<td>Royal Devon and Exeter NHS Foundation Trust</td>
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<td>Plymouth Hospitals NHS Trust</td>
<td>Mr A Marchbank</td>
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<td>University Hospitals Bristol NHS Foundation Trust</td>
<td>Dr P Wilson</td>
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<td>Oxford Radcliffe Hospitals NHS Trust</td>
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<td>Royal Gwent Hospital, Newport</td>
<td>Dr A Ionescu</td>
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<tr>
<td>Singleton Hospital, Swansea</td>
<td>Dr V Vigneswaran</td>
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<td>Withybush Hospital, Haverfordwest</td>
<td>Dr V Vigneswaran</td>
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<td>Buckinghamshire Healthcare NHS Trust</td>
<td>Dr N Panakis</td>
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<td>Colchester Hospital University NHS Foundation Trust</td>
<td>Dr S Cooper</td>
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<td>Dorset County Hospital NHS Foundation Trust</td>
<td>Dr M Bayne</td>
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<td>Poole Hospital NHS Foundation Trust</td>
<td>Dr M Bayne</td>
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<td>Nevill Hall Hospital, Abergavenny</td>
<td>Dr M Button</td>
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<td>Weston Area NHS Trust</td>
<td>Dr M Tomlinson</td>
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<td>Imperial College Healthcare NHS Trust</td>
<td>Dr C Lewanski</td>
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<td>Royal Berkshire NHS Foundation Trust</td>
<td>Dr J Gildersleve</td>
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<td>Royal Marsden NHS Foundation Trust</td>
<td>Dr M Ahmed</td>
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PATIENT INFORMATION SHEET

Surgical and large bore pleural procedures in Malignant pleural Mesothelioma And Radiotherapy Trial (SMART trial)

A Randomised Controlled Trial evaluating whether prophylactic radiotherapy reduces the incidence of procedure tract metastases.

1. Study Title
This is a research study examining the role of radiation treatment (radiotherapy) after chest wall procedures (such as surgery, thoracoscopy or chest drain insertion), in patients with cancer of the lining of the lung (mesothelioma). It will try to identify the best timing for radiotherapy to be given in order to minimise the risk of the cancer spreading during the procedure.

‘Randomised Controlled Trial’ means that patients who take part will be randomly allocated to either receive radiotherapy immediately after the procedure or radiotherapy later on, if a lump is discovered near the procedure site.

2. Invitation
You have been invited to take part in this research study. However before you decide to take part, it is important for you to understand why the research is being done and what it will involve, therefore please take time to read the following information carefully. It is a good idea to discuss taking part in the trial with your family and/or GP before making a decision. If you would like to take time to do this please let us know and a further appointment will be made to see you in due course. Please feel free to ask us if there is anything that is not clear or if you would like more information.

3. What is the purpose of the trial?
Radiotherapy is not able to change the course of mesothelioma but may prevent or suppress the spread of the cancer through the chest wall following surgery. It is often given to patients soon after a chest wall procedure to reduce the risk of this happening. The radiotherapy involves attending hospital on 3 consecutive days soon after the diagnosis and may also be associated with mild side effects (as described below).

Recent research suggests that cancer spreading through the chest wall in mesothelioma may not be as common as previously thought and some studies suggest that radiotherapy soon after the procedure may not actually reduce the chances of this happening.

Hence it is important that we know when it is best to give radiotherapy in this situation. This trial will endeavour to answer this question.
4. Why have I been chosen?
You have been chosen to consider taking part in this trial because you have mesothelioma and have recently had a procedure to your chest. We would like to know whether immediate radiotherapy is useful for patients in exactly your situation.

This study is taking place across many centres in the United Kingdom and 203 patients will be asked to participate.

5. Do I have to take part?
No, it is up to you to decide whether or not to take part. If you do decide to take part you will be asked to sign a consent form and you will be given a copy for your records along with this information sheet.

If you decide to take part, you are free to withdraw at any time without giving a reason. A decision to withdraw or a decision not to take part will not affect your future medical care.

6. What will happen to me if I take part?
Your doctor will perform an initial assessment, including finding out about your current health and medications and examining the area of your chest where you had the procedure done. You will also be asked to complete questionnaires about your current level of pain and how your illness is affecting your life, which will take about 10 minutes.

You will then be randomly allocated to receive either immediate radiotherapy or deferred radiotherapy in the event that you develop a lump near the procedure site.

If you are allocated to the immediate radiotherapy group, an appointment will be arranged with an oncologist to plan the treatment you will receive. This will take about 30 minutes. After this you will need to attend the hospital on 3 consecutive days to receive the treatment. Each visit takes about 30 minutes.

All patients will be seen in clinic at 1, 3, 6, 9, 12 months after entry into the trial. Again details of your current health and medications will be recorded. Your chest will be examined to look for any lumps near the procedure site and you will be asked to fill in some more questionnaires on quality of life and pain.

When you are not seen in clinic, you will receive a phone call once a month from a nurse who will ask if anything has changed around the procedure site on your chest. They will explain what to look out for and if necessary, a clinic appointment will be arranged for you to see the doctor. Each month you will also be asked to complete a score sheet about your current pain levels, which you will then post back to the hospital.
Should a lump be felt near the site of the procedure you will be seen by the
doctor and if necessary, radiotherapy will be arranged shortly afterwards and
given over 3 working days. If you were in the immediate radiotherapy group, you
will be able to discuss with the doctor whether further radiotherapy is necessary.

Patients who have been involved in the study at Oxford and Bristol may also be
invited to undertake an additional short interview at the 6 month follow up visit to
discuss their experiences of the trial and treatment so far with a trial nurse. This
is an extra part of the study which is entirely voluntary and we are hoping to
interview about 20 people in total. These interviews will be recorded but any
information used from these interviews will not be identifiable to you.

7. If I take part, which aspects of my treatment will be
‘experimental’ or ‘extra’?
As immediate radiotherapy is already commonly given in centres across the UK, the
treatment itself is not experimental. This study is trying to work out the best
time for it to be given to patients to maximise its benefit without causing undue
inconvenience.

The first trial visit will be extra to your normal clinical care in order to enrol you
into the study. The other follow up visits in the trial are what you would receive
as part of your normal clinical care, so these visits will not be extra, however the
questionnaires and pain scores are an addition for the trial only.

As part of the trial, a nurse will contact you once a month to ensure we respond
quickly to any changes you notice around the procedure site.

8. About the radiotherapy
Regardless of whether you receive radiotherapy at the beginning of the trial or
later on should you develop a lump, the radiotherapy you will be given is the
same.

It will be given every day for 3 days and you will be able to go home after each
dose.

Prior to the first treatment you will meet a radiotherapy specialist to discuss and
plan the treatment. Each radiotherapy appointment takes about 15 minutes and
you will be free to go home once you have received the treatment. The
procedure itself is not painful.
Possible Side effects
Most patients do not experience severe side effects from this type of radiotherapy. However some patients notice mild side effects such as:

- Feeling more tired than usual
- Skin reactions - these may occur in the area treated and may develop a few days or weeks after the radiotherapy. The skin may become pink and might feel sore or itchy.
- The skin is more sensitive than normal after radiotherapy. We advise against using perfumed creams and soaps on the treated area and keeping the area covered if you are in the sun.

At each clinic visit we will carefully assess and record any side effects you have noticed from the radiotherapy.

9. Will my medical information be kept confidential?
If you consent to join the study, your medical records may be looked at by:

- Key members of the research team (doctors and nurses who would usually be involved in your care as well as the doctors and nurses who are co-ordinating the trial)
- Representatives of the Sponsor (North Bristol NHS Trust) or the Regulatory Authorities to check the study is being carried out correctly.

All of these individuals will have a duty of confidentiality to you as a research participant. It is normal practice that if the radiotherapy is provided at a different hospital, personal and clinical information regarding your care will be shared between these sites.

Information about you will be collected for analysis by the Sponsor’s trial team and other collaborators involved in the study. This will include information about your health and other details such as your date of birth and gender. This information will be recorded and stored on a secure database, accessible only to the research team. You will be allocated a personal study number to identify you, so identifiable information (such as your name and contact details) will not be stored on the study database.

Some identifiable details, such as your name, address and NHS number, may be transferred to the Sponsor’s trial team on paper or electronic records. This will only be done where necessary for the purposes of monitoring and follow-up. In these instances, the information that identifies you will be kept completely secure and accessible only to authorised individuals within the Sponsor’s trial team.
Information held by the NHS and records maintained by the NHS Information Centre may be used by the Sponsor’s trial team to keep in touch with you and follow up your health status.

10. What are the possible disadvantages and risks of taking part?
As radiotherapy of this type is already administered in many centres across the UK, the side effect and safety profile is already well established. The main risk is experiencing a side effect to radiotherapy, but these are generally mild (as described above). You will need to attend hospital on four occasions for the planning and treatment.

We do not know if by having deferred radiotherapy, your chances of the cancer spreading at the procedure site are higher or not. This is what we are trying to find out from this study.

You will need to complete some questionnaires for the trial purposes, but these only take a few minutes and you will be provided with stamped addressed envelopes to return them in.

Radiotherapy is associated with some additional radiation exposure. However, in patients with mesothelioma, this does not result in an additional significant risk given the long time lag it would take for it to cause harm.

11. What are the possible benefits of participating in the trial?
Regardless of which treatment group you are allocated to, you will receive radiotherapy should it become necessary. You will have regular contact with the trial team and be followed up regularly.

Regardless of the trial results, you will be helping us find out how patients with mesothelioma should be treated in the future. You will be contributing to our understanding of the disease and helping us to develop better ways to treat your illness in the future.

12. What if new information becomes available?
The trial team will continue to review all new research data. If new information that influences the trial becomes available, alterations will be made accordingly. If this happens we will discuss whether you want to continue in the study and provide you with all the information you need to make this decision.

13. What if there is a problem?
If you have a concern about any aspect of this study you should ask to speak to the study doctor who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the NHS complaints procedure. The study doctor or the hospital switchboard can provide you with contact details for the complaints department.
If you are harmed as a result of your participation in the study due to someone’s negligence, North Bristol NHS trust will provide indemnity and/or compensation via the NHS indemnity scheme.

If you are harmed as a result of your participation in the study, not due to negligence, North Bristol NHS trust will sympathetically consider any claim for compensation.

14. Who is organising and funding the research?
North Bristol NHS Trust is sponsoring the research, which means that the trust has overall responsibility for the safe and appropriate conduction of the trial.

The trial has been funded by a grant from the National Institute of Health Research ‘Research for Patient Benefit’ scheme.

No payment will be made to trial doctors or nurses for including you in the trial.

15. Who has reviewed the trial?
This study has been reviewed and approved by a Research Ethics Committee, the Oxford Respiratory Trials Unit and the clinical trials team at North Bristol NHS Trust as well as the doctors and research department at your own hospital.

External experts have also reviewed the trial as part of organising funding for the study.

16. What will happen to the results of the trial?
When the study has finished and the results have been analysed, they will be published in a medical journal so that other doctors can read them. If you would like us to write to you personally, explaining the study findings, please indicate this on your consent form.

17. What do I need to do?
After reading this sheet, you will be invited to ask questions about the trial. If you would like to take part, we will ask you to sign a consent form. Your GP will be informed that you are taking part, with your consent.

If you wish to take a few days to consider whether to take part or would like to discuss the trial with your GP, please inform us.

If you decide not to participate, your routine care or legal rights will not be affected in any way. You can withdraw from the study at any time without giving a reason.

Thank you for taking the time to read this information and considering taking part in the trial.
Chief investigator:
Dr. N. Maskell (Consultant in Respiratory Medicine, North Bristol Lung Centre)

Contact details for local PI and recruiting centre here
Surgical and large bore pleural procedures in malignant pleural Mesothelioma And Radiotherapy Trial (SMART trial) - RCT evaluating whether prophylactic radiotherapy reduces the incidence of procedure tract metastases. Chief investigator: Dr. Nick Maskell. REC: 11/SC/0408

PATIENT CONSENT FORM

Surgical and large bore pleural procedures in malignant pleural Mesothelioma and Radiotherapy Trial (SMART)
A randomised controlled trial evaluating whether prophylactic radiotherapy reduces the incidence of procedure tract metastases.

1. I confirm that I have read and understand the patient information sheet dated …../…../……. (Version ………) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my future medical care or legal rights being affected as a consequence.

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals involved in the running of the trial, from the regulatory authorities or from the NHS, where it is relevant to my taking part in the research. I give permission for these individuals to have access to my records.

4. I give permission for my trial data, some of which may identify me, to be transported from my hospital site to the trial co-ordinating centres at Bristol and Oxford for the purposes of analysis, monitoring and follow up.

5. I understand that information held by the NHS and records maintained by the NHS Information Centre and the NHS Central Register may be used to help contact me and provide information about my health status.

6. I agree to take part in this study.

7. I would like my GP (Dr…………………………………..) to be notified about my participation in the study and I give my permission for you to contact them.

8. Would you like to know the results of the trial when they are published? Yes/No

____________________________________  __________________________  __________________
Name of patient                         Date (dd/mm/yyyy)             Signature

____________________________________  __________________________  __________________
Name of researcher                      Date (dd/mm/yyyy)            Signature

3 copies: 1 for the patient, 1 for recruiting centre trial notes, 1 for hospital notes

SMART Consent form Version 3, Date 11.01.2012
Respiratory Research Unit  
North Bristol NHS Trust  

SMART Trial  

TRIAL SPECIFIC PROCEDURE  
Version 4  

RADIOTHERAPY  

Issue Date: 16.07.2012  
Effective Date: 16.07.2012  
Review Date: 16.07.2013  

Authored by  
Dr Amelia Clive  
Dr Paula Wilson  
Co-investigator  
Co-investigator  

Reviewed by  
Joanna Strickland  
Dr Emma de Winton  
Dr Nick Maskell  
Dr Peter Jenkins  
Dr Niki Panakis  
Trials Administrator  
Co-investigator  
Chief Investigator  
Co-investigator  
Co-investigator  

Authorised by  
Dr Nick Maskell  
Signature:  
Date: 16.07.2012
PATIENTS IN THE IMMEDIATE RADIOTHERAPY ARM

Timing of radiotherapy

For patients in the immediate (prophylactic) radiotherapy arm, radiotherapy should be given within 35 days of the pleural procedure for which the patient has been randomised. Under exceptional circumstances, the first fraction may be postponed for up to 42 days but a reason must be clearly stated.

Planning appointment:

All patients will attend a radiotherapy planning appointment with the clinical oncologist to plan and consent for the radiotherapy treatment (if consent has not already been obtained).

Technique:

The field should be marked with the patient in the most appropriate, reproducible and comfortable position for radiotherapy.

Volume to be treated:

For surgical and large bore pleural procedure scars, the total radiotherapy field is equivalent to the PTV (as defined below):

- **Suggested Clinical Target Volume (CTV):** chest drain and surgical sites/scars with at least a 3cm margin

- **Suggested Planning Target Volume (PTV):** CTV + 0.5cm if using kV photons or CTV +1cm if using electrons

For patients with an indwelling pleural catheter in situ, the radiotherapy field is equivalent to the PTV (as defined below):

- **Suggested Clinical Target Volume (CTV):** pleural puncture site, the whole of the catheter tract and the skin exit site with at least a 3cm margin

- **Suggested Planning Target Volume (PTV):** CTV + 0.5cm if using kV photons or CTV +1cm if using electrons

The volume to be treated must be acceptable to the treating clinical oncologist.

Diagnostic CT scans can be used to assess treatment depth to the chest wall. The treatment area should be no less than 7cm in any one direction.
Shielding can be used as appropriate, as long as this does not compromise the above treatment margins.

If matching fields are required due to the site and position of the scars, then use clinical discretion and follow your local policies, for example match the 50% edge of fields.

**Beam Arrangement:**

A single direct beam will be used in the majority of cases. If an alternative beam arrangement is considered necessary then it must be documented on the Clinical Record Form (CRF).

**Dose:**

21 Gray in 3 fractions over 3 working days prescribed following normal departmental procedures for electrons or applied if using kV photons. This dose should not be given over spinal cord, but if any concern regarding this then the dose may need to be altered and recorded on the Clinical Record Form (CRF).

**Energy:**

The preferred procedure is that patients are treated using electrons, of appropriate energy to treat the chest wall to at least 90%. Kilovoltage (kV) photons (minimum 220kV) can be used if electrons are not available as long as the depth to chest wall is adequate. Where it is necessary due to bulky chest wall or pleural disease, megavoltage photons (MV) can be used as clinically appropriate.

**Bolus:**

Bolus should be used as necessary to ensure that the skin dose is at least 90%.

**Record:**

The radiotherapy given should be recorded in the patient's clinical notes. It is good clinical practice for centres to photograph the radiotherapy field at the first session to ensure patient position and fields for subsequent fractions are similar. If this is usual practice at the individual radiotherapy centre, a photograph will be taken but this is not a requirement for the trial and the photograph will not be forwarded to the trial team.
In addition, the details should be completed on the radiotherapy CRF, to include the total dose, number of treatment fractions, number of days of treatment course, field size, type and dose of energy used, whether bolus or shielding was used, protocol deviations and any side effects noted during the radiotherapy course.

The CRF should be returned to the trial team at the recruiting centre.

PATIENTS IN THE DEFERRED RADIOTHERAPY ARM WHO DEVELOP A PROCEDURE TRACT METASTASIS

Timing

For patients in the deferred radiotherapy arm, radiotherapy should be given within 35 days of a PTM being confirmed at the clinic visit.

Planning appointment:

All patients will attend a radiotherapy planning appointment with the clinical oncologist to plan and consent for the radiotherapy treatment (if consent has not already been obtained in a clinic).

Technique:

The field should be marked with patient in the most appropriate, reproducible and comfortable position for radiotherapy.

Volume to be treated:

The total radiotherapy field is equivalent to the PTV (as defined below):

- Suggested Clinical Target Volume (CTV): palpable nodule with at least a 2cm margin
- Suggested Planning Target Volume (PTV): CTV + 0.5cm if using kV photons or CTV +1cm if using electrons

The volume to be treated must be acceptable to the treating clinical oncologist.

Diagnostic CT scans can be used to assess treatment depth to the chest wall. Shielding can be used as appropriate, as long as this does not compromise the above treatment margins.
If matching fields are required due to the site and position of nodules, then use clinical discretion and follow your local policies, for example match the 50% edge of fields.

**Beam Arrangement:**

A single direct beam will be used in the majority of cases. If an alternative beam arrangement is considered necessary then it must be documented on the Clinical Record Form (CRF)

**Dose:**

21Gray in 3 fractions over 3 working days prescribed following normal departmental procedures for electrons or applied if using kV photons. This dose should not be given over the spinal cord, but if there is any concern regarding this then the dose may need to be altered and recorded on the CRF.

**Energy:**

The preferred procedure is that patients are treated using electrons, of appropriate energy to treat the chest wall to at least 90%. Kilovoltage (kV) photons (minimum 220kV) can be used if electrons are not available as long as the depth to chest wall is adequate. Where it is necessary due to bulky chest wall or pleural disease, megavoltage photons (MV) can be used as clinically appropriate.

**Bolus:**

Bolus should be used as necessary to ensure that the skin dose is at least 90%.

**Record**

The radiotherapy given should be recorded in the patient’s clinical notes. It is good clinical practice for centres to photograph the radiotherapy field at the first session to ensure patient position and fields for subsequent fractions are similar. If this is usual practice at the individual radiotherapy centre, a photograph will be taken but this is not a requirement for the trial and the photograph will not be forwarded to the trial team.

In addition, the details should be completed on the radiotherapy CRF, to include the total dose, number of treatment fractions, number of days of treatment course, field size, type and dose of energy used, whether bolus or shielding was used, protocol deviations and any side effects noted during the radiotherapy course.

The CRF should be returned to the trial team at the recruiting centre.
PATIENTS IN THE IMMEDIATE RADIOTHERAPY ARM WHO DEVELOP A PROCEDURE TRACT METASTASIS

For patients in the immediate radiotherapy arm, further radiotherapy treatment if a procedure tract metastasis develops will be at the discretion of the oncologist. The treatment given should be recorded on the SMART trial radiotherapy CRF, which should then be returned to the trial team.

In order to establish whether the tract metastasis is within the previous radiotherapy field, on the edge of the field or distant to the radiotherapy field, the clinician should ideally have access to the clinical photograph taken at the time of radiotherapy.

RADIOThERAPY FOR OTHER INDICATIONS

For patients who are enrolled in the SMART trial who require radiotherapy for another indication, the radiotherapy regime is at the discretion of the oncologist responsible for the patient’s care. However, if the radiotherapy given is within a 10 cm margin of the procedure site, it should be recorded on a SMART trial radiotherapy CRF, which should then be returned to the trial team.

TOXICITY AND FOLLOW UP

In all patients who have received chest radiotherapy during the trial follow up period, skin toxicity will be assessed at all clinical follow up visits using RTOG/EORTC toxicity grading. Patients will be asked about other side effects by completing a questionnaire at the clinic visit after the radiotherapy is given.

FURTHER ADVICE

If further radiotherapy advice is required regarding treatment planning or complex cases, clinicians are encouraged to liaise directly with the trial clinical oncologists, who are happy to give advice on a case by case basis.

Their contact details are:

Dr Paula Wilson  paula.wilson@uhbristol.nhs.uk
Dr Niki Panakis  niki.panakis@ouh.nhs.uk
Dr Emma De Winton  emma.dewinton@nhs.net
SMART Semi-structured Interview Trial Specific Procedure.

Respiratory Research Unit
North Bristol NHS Trust

SMART Trial

TRIAL SPECIFIC PROCEDURE
Version 3

SEMI-STRUCTURED INTERVIEW

Issue Date: 30.10.2012
Effective Date: 30.10.2012
Review Date: 30.10.2013

Authored by Dr Amelia Clive Co-investigator
Reviewed by Joanna Strickland Trials Administrator
Nikki Jordan Co-investigator
Helen Clayson Co-investigator
Anna Morley Co-investigator

Authorised by Dr Nick Maskell Chief Investigator

Signature: Date: 30.10.2012

Surgical and large bore procedures in malignant pleural Mesothelioma And Radiotherapy Trial (SMART trial) - RCT evaluating whether prophylactic radiotherapy reduces the incidence of procedure tract metastases. Chief investigator: Dr. Nick Maskell.

REC: 11/SC/0408
SEMISTRUCTURED QUALITATIVE INTERVIEW

The semi-structured interview should address the same general questions for each patient whilst allowing you to use your own follow-up questions to gain further insights or explore unexpected responses.

Prior to the interview

Patients should have read and understood the patient information sheet and have been given sufficient time to consider it and ask questions.

Written consent should be taken prior to performing the interview.

Please ensure that the audio-recording equipment is working prior to starting the interview. Once both the interviewer and trial participant are in position, test that both voices can be clearly heard by playing back a short section of speech.

The interview

Press record on the audio-recording equipment and ensure the light has come on to indicate it is recording.

Start the recording by stating the date, time and location (hospital/patient’s home) of the interview. Then state the patient’s trial number and the name of the interviewer.

Briefly introduce yourself and thank the patient for participating.

Reconfirm consent to conduct the interview. Explain that the interview is confidential and any information used will be anonymised prior to publication.

Explain that you would like to ask them a few questions about your experiences of participating in the SMART trial

For all patients, ask:

In your own words, can you tell me what you know about your illness?

Would you like more information about your illness?

If yes, in what format would you like the information to be given to you? Would you like to talk to someone? Or would you rather written information?

I believe you are taking part in the SMART trial, can you tell me what you know about it?

Which group within the study were you allocated to?

How did you feel about going into that group?
What is your experience of your care in the trial?

Has the trial affected your quality of life in any way? (prompt the patient regarding quality of life if necessary - For example- Has the trial affected the things that you do? Your feelings? Your finances?)

For patient in the immediate radiotherapy group:

What were your experiences of the immediate (prophylactic) radiotherapy treatment?

What information were you given about the potential risks and benefits of radiotherapy?

Was the information you were given about the radiotherapy treatment helpful and adequate?

For patients in the deferred radiotherapy group:

What are your experiences of the deferred (watch and wait) treatment?

What information were you given about the potential risks and benefits of deferred (watch and wait) treatment?

Do you feel that the information you were given about the deferred (watch and wait) treatment was helpful and adequate?

For all patients, ask:

Have you had any problems or worries about the procedure site?

Is there anything else about the trial that you would like to discuss?

Close interview and thank them for participating.

During the interview

During the interview, the interviewer is encouraged to intermittently check that the patient is happy to continue being interviewed. If the patient does not wish to continue, the interview should be stopped.

Short notes can be taken during the interview if the interviewer wishes to do so.

Intermittently during the interview please check that the recording light on the digital recording device is still on.

After the interview
Stop the recording and thank the patient again for participating.

Offer them an information sheet about local and national support services and the patient advice and liaison service (PALS) should they require it. If other information needs have been highlighted in the interview or they would like the information in a different format, please arrange for these to be addressed.

If unaddressed physical or psychological symptoms have been raised by the patient during the interview, a referral to the palliative care team or GP should be considered.

Ensure the patient’s next follow up appointment is arranged.

Once the patient has left, write brief notes summarising the interview.

Save the recording of the interview to the encrypted memory stick provided.

Return the memory stick and copies of any notes taken during and after the interview to the trial team at Southmead.
Respiratory Research Unit  
North Bristol NHS Trust  

SMART Trial  

TRIAL SPECIFIC PROCEDURE  
Version 1  

CHEST EXAMINATION  

Issue Date: 05.09.2011  
Effective Date: 05.09.2011  
Review Date: 05.09.2012  

Authored by  
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Co-investigator  

Reviewed by  
Joanna Strickland  
Dr Naj Rahman  
Dr Nick Maskell  
Trials Administrator  
Co-investigator  
Chief Investigator  

Authorised by  
Dr Nick Maskell  
Signature:  
Chief Investigator  
Date: 05.09.2011
Clinical definition of a procedure tract metastasis (PTM)

A Procedure Tract Metastasis will be defined as a clinically palpable nodule of at least 1 cm diameter felt within 7 cm of the boundaries of the procedure tract by two independent assessors.

The assessors should be doctors, nurses or radiographers, who have read the chest examination SOP and feel confident to perform the examination.

Key points

- The chest examination must be performed by two assessors at each clinic visit
- In the event of disagreement between the assessors, they should examine the patient together to resolve the dispute.
- In the event of a nodule developing which does not meet the clinical definition of PTM above (for example the nodule is < 1 cm), a further clinic appointment should be arranged in 1 month to re-examine the patient to see if the definition has been met.

Chest wall examination

- Discuss with the patient what you are planning to do with the patient and wash your hands.
- Ask the patient if they would like a chaperone in the room while they are examined
- Ensure the patient is suitably exposed to fully visualise the procedure site
- Ensure the patient is in a comfortable position whereby the whole procedure site can be easily seen.
- Monitor the patient for any chest wall tenderness throughout the examination.
- Observe the chest wall and take note of:
  - Whether the procedure site scar is completely healed
  - If there are any other skin changes around the scar, including excoriation, rashes, blistering or erythema
  - Any visible chest wall nodules
- Carefully palpate along the procedure tract with the flat of your hand to feel for any nodulation. Take note of any tenderness.
- Run one finger over the procedure site and also between the ribs that cover the procedure tract to feel for any nodulation. Take note of any tenderness.
• For patients with an indwelling catheter in situ, run your finger either side of the tunnelled catheter, feeling for any extra nodules. Pay particular attention to the site where the catheter passes into the pleural cavity.

• If a nodule is palpated, you need to:
  o Measure and record the maximum diameter of the nodule using the tape measure provided in the trial pack
  o Note the location of the nodule in relation to the procedure site and measure the minimum distance from one to the other with the tape measure provided (from the edge of the procedure site to the closest edge of the nodule). Annotate the chest wall diagram in the CRF to indicate it’s location
  o Feel whether the nodule is tethered to the chest wall or mobile
  o Note whether the nodule is tender to palpate and ask the patient and record whether it is:
    ▪ not tender
    ▪ mildly tender
    ▪ moderately tender
    ▪ severely tender

• Allow the patient to dress and wash your hands
• Record your findings on the follow up visit CRF and in the patient’s notes
• Ensure both assessors have signed and dated the CRF
Surgical and large bore pleural procedures in Malignant Pleural Mesothelioma And Radiotherapy Trial (SMART Trial)

Statistical Considerations and Analysis Plan

A Randomised Controlled Trial evaluating whether prophylactic radiotherapy reduces the incidence of procedure tract metastases.

Chief Investigator:
Dr. Nick Maskell
R and D number: 2651
REC: 11/SC/0408
ISRCTN72767336
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1. **Study Overview**

Malignant pleural mesothelioma (MPM) is a fatal primary tumour of the pleura and the UK incidence continues to rise. Patients often undergo multiple pleural procedures in order to obtain a diagnosis. Unfortunately there is a risk of tumour seeding along the procedure tracts and subsequent development of painful procedure tract metastases (PTM), which can be very difficult to treat.

Prophylactic radiotherapy has been used for many years with a view to preventing procedure tract metastases, however the results of previous under-powered RCTs are conflicting. This randomised controlled trial endeavours to identify the optimal timing of chest wall radiotherapy in this patient group and examine its effectiveness.

This robust multicentre study will randomise 203 patients with confirmed MPM who have undergone a large bore thoracic procedure to receive immediate (prophylactic) radiotherapy or deferred radiotherapy should they develop a PTM (See below for study flow diagram). Patients will be carefully followed up for the development of PTM and quality of life measures and pain scores will be evaluated. By so doing, we hope to answer the heavily debated question about the role and optimal timing of prophylactic radiotherapy in malignant pleural mesothelioma.

2. **Randomisation**

Following informed consent, patients will be randomly assigned (1:1) to receive either immediate prophylactic radiotherapy or deferred radiotherapy in the event a nodule develops near the procedure site.

Treatment allocation will be performed by the Oxford Respiratory Trials Unit using a validated computer software program. Block randomisation with minimisation with a random component will be used.

The minimisation factors are:
- Histological tissue type of mesothelioma (epithelioid only or other)
- Indwelling pleural catheter or other pleural procedure
- Surgical procedure (ie open pleural biopsy, thoracotomy or VATS) or non-surgical procedure

Patients and clinicians will not be blinded to treatment allocation; however the data analysis will be conducted in a blinded fashion.

3. **Sample Size**

Previous studies in this field have addressed the presence or absence of tumour in patients at an outcome assessment point rather than the hazard ratio comparing treatment arms. This is sensible because the treatment proposed (prophylactic radiotherapy) is not likely to change the speed with which the events occur, but rather prevent them from occurring. This violates the necessary assumptions of survival models, and thus for this study, proportional comparison methods are employed as the primary outcome measure (at 12 months or death, whichever is first) and therefore are used for the sample size calculation. Time to event data will be modelled using regression analysis, but this will form part of the secondary analysis.

Patients will be followed up for 12 months or until death (whichever is first) from randomisation for the primary outcome measure (presence of Procedure Tract Metastases, PTM). Internal audit data show a PTM rate of <2% in those treated with prophylactic radiotherapy who underwent ‘large’ bore procedures as studied here, in comparison to a rate of between 8 and 40% in the published literature of patients not undergoing prophylactic radiotherapy.
Assuming conservatively the rate of PTM in the intervention group to be 2% and the rate of PTM in the “control” group to be 15%, a total of 180 patients are required to be randomised 1:1 to demonstrate a difference between treatment arms with 90% power at the 5% significance level. With an estimated lost to follow up rate of 3%, this number is increased to 185 patients randomised 1:1. Various power modelling scenarios are illustrated in the table below, demonstrating adequate power with varied control and intervention event rates if 203 patients are recruited.

<table>
<thead>
<tr>
<th>Intervention Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylactic radiotherapy</td>
<td>As needed radiotherapy</td>
</tr>
<tr>
<td>90% power (alpha 0.05, 3% loss to FU)</td>
<td>80% power (alpha 0.05, 3% loss to FU)</td>
</tr>
<tr>
<td>Incidence of PTM at 12 months (%)</td>
<td>12</td>
</tr>
<tr>
<td>1</td>
<td>203</td>
</tr>
<tr>
<td>2</td>
<td>269</td>
</tr>
<tr>
<td>3</td>
<td>357</td>
</tr>
<tr>
<td>4</td>
<td>482</td>
</tr>
<tr>
<td>5</td>
<td>670</td>
</tr>
</tbody>
</table>

Table 1: Sample size calculations for different predicted PTM rates. All rates include a projected 3% loss to follow up. The figures highlighted in red are those which are achievable within the proposed sample size.
Surgical and large bore pleural procedures in malignant pleural Mesothelioma And Radiotherapy Trial (SMART trial) - RCT evaluating whether immediate radiotherapy reduces the incidence of procedure tract metastases. Chief investigator: Dr. Nick Maskell. REC: 11/SC/0408.

4. Study overview flow diagram

A histocytological diagnosis of malignant pleural mesothelioma

Inclusion Criteria
1. A histocytologically proven diagnosis of malignant pleural mesothelioma as confirmed by an MDT meeting
2. One of the following pleural interventions within the past 35 days:
   a. Open pleural biopsy
   b. Surgical thoracotomy or VATS
   c. Local anaesthetic thoracoscopy
   d. Large bore chest tube insertion (≥20 French inserted by either a seldinger technique or blunt dissection)
   e. Indwelling pleural catheter insertion
3. Written informed consent

Exclusion Criteria
1. Age < 18 years
2. Expected survival < 4 months
3. Pregnancy or lactation
4. Inability to give informed consent or comply with the protocol
5. Previous radiotherapy which would result in an unacceptable overlap with the proposed treatment field
6. The patient does not have access to a telephone
7. A clinically palpable nodule of at least 1cm diameter felt within 7cm of the margins of the procedure site at the initial trial visit

Baseline investigations
- History: To document histology, performance status and previous pleural procedures
- Physical examination: for evidence of chest wall disease. Also to measure pleural procedure scar and annotate a diagram to indicate position.
- Details of treatment planned
- EQ5D/QLQ-C30 quality of life questionnaires and chest wall pain Visual Analogue Scale (VAS) score.

RANDOMISATION
Minimising by histology, indwelling pleural catheter or other procedure and surgical procedure or not.

Immediate Radiotherapy Arm
First dose of prophylactic radiotherapy given within 35 days of pleural procedure.
21Gy in three fractions (over 3 working days).
Radiotherapy field to encompass scar with at least a 3cm margin.

Deferred Radiotherapy Arm
No radiotherapy initially
If the patient develops a procedure tract metastasis, radiotherapy is given within 35 days of it being confirmed at a clinic visit
21Gy in 3 fractions (over 3 working days).
Radiotherapy field to encompass nodule with at least a 2cm margin.

Follow up
- Clinic visits at 1, 3, 6, 9 and 12 months with the local clinician (standard care). At each clinic visit:
  o History and physical examination for evidence of PTM and skin toxicity from radiotherapy
  o Documentation of other treatments received since last visit
  o Documentation of chemotherapy response (if given and known)
  o If the patient has had radiotherapy, questionnaire regarding the experience and side effects
  o EQ5D, QLQ-C30 and chest wall pain VAS completed
  o If PTM has developed, symptom questionnaire, measure and refer for radiotherapy (as per protocol)
- On the months that patients are not seen in clinic, a trial nurse will undertake a monthly follow up phone call consultations for 12 months. If the patient has new symptoms or signs around the biopsy site an urgent clinic appointment will be made for further assessment
- A visual analogue scale (VAS) pain score for chest wall pain will be recorded by the patient every month and returned to the trial team in a stamped addressed envelope
- At 6 months, patients at Bristol and Oxford offered semi-structured qualitative interview with a research nurse.
5. General Analysis Principles

All data will be analysed on intention-to-treat principles and all randomised patients in whom an outcome is available will be included in the analysis. More information on which participants will be included in each analysis is available in later sections. Data collected to the point at which a patient withdraws from the study will be included in the final analysis unless consent for this is withdrawn.

For continuous outcomes, analyses will adjust for the minimisation factors (see below) and the outcome measured at baseline (provided there is not substantial missing baseline data). For binary outcomes, if the number of events allows, the analysis will adjust for the minimisation factors (see below). If major baseline imbalances between the treatment arms are identified, these may also be adjusted for in the regression models.

For missing baseline data, if the numbers are small, median imputation will be used. If the numbers with missing data are large, alternative analysis methods may be used, which don’t account for baseline values.

CONSORT data will be presented including; the number of patients screened for the study and the numbers randomised. Reasons for exclusions after randomisation will be given.

All p values will be 2 sided, and the significance level is set at 5%.

Analysis for all outcomes will be presented as:

1. The number of participants included in the analysis, by treatment group;
2. A summary statistic for the outcome, by treatment group (for example, mean (SD) or median (2.5th-97.5th centile) for continuous outcomes; number(%) for binary outcomes)
3. A treatment effect, with a 95% confidence interval and p value

Analysis of some of the listed outcome measures will only be meaningful if a sufficient number of events (PTMs) are recorded in both treatment arms. If the numbers are not sufficient to undertake formal statistical analysis, the data will be reported descriptively and reasons will be stated.

6. Outcome measures

Primary Outcome

1. The incidence of development of PTM (as defined below) within 7 cm of the site of pleural intervention within 12 months from randomisation

Secondary Outcome

Chest pain

1. Summary score of the VAS score ‘On average how much chest pain have you felt today?’ (calculations described below) from randomisation to 12 months post randomisation.
2. Summary score of the VAS score ‘How much has chest pain bothered you today?’ (calculations described below) from randomisation to 12 months post randomisation.
3. Summary score of the VAS score ‘On average how much pain have you felt today from the site of your previous chest wall procedure?’ (calculations described below) from randomisation to 12 months post randomisation.

4. Summary score of the VAS score ‘How much has pain from the site of your previous chest wall procedure bothered you today?’ (calculations described below) from randomisation to 12 months post randomisation.

QOL

5. The summary score (calculations described below) of the following QLQ-C30 questionnaire domains, from randomisation to 12 months post randomisation:
   a. Global health status
   b. Pain
   c. Physical functioning score

6. The change in the following QLQ-C30 questionnaire domains, from randomisation to month 1 post randomisation:
   a. Global health status
   b. Physical functioning
   c. Fatigue
   d. Pain
   e. Appetite loss

7. The summary score (calculations described below) of the EQ5D utility score from randomisation to 12 months post randomisation.

Analgesia requirements

8. The summary dose (calculations described below) of the daily oral morphine equivalent dose (MED) from randomisation to 12 months post randomisation.

Size, severity and time to development of PTM

9. Time to development of PTM within 7cm of the procedure site, in days, from the date of randomisation to the date the diagnosis of PTM was confirmed.

10. For patients who develop a PTM within 7cm of the randomised procedure site, the summary size of the PTM (as calculated below) from diagnosis of the PTM to 12 months post randomisation.

11. For patients who develop a PTM within 7cm of the randomised procedure site, the summary chest pain VAS score (as calculated below) from diagnosis of the PTM to 12 months post randomisation.

12. The incidence of development of a painful PTM (as defined below) within 7 cm of the site of pleural intervention within 12 months from randomisation
13. For patients who develop a PTM within 7cm of the randomised procedure site, the summary dose (as calculated below) of the daily oral morphine equivalent dose (MED) from randomisation to 12 months post randomisation.

14. Time, in days, from diagnosis of PTM to death

15. The incidence of development of a chest wall nodule anywhere on the ipsilateral hemithorax within 12 months from randomisation

Safety/ Adverse Events

16. The number of patients experiencing at least one serious adverse event related to radiotherapy or procedure tract metastasis

Patient experience of the trial

17. Qualitative analysis of the semi-structured interviews will be performed to identify emergent themes. The results of this will be published separately to the main paper.

Health Economics

18. Resource use and costs over the 12 months post randomisation.

19. Generic health related quality of life (HRQoL) and quality adjusted survival

7. Analysis of the Primary Outcome: Incidence of PTM within 12 months

A Procedure Tract Metastasis (PTM) will be defined as a clinically palpable nodule of at least 1 cm diameter felt within 7cm of the margins of the procedure site as confirmed by two independent assessors. One of the assessors must be a doctor who feels that clinically the nodule is a tract metastasis. The assessors will be doctors, nurses or radiographers who have read the chest wall examination SOP and feel confident to undertake the examination.

The development of a PTM meeting the above criteria at any time during their 12 month trial follow up period will be included as an event. In patients who die before the end of their 12 month follow up, the development of a PTM at any time from trial entry to death will be included as an event for the purposes of the primary analysis. If they die without having developed a tract metastasis at any stage of their trial follow up, they will be classified as not having a PTM.

The time to development of a procedure tract metastasis will be defined as the time, in days, between randomisation and a PTM (meeting the above criteria) being confirmed by a doctor at a SMART trial clinic visit. The median duration of follow up and median survival for the 2 treatment arms will also be reported.

The proportion of patients developing a PTM within 7cm of the randomised procedure site within 12 months from randomisation or until death or loss to follow up (LTFU) (whichever is sooner) will be calculated for the immediate and deferred radiotherapy arms of the trial. These will then be compared using Fishers Exact Test. Alternatively, if the number of events allows, logistic regression will be performed, adjusting for the minimisation variables and any substantial baseline imbalances.
The main analysis of the primary outcome will be an intention to treat analysis, including all consented patients according to the treatment arm they were randomised to. Patients who are LTFU will be included in the analysis according to their outcome at their last available follow up.

A secondary, per protocol analysis will also be performed for the primary outcome, excluding patients where there were major protocol violations.

The following situations would be classed as a major protocol violation:
- Failure to give immediate radiotherapy in those randomised to the immediate RT arm
- Failure to meet the eligibility criteria for the study
- Major violations to the radiotherapy protocol, including:
  - Giving <21Gy in 3# of radiotherapy
  - Giving RT >42 days after the pleural intervention in the immediate RT arm, or development of a chest wall nodule if in the deferred RT arm.
  - Using a RT field size less than that stipulated in the protocol.

The following subgroup analyses will be performed for the primary outcome:
- By the type of pleural intervention randomised (large bore chest drain, local anaesthetic thoracoscopy, IPC or thoracic surgery)
- By tumour subtype (epithelioid only or other)
- Patients who were alive and in trial follow up for at least 6 months (yes/ no)
- Patients who received chemotherapy for mesothelioma within 12 months from trial entry (yes/ no)

8. Analysis of the Secondary Outcomes

a) Chest wall pain VAS Scores

Patients in the trial have completed four VAS scores once a month from randomisation until 12 months post randomisation:
- (a) On average how much chest pain have you felt today?
- (b) How much has chest pain bothered you today?
- (c) On average how much pain have you felt today from the site of your previous chest wall procedure?
- (d) How much has pain from the site of your previous chest wall procedure bothered you today?

The VAS scores will be measured according to the standard operating procedure by 2 independent assessors. The 4 different questions will be analysed separately.

For each patient, a graph of the VAS scores over time from randomisation until 12 months post-randomisation will be produced, and the area under the curve (AUC) will be calculated using the trapezium rule. If there are missing data points, the area under the curve will be calculated using the available data only.

The calculated AUC will be divided by the number of days after randomisation that the patient remained in the study to account for patients with different durations of follow-up. Patients will be considered in the study until the final day in which a VAS score was completed. This will give a summary score for each patient.
The summary scores for patients in the 2 treatment arms will be compared by means of a linear regression model, adjusting for minimisation factors, baseline imbalances (if present) and the patient’s VAS score recorded at randomisation.

All patients who have provided at least one VAS score after randomisation will be included in the analysis. Reasons for exclusions will be given. The median number of time points used for calculation of the AUC per patient will be reported.

b) Quality of life status (QLQ-C30)

Area under the curve analysis

A score out of 100 will be calculated for each of the required sub-scales each time a patient completes a QOL questionnaire.

Each sub-scale will be analysed separately.

For each patient, the sub-scale scores recorded each time a QOL questionnaire is completed will be used to produce a graph of the sub-scale score over time. The area under the curve (AUC) will be calculated using the trapezium rule. If there are missing data points, the area under the curve will be calculated using the available data only.

The calculated AUC will be divided by the number of days post randomisation the patient remained in the study to account for patients with different durations of follow-up. Patients will be considered in the study until the final day in which a sub-scale score was recorded. This will give a summary score for each patient.

The summary scores for patients in the 2 treatment arms will be compared by means of a linear regression model, adjusting for minimisation factors, baseline imbalances (if present) and the sub-scale score at randomisation.

All patients who have at least one sub-scale score recorded after randomisation will be included in the analysis. Incompletely completed questionnaires where calculation of the sub-scale score is not possible will be excluded. Reasons for exclusions will be given. The median number of time points used for calculation of the AUC per patient will be reported.

Change from baseline to month 1

The absolute change in 5 of the QLQ-C30 sub-scales (stated above) from randomisation to month 1 will be compared between the 2 treatment groups (to evaluate whether having prophylactic radiotherapy affects QOL in the first month). Each sub-scale will be analysed separately.

All patients who have completed at least one sub-scale score recorded after randomisation will be included in the analysis. Incompletely completed questionnaires where calculation of the sub-scale score is not possible will be excluded. Reasons for exclusions will be given.

The absolute change in the sub-scale score for patients in the 2 treatment arms will be compared by means of a linear regression model, adjusting for minimisation factors, baseline imbalances (if present) and the sub-scale score at randomisation.
c) **Quality of life status (EQ5D)**

The EQ5D is a standardised measure of health status and consists of 2 parts – the descriptive system (which comprises of 5 questions and results in a ‘utility score’) and a visual analogue scale (providing a score out of 100). The utility score will form the basis of the analysis. The VAS Score will be used to validate the findings of the utility score.

The questionnaires will be scored according to the EQ5D user guide. A utility score will be calculated each time a patient completes a questionnaire using the responses from the descriptive system.

The utility scores will be analysed, using the following methodology:

For each patient, the result calculated each time the patient completed an EQ5D questionnaire will be used to produce a graph of the score over time. The area under the curve (AUC) will be calculated using the trapezium rule. If there are missing data points, the area under the curve will be calculated using the available data only.

The calculated AUC will be divided by the number of days post randomisation the patient remained in the study to account for patients with different durations of follow-up. Patients will be considered in the study until the final day in which the EQ5D was completed. This will give a summary score for each patient.

The summary scores for patients in the 2 treatment arms will be compared by means of a linear regression model, adjusting for minimisation factors, baseline imbalances (if present) and the utility score at randomisation.

All patients who have completed at least one EQ5D after randomisation will be included in the analysis. Incomplete questionnaires where calculation of the score is not possible will be excluded. Reasons for exclusions will be given. The median number of time points used for calculation of each AUC per patient will be reported.

d) **Analgesia requirements**

The daily oral morphine equivalent dose (MED) that each patient is receiving will be calculated at randomisation and at each SMART trial follow up visit. This will be calculated from the opiate analgesia that the patient is taking regularly as documented on the clinic follow up CRF (PRN analgesia will not be included in the calculation). The oral morphine equivalent doses will be calculated according to the equivalent doses detailed in the British National Formulary (BNF).

For each patient, a graph of the MED over time from randomisation until 12 months post-randomisation will be produced, and the area under the curve (AUC) will be calculated using the trapezium rule. If there are missing data points, the area under the curve will be calculated using the available data only.

The calculated AUC will be divided by the number of days after randomisation that the patient remained in the study to account for patients with different durations of follow-up. This will give a summary dose for each patient. Patients will be considered in the study until the final date that a MED was calculated. If the patient is not taking any opiates, the MED will be recorded as 0.

The summary doses for patients in the 2 treatment arms will be compared by means of a linear regression model, adjusting for minimisation factors, baseline imbalances (if present) and the MED calculated at randomisation.
e) Size, severity and time to development of PTM

i. Time to development of PTM

The time to development of PTM within 7cm of the randomised procedure site from the date of randomisation to the date on which the diagnosis of PTM was confirmed will be calculated in days. Kaplan Meier survival curves will be constructed, censoring patients at death or loss to follow up (whichever is sooner) for the 2 treatment arms. If the number of events allows, a Cox proportional hazard model and log rank test will be performed adjusting for the minimisation factors and baseline imbalances (if present).

ii. The summary size of the PTM

The maximum diameter of a PTM (in centimetres) will be recorded at every SMART trial clinic visit.

For each patient who develops a PTM within 7cm of the randomised procedure site, a graph of maximum PTM diameter (in centimetres) over time from the date of diagnosis of PTM until 12 months post-randomisation will be produced and the area under the curve (AUC) will be calculated using the trapezium rule. If there are missing data points, the area under the curve will be calculated using the available data only.

The calculated AUC will be divided by the number of days after the PTM was diagnosed that the patient remained in the study to account for patients with different durations of follow-up. Patients will be considered in the study until the final day in which the PTM was measured. This will give a summary size for each patient. If the PTM is only measured once, this measurement will be used as the summary size.

If numbers allow, the summary sizes for patients in the 2 treatment arms will be compared by means of a linear regression model, adjusting for minimisation factors and baseline imbalances (if present).

All patients who are diagnosed with a PTM within 7cm of the randomised procedure site will be included in the analysis. Reasons for exclusions will be given. The median number of time points used for calculation of the AUC per patient will be reported.

iii. Summary chest pain VAS scores (for those patients who developed a PTM)

A subgroup analysis evaluating the chest pain VAS summary scores will be performed only including those patients in the study who developed a PTM during trial follow up.

For patients who develop a PTM within 7cm of the randomised procedure site, the VAS Score ‘On average how much pain have you felt today from the site of you previous chest wall procedure?’ will be used to evaluate their chest pain over time.

For each patient, a graph of the VAS score measurement over time from the date of diagnosis of PTM until 12 months post-randomisation will be produced and the area under the curve (AUC) will be calculated using the trapezium rule. If there are missing data points, the area under the curve will be calculated using the available data only.
The calculated AUC will be divided by the number of days after diagnosis of PTM that the patient remained in the study to account for patients with different durations of follow-up. Patients will be considered in the study until the final data that a VAS score was completed. This will give a mean summary score for each patient.

If numbers allow, the summary VAS scores for patients in the 2 treatment arms will be compared by means of a linear regression model, adjusting for minimisation factors, baseline imbalances (if present) and the patient’s VAS score recorded at diagnosis of the PTM.

All patients who have provided at least one VAS score after diagnosis of the PTM will be included in the analysis. Reasons for exclusions will be given. The median number of time points used for calculation of the AUC per patient will be reported.

iv. **The incidence of painful PTM**

For those patients who develop a PTM within 7cm of the pleural intervention site, the PTM will be classified as to whether the PTM was painful at presentation or not, according to whether or not it was tender at presentation. This will be tabulated by treatment arm and the proportion of patients with a painful PTM will be compared between treatment arms using Fisher’s Exact Test (if numbers allow).

v. **Summary dose for the MED (for those patients who developed a PTM)**

A subgroup analysis evaluating the MED summary doses will be performed only including those patients in the study who developed a PTM during trial follow up.

For each patient, a graph of the MED over time from diagnosis of PTM until 12 months post-randomisation will be produced, and the area under the curve (AUC) will be calculated using the trapezium rule. If there are missing data points, the area under the curve will be calculated using the available data only.

The calculated AUC will be divided by the number of days after diagnosis of PTM that the patient remained in the study to account for patients with different durations of follow-up. This will give a summary dose for each patient. Patients will be considered in the study until the final date that a MED was calculated. If the patient is not taking any opiates, the MED will be recorded as 0.

If numbers allow, the summary doses for patients in the 2 treatment arms from PTM diagnosis to 12 months post randomisation will be compared by means of a linear regression model, adjusting for minimisation factors, baseline imbalances (if present) and the MED calculated at diagnosis of the PTM.

vi. **Time from PTM diagnosis until death**

The time from the diagnosis of PTM within 7cm of the randomised procedure site to death will also be calculated in days. Kaplan Meier survival curves will be constructed, censoring patients at death or loss to follow up (whichever is sooner). If the number of events allows, a Cox proportional hazard model and log rank test will be performed adjusting for the minimisation factors and baseline imbalances (if present) to compare the 2 treatment arms.

vii. **The incidence of development of a chest wall nodule anywhere on the ipsilateral hemithorax.**
The incidence of development of a chest wall nodule anywhere on the ipsilateral hemithorax within 12 months from randomisation will be analysed. The analysis methods will be the same as those described in section 7, however, all chest wall nodules on the ipsilateral hemithorax will be included in this analysis, regardless of their distance from the randomised procedure site.

f) Safety/Adverse Events

The number of patients experiencing at least one serious adverse event related to radiotherapy or procedure tract metastasis will be compared between the 2 treatment arms using Fisher’s Exact Test.

The overall survival in days from the date of randomisation to death will be compared between the 2 groups using a Kaplan Meier Survival Curve and a log rank test.

The rate of acute and chronic radiotherapy toxicity (specifically skin toxicity, subcutaneous tissues toxicity, nausea, tiredness/lethargy and ‘other’) will be presented descriptively and tabulated for all patients receiving radiotherapy in the trial by treatment arm (see table 4). For skin toxicity and subcutaneous tissues toxicity the maximum recorded severity will be presented, using the RTOG grade 0-5.

The relative incidence of the following IPC complications will be presented by treatment group (see table 4):

- Pleural infection
- IPC blockage
- IPC fracture
- Local skin cellulitis
- Drain dislodgment
- Damage to the plastic of the IPC
- Difficulties removing IPC


g) Patient experience of the trial

Qualitative analysis of the semi-structured interview transcripts will be performed to identify emergent themes. The results will be reported descriptively and are likely to be reported separately to the main paper.

The results of the patient questionnaires evaluating their experience of receiving radiotherapy in the trial will be reported descriptively.

Additionally, the questionnaires completed by patients regarding their experience of developing a PTM will be presented descriptively.

h) Health Economics

The perspective adopted in the economic evaluation will be that of the National Health Service (NHS). An economic evaluation adherent to guidelines for good economic evaluation practice will be undertaken integral to the main trial. A within-trial cost-utility analysis will explore the incremental cost per QALY gained by immediate radiotherapy compared with deferred radiotherapy. Cost and effect results will be reported as means with standard deviations, with mean differences between the two patient groups reported alongside 95% confidence intervals (CI). Incremental cost-effectiveness will be calculated by dividing the difference in costs by the difference in effects. Uncertainty around the incremental cost-effectiveness ratio (ICER) will be explored using non-parametric bootstrapping.
The Resource use and costs over the 12 months post randomisation will be calculated and compared between the 2 treatment arms. This will include the following:

- Interventions under study, i.e. number of radiotherapy sessions;
- Hospitalisation and other hospital resource use, including hospital stays and readmissions; outpatient visits; and accident and emergency contacts (including use of ambulance); and
- Medications associated with treatment of mesothelioma.

Hospital resource use will be valued using NHS Reference Costs. Medication costs will be valued using the prices listed in the British National Formulary.

Generic health related quality of life (HRQoL) and quality adjusted survival will be calculated and compared between the 2 treatment arms.

HRQoL will be measured using the EuroQol-5 Dimensions 5-levels (EQ-5D-5L) questionnaire. The EQ-5D is a standardised measure of health providing a simple generic measure of health for clinical and economic appraisal, and is the most widely used HRQoL measure in adults in the UK. The EQ-5D is designed for self-completion by respondents, with instructions included in the questionnaire, and generally takes no more than a few minutes to complete.

In this study, the EQ-5D-5L will be administered at baseline, 1, 3, 6, 9 and 12 months. Responses will be converted into utilities using tariffs estimated from a representative sample of the UK population.

Survival information collected from the trial will be combined with EQ-5D utilities to generate Quality Adjusted Life-Years (QALYs), which is the outcome measure preferred by the National Institute for Health and Clinical Excellence.

9. Other data to be presented in the primary paper

Patient characteristics

The baseline patient characteristics will be tabulated by treatment arm (see table 1). The treatments given to patients during trial follow up will be tabulated (see table 6).

Rate of tract metastasis according to randomised procedure type

The rate of development of PTM and median time to development of PTM according to the randomised procedure type will be tabulated by treatment arm (see table 7).

Protocol Deviations

Protocol Deviations will be reported. Deviations to the radiotherapy protocol will be tabulated (see table 5). Other important protocol deviations, such as patient withdrawals, inappropriate randomisations and GCP breeches will be presented descriptively. No formal statistical analysis will be performed.

Radiotherapy

The type of radiotherapy machine used to administer the treatment (electrons, kv photons etc) will be tabulated according to treatment arm (see table 5). Additionally, for those patients in the immediate RT
arm of the trial, who develop a PTM, data will be presented regarding the relationship of the PTM to the RT field (within the field, on the edge of the field or outside the field) (see table 2).

**Figure 1: Consort Flowchart**

- Number screened
- Number randomised
- Number allocated
  - Deferred RT
  - Immediate RT
    - Number who received intervention as assigned
    - Number who did not receive intervention (with reasons)
- Number included in primary analysis
  - Number not included in primary analysis (with reasons)
- Number who completed 6 months FU
  - Number died prior to 12 months FU
  - Number LTFU
- Number who completed 12 months FU
  - Number died prior to 12 months FU
  - Number LTFU
- Number who completed 12 months FU
  - Number died prior to 12 months FU
  - Number LTFU
- Number included in primary analysis
  - Number not included in primary analysis (with reasons)
Table 1: Baseline patient characteristics at randomisation by treatment arm.

<table>
<thead>
<tr>
<th></th>
<th>Deferred RT arm</th>
<th>Immediate RT arm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n= ...</td>
<td>n= ....</td>
</tr>
<tr>
<td>Male</td>
<td>xx (xxx) n=xxx</td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Time from diagnosis to randomisation (days)</td>
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<td>WHO Performance Score</td>
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<tr>
<td>Karnofsky Performance Score</td>
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<td>BMI</td>
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<td>Extra-thoracic spread on imaging</td>
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<td>Histological subtype</td>
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<tr>
<td>Epithelioid only</td>
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<td>Sarcomatoid</td>
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<td>Biphasic (mixed)</td>
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<td>Desmoplastic</td>
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<tr>
<td>Basis for diagnosis</td>
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<td>Pleural fluid cytology</td>
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<td>Side of disease</td>
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<td>Left</td>
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<td>Right</td>
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<td>Smoking status</td>
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<td>Current smoker</td>
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<tr>
<td>Ex smoker</td>
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</tr>
<tr>
<td>Never smoker</td>
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<tr>
<td>Comorbidities</td>
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<td>Respiratory disease</td>
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<td>Cardiac disease</td>
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<tr>
<td>Chronic renal failure</td>
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<td>Diabetes</td>
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<td>Steroid use</td>
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<td>Symptomatic pleural effusion at presentation</td>
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<tr>
<td>Chest pain at presentation</td>
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<td></td>
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<tr>
<td>Previous pleurodesis</td>
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<tr>
<td>Type of intervention randomised</td>
<td>Large bore chest drain insertion</td>
<td></td>
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<td>---------------------------------</td>
<td>----------------------------------</td>
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</tr>
<tr>
<td></td>
<td>Local anaesthetic thoracoscopy</td>
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<tr>
<td></td>
<td>Thoracotomy</td>
<td></td>
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<tr>
<td></td>
<td>VATS procedure</td>
<td></td>
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<td></td>
<td>Indwelling pleural catheter insertion</td>
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<tr>
<td></td>
<td>Other</td>
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<tr>
<td>Number of pleural puncture sites from randomised intervention</td>
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<tr>
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<td></td>
<td>≥3</td>
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</table>

<table>
<thead>
<tr>
<th>Previous chemotherapy received for mesothelioma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous RT received for mesothelioma</td>
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<tr>
<td>Baseline oral morphine equivalent dose (mg)</td>
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<td>Baseline QOL</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Overall chest pain VAS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of trial follow up</td>
</tr>
<tr>
<td>Overall survival from randomisation to death</td>
</tr>
<tr>
<td>Overall survival from diagnosis of mesothelioma to death</td>
</tr>
</tbody>
</table>
Table 2: Results for Procedure Tract Metastasis Development within 7cm of the randomised procedure site

<table>
<thead>
<tr>
<th></th>
<th>Treatment arm</th>
<th>Treatment effect (95% CI) (deferred vs immediate RT) [If number of events allows]</th>
<th>p-value [If number of events allows]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deferred RT arm n= ...</td>
<td>Immediate RT arm n= ....</td>
<td></td>
</tr>
<tr>
<td>Number of patients developing a PTM, n (%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Number of patients developing a painful PTM, n(%)</td>
<td></td>
<td></td>
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<tr>
<td>Time to development of PTM from randomisation (days), median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from development of PTM to death (days), median (IQR)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Summary size of PTM from diagnosis of PTM to 12 months post randomisation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summary chest pain VAS Score from diagnosis of PTM to 12 months post randomisation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summary MED dose from diagnosis of PTM to 12 months post randomisation</td>
<td></td>
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<tr>
<td>Number of patients developing a chest wall nodule anywhere on the ipsilateral hemithorax, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>Location of PTM in relation to the Immediate RT field</td>
<td>Within the RT field</td>
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<tr>
<td></td>
<td>On the edge of the RT field</td>
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<tr>
<td></td>
<td>Outside the RT field</td>
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</tr>
</tbody>
</table>

PTM= Procedure Tract Metastasis within 7cm of randomised procedure site; RT= Radiotherapy; 95% CI= 95% Confidence Interval; IQR= Interquartile Range; VAS= Visual Analogue Scale; NA= Not Applicable
Table 3: Results of VAS Score and Quality of Life Variable

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number included in analysis</th>
<th>Median number of time points used to generate summary score</th>
<th>Summary score (mean, SD)</th>
<th>Treatment effect (95% CI) deferred vs immediate RT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>'On average how much chest pain have you felt today' summary VAS score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>'On average how much has chest pain bothered you today' summary VAS score</td>
<td></td>
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<tr>
<td>'On average how much pain have you felt today from the site of your previous chest wall procedure' summary VAS score</td>
<td></td>
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<tr>
<td>'On average how much has pain from the site of your previous chest wall procedure bothered you today' summary VAS score</td>
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<tr>
<td>QLQ-c30 Global health status summary score</td>
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<tr>
<td>QLQ-c30 Physical functioning summary score</td>
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<tr>
<td>QLQ-c30 Pain summary score</td>
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<tr>
<td>EQ5D summary score</td>
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<tr>
<td>Change in QLQ-C30 Global health status from randomisation to 1 month</td>
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<tr>
<td>Change in QLQ-C30 physical functioning from randomisation to 1 month</td>
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<tr>
<td>Change in QLQ-C30 Fatigue from randomisation to 1 month</td>
<td></td>
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</tr>
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</table>
Surgical and large bore pleural procedures in malignant pleural Mesothelioma And Radiotherapy Trial (SMART trial) - RCT evaluating whether immediate radiotherapy reduces the incidence of procedure tract metastases. Chief investigator: Dr. Nick Maskell. REC: 11/SC/0408.

| Change in QLQ-C30 pain from randomisation to 1 month | | | | | |
| Change in QLQ-C30 appetite loss from randomisation to 1 month | | | | | |

PTM= Procedure Tract Metastasis within 7cm of randomised procedure site; RT= Radiotherapy; 95% CI= 95% Confidence Interval; SD= Standard Deviation; IQR= Interquartile Range; VAS= Visual Analogue Scale; NA= Not Applicable

**Table 4: Adverse Events**

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>RTOG Toxicity Grade (if applicable)</th>
<th>Deferred radiotherapy arm (n=...) n (%)</th>
<th>Immediate radiotherapy arm (n=...) n (%)</th>
<th>p-value (if numbers allow)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious Adverse Events related to RT or PTM</strong></td>
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<tr>
<td><strong>Early radiotherapy side effects</strong></td>
<td>Skin toxicity</td>
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<td></td>
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<td></td>
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<td>2</td>
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<td>5</td>
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<tr>
<td></td>
<td>Nausea</td>
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<td></td>
<td>Tiredness/lethargy</td>
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<tr>
<td></td>
<td>Other</td>
<td></td>
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<tr>
<td><strong>Late radiotherapy side effects</strong></td>
<td>Skin toxicity</td>
<td>1</td>
<td></td>
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<td></td>
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<td>2</td>
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<td></td>
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<td>5</td>
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<tr>
<td></td>
<td>Subcutaneous tissues toxicity</td>
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<td></td>
<td></td>
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<td>5</td>
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<tr>
<td></td>
<td>Nausea</td>
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<tr>
<td></td>
<td>Tiredness/lethargy</td>
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<td></td>
<td>Other</td>
<td></td>
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<tr>
<td><strong>IPC complications</strong></td>
<td>Pleural infection</td>
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<td>IPC Blockage</td>
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<td>IPC fracture</td>
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<td></td>
<td>Local skin cellulitis</td>
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<tr>
<td></td>
<td>Drain dislodgment</td>
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<tr>
<td></td>
<td>Damage to the IPC plastic</td>
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<tr>
<td></td>
<td>Difficulties removing the IPC</td>
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</tbody>
</table>

RTOG= Radiation Therapy Oncology Group; IPC= Indwelling Pleural Catheter; PTM= Procedure Tract Metastasis; RT= Radiotherapy; IQR= Interquartile Range.
Table 5: Radiotherapy received

<table>
<thead>
<tr>
<th>Total number of patients receiving SMART trial RT, n (%)</th>
<th>Deferred radiotherapy arm (n=...)</th>
<th>Immediate radiotherapy arm (n=...)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT modality used, n (%)</td>
<td>Electrons</td>
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<tr>
<td></td>
<td>Kv photons</td>
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<tr>
<td></td>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>RT protocol deviations, n (%)</td>
<td>Failure to give RT when indicated according to the protocol (with reasons if available)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RT given out of the stipulated time-frame</td>
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</tr>
<tr>
<td></td>
<td>RT field margin smaller than that stipulated in the protocol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other RT protocol deviation</td>
<td></td>
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</tbody>
</table>

RT= Radiotherapy; kv= kilovolts; MV= megavolts.

Table 6: Mesothelioma treatments received after trial entry

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Deferred Radiotherapy arm (n=xxx)</th>
<th>Immediate Radiotherapy arm (n=xxx)</th>
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</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
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</tr>
<tr>
<td></td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>RT according to SMART trial protocol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other palliative RT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Thoracic surgery</td>
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<td></td>
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<tr>
<td>Palliative Care involvement</td>
<td></td>
<td></td>
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<tr>
<td>Cordotomy</td>
<td></td>
<td></td>
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<tr>
<td>Pleural interventions</td>
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<tr>
<td>Other</td>
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</table>
Table 7: Subgroup analyses for the primary outcome

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Total number of patients (n=...)</th>
<th>Median time to development of procedure tract metastasis from randomisation (days), median (central range)</th>
<th>Number of patients developing a PTM, n (%)</th>
<th>Deferred radiotherapy arm (n=...)</th>
<th>Immediate radiotherapy arm (n=...)</th>
<th>p-value (if numbers allow)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomised procedure type</strong></td>
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<tr>
<td>Large bore chest drain insertion (&gt;20Fr)</td>
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<tr>
<td>Local anaesthetic thoracoscopy</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Thoracic surgery (thoracotomy or VATS)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Indwelling pleural catheter insertion</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td><strong>Tumour subtype</strong></td>
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<tr>
<td>Epithelioid only</td>
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<td>Other</td>
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<tr>
<td><strong>Patients followed up for ≥6 months</strong></td>
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<tr>
<td><strong>Chemotherapy after trial entry</strong></td>
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<td>Yes</td>
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<td>No</td>
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</tr>
</tbody>
</table>

PTM= Procedure Tract Metastasis; VATS= video assisted thoracic surgery
SMART Trial

ETHICAL APPROVAL AND PROTOCOL AMENDMENTS

Ethical Approval: Granted by NRES Committee South Central – Southampton B on 28th September 2011.

1. Substantial Amendment. Date: 13/10/2011. Accepted by REC 18/10/2011

1. Changing the definition of a procedure tract metastasis to a 7cm margin from the procedure site (protocol sections 4.3.2, 6.1)
2. Changes to the Inclusion/Exclusion Criteria
   a. Changing exclusion criteria 7 to exclude patients with chest wall nodules within 7cm of the procedure site. (IRAS form sections A6-2, A17-2; protocol sections 2.2; 3.3)
   b. Clarification that drains inserted by either a seldinger technique or blunt dissection can be enrolled (IRAS form sections A6-2, A17-1; protocol sections 2.2, 3.2)
3. Changing the minimisation criteria to include surgical procedure or other and removing plan for chemotherapy. (IRAS form section A61; protocol sections 2.2, 4.2.2)
4. Changes to the secondary endpoints
   a. Adding health economic analysis to the research questions and secondary endpoints. (IRAS form sections A11, A58; protocol sections 2.1; 6.1)
   b. Secondary endpoint number 3 should read ‘analgesia requirements’ (IRAS form section A11; protocol section 6.1)
5. Clarification in the main protocol that chemotherapy should not be started until 2 weeks after the radiotherapy is completed (protocol section 4.3.2).
6. Changes to the Radiotherapy Trial Specific Procedure
   a. Adding a line regarding taking photos of the radiotherapy field
   b. Clarifying when a trial radiotherapy CRF needs to be completed
   c. Clarifying that the volume to be treated should include the PTV and that it should be acceptable to the treating oncologist.
   d. Standardising the wording in the main protocol relating to the radiotherapy protocol to ‘trial specific procedure’ (rather than SOP) (protocol sections 4.2.3, 4.3.2)
7. Only reporting of SAEs after each trial clinic visit (protocol section 7.1).
8. Changes to the consent form:
   a. Only 3 copies of the consent form to be taken
   b. Clarification that information will be forwarded to Oxford and Bristol
c. Asking for consent to obtain information from NHS registers

9. Changes to the Patient information sheets:
   a. Addition regarding obtaining information from NHS registers.

10. The extra boxes for patient details have been removed from the GP letters.

11. Database management to be provided by the trial team at the Oxford Respiratory Clinical Trials Unit. (IRAS sections A6-2, A36, A38; protocol section 8)

12. Increasing the number of recruiting centres to 17 and changes to PIs and recruiting centres:
   a. At Plymouth Hospitals NHS Foundation Trust, the PI will be Mr Adrian Marchbank
   b. At Royal Devon and Exeter NHS Foundation Trust, the PI will be Dr Liz Toy
   c. At Portsmouth Hospitals NHS Trust, the PI will be Dr Lesley Bishop
   d. At Great Westen Hospitals NHS Foundation Trust, the PI will be Dr Anthony Kerry
   e. Llandough Hospital has been removed as a recruiting centre
   f. Addition of Blackpool, Dorchester and Torbay as recruiting centres
      (IRAS form Part C; Protocol section 3.1)

2. Non substantial Amendment. Date 11.01.2012.
   Accepted by REC 11.01.2012
   Alteration of wording of standard consent form and semistructured interview
test consent form.

3. Non substantial Amendment. Date 12.01.2012
   Accepted by REC 12.01.2012
   Addition of additional recruiting centres.

4. Substantial Amendment. Date: 01.02.2012
   Accepted by REC 07.03.2012
   1. Removal of stratiﬁying by centre (protocol section 4.2.2; IRAS section 61-1)
   2. Change need to inform the trial team if a different RT beam is used to
documenting it on CRF, clarification of wording regarding field, CTV and PTV
   3. Updating TSC membership (Protocol section 10.2)
   4. Removal of site speciﬁc logos from VAS score sheets and questionnaires
   5. Changes to VAS score format for administration purposes
   6. Clarification of requirement for centres to have recent audit data for
radiotherapy quality assurance. (protocol section 3.1)

5. Non substantial Amendment. Date 05.03.2012
   Accepted by REC 16.03.2012
   Clarification of wording in VAS score

6. Non substantial Amendment. Date 30.03.2012
   Accepted by REC 11.04.2012
   Addition of new sites
7. Substantial Amendment. Date 16/07/2012
Accepted by REC 01.08.2012

1. Addition of 2 extra questions to the semi-structured interview
2. Change to inclusion criteria to include large bore pleural procedures within 35 days of the pleural intervention (Protocol section 3.2, IRAS sections A6-2, A17-1)
3. Change to timeframe for radiotherapy to within 35 days (but a maximum of 42 days) (Protocol section 4.2.3, IRAS section A13)
4. clarification to wording about SAEs (Protocol section 7.1)
5. Change of name in research team (Protocol section "research team contact details", IRAS sections A3, A63)
6. Removal of sites from the R&D form (Blackpool, Southampton, Isle of Wight, Salisbury, UCLH, The Royal Brompton, South Devon) (protocol section 10.3, IRAS section C)

8. Non-substantial Amendment. Date 25/07/2012
Accepted by REC 06.08.2012

1. Change of PI at UHB from Dr. Paula Wilson to Dr. Charles Comins (maternity cover)

9. Non-substantial Amendment Date 16/10/2012
Accepted by REC 31.10.2012

1. Clarification regarding patient withdrawals (protocol section 5)
2. Extension of recruitment period from 15 to 24 months

10. Substantial Amendment Date 30/10/2012
Accepted by REC 07.12.2012

Change to Semi-structured interview TSP
Adding option of an extra semi-structured interview for patients who develop a PTM after their 6 month follow up (protocol 4.3.3 & semi-structured interview PIS)
Clarifying wording of semi-structured interview PIS.

11. Non-substantial Amendment Date 27/02/2013
Acknowledged by REC 06.03.203

Addition of new site – Glangwili General Hospital, Carmarthenshire

12. Non-substantial Amendment Date 13/03/2013
Acknowledged by REC 02.05.2013

Addition of new PIC site – Royal Brompton and Harefield NHS Trust

13. Non-substantial Amendment Date 12/04/2013
Acknowledged by REC 02.05.2013

Addition of new PIC site – Worcester Royal Hospital
14. **Non-substantial Amendment Date 26.04.2013**
Acknowledged by REC

Addition of new sites – Royal Berkshire NHS Foundation Trust and The Royal Marsden NHS Foundation Trust

15. **Non-substantial Amendment Date 21.08.2013**
Acknowledged by REC

1. Extension of recruitment period from 24 to 36 months
2. Addition of PIC site – Heatherwood and Wexham Park Hospitals NHS Foundation Trust (King Edward VII Hospital)