Standard or PalliativE Care In Advanced Lung cancer

Does early referral of patients with metastatic non-small cell lung cancer to UK specialist palliative care services make a difference in their quality of life or survival?

Sponsor: Sheffield Teaching Hospital NHS Foundation Trust

Funded by NIHR Health Technology Assessment Programme

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Summary of Protocol Amendments

Amendment No.	Date of Amendment	Protocol Version No.	Type of Amendment	Summary of Amendment
a	8 Apr 2016	1.0a	Minor	Several minor corrections were also made at this time, including a reduction of the archiving period to 5 years from the previously stated 25 years.

Chief Investigator and Clinical Coordinator	Prof Sam H Ahmedzai Academic Unit of Supportive Care School of Medicine & Biomedical Science The University of Sheffield S10 2RX ☎ +44 (0) 114 271 3082
Deputy Clinical Co-ordinator & Lead Respiratory Physician	Dr Robert Milroy NHS Greater Glasgow & Clyde Health Board ☎ +44 (0) 141 211 4539 (via Secretary)
Medical Oncologists	Prof Penella Woll & Dr Sarah Danson, Sheffield Teaching Hospitals NHS Foundation Trust
Clinical Oncologists	Drs Patricia Fisher & Matthew Hatton, Sheffield Teaching Hospitals NHS Foundation Trust
Palliative Physician	Dr Bill Noble, Sheffield Teaching Hospitals NHS Foundation Trust
Statistical Lead	Prof Lucinda Billingham, Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham, Birmingham, B15 2TT
Trial Statistician	Richard Fox, CRCTU, University of Birmingham, Birmingham
Health Economics Lead	Dr Tracey Young, The University of Sheffield
Qualitative Research & Nursing Lead	Dr Tony Ryan, The University of Sheffield ☎ +44 (0) 141 222 2062
Patient and Public Advocate	Mrs Jacqui Gath
Senior Trial Manager	Drs Jenny Barnwell (former), and Sarah Bowden, CRCTU, University of Birmingham, Birmingham
Senior Trial Coordinator	Mr Clive Stubbs, CRCTU, University of Birmingham, Birmingham
Trial Coordinator	Dr Ann M Pope, CRCTU, University of Birmingham, Birmingham

Special Trial Office

Cancer Research UK Clinical Trials Unit (CRCTU)
School of Cancer Sciences, University of Birmingham, Birmingham, B15 2TT, UK

Enquiries:

☎ +44 (0) 121 414 6372 🖷 +44 (0) 121 414 2230 ✉ SPECIAL@trials.bham.ac.uk

Patient Registration/Randomisation:

☎ +44 (0) 800 371 969 (9.00 am till 5.00 pm Monday to Friday)

Serious Adverse Event Reporting:

🖷 +44 (0) 121 414 2230 🖷 +44 (0) 121 414 7989

Signature page

The SPECIAL Trial

Protocol version 1.0a, 8 April 2016

Authorisation

The following persons are authorised to sign the final protocol and protocol amendments for the sponsor: Prof Sam H Ahmedzai (Chief Investigator) and for the trial coordinating centre, CRCTU representative: Prof Lucinda Billingham,

This protocol has been approved by:

Name:	Professor Sam H Ahmedzai	Signature:	
Role:	Chief Investigator	Date:	09 / MAY / 2016

Name:	Professor Lucinda Billingham	Signature:	
Role:	CRCTU Representative	Date:	09/05/2016

This protocol describes the SPECIAL Trial and provides information about procedures for patients taking part in the SPECIAL Trial. The protocol should not be used as a guide for treatment of patients not taking part in the SPECIAL Trial.

Trial Synopsis

Protocol Title:	Does early referral of patients with metastatic non-small cell lung cancer to UK specialist palliative care services make a difference in their quality of life or survival?
Protocol Short Name:	Standard or PalliativE Care In Advanced Lung Cancer (SPECIAL)
Chief Investigator:	Prof Sam H Ahmedzai, Professor of Palliative Medicine
Sponsor:	Sheffield Teaching Hospitals NHS Foundation Trust
Trial Design:	Feasibility Stage: Prospective observational, multicentre, trial Randomised Stage: Prospective, two arm, multicentre, randomised, non-blinded, clinical trial
Main Objectives:	
Clinical	• Does early referral benefit patients? • Are there any adverse consequences • Does a formal holistic needs assessment improve specialised palliative care (SPC) • Are carers needs adequately recognised?
Organisational	• What are the current services available? • Can communication between cancer services and palliative care be enhanced? • Can the treatment transition be better managed? • Can the interfaces between hospital/hospice and community-based services be improved? • Do the current pathways for advanced Non-Small Cell Lung Cancer (NSCLC) need to be revised?
Cost-effectiveness	• Current NHS costs of anti-cancer treatment in hospital vs. home for patients receiving SPC • Does early referral for SPC affect the cost or the Quality Adjusted Life Years (QALY)
Main Outcome Measures:	
Feasibility Stage	In summary, to assess: • The number of potentially eligible patients and the proportion consenting to registration in the three or four participating centres, and to evaluate adequate acceptance rate for patient willingness to be randomised • Patient pathway planning and scoping for Randomised Controlled Trial (RCT) adaptation • Feasibility of using quality of life (QoL) and resource use questionnaires • To inform design for large scale RCT
RCT Stage - Primary	To compare the two treatment arms in terms of the two co-primary outcome measures: (i) Global Health Status Score (GHSS) at three months post randomisation (ii) Quality-adjusted survival time (QAS) over six months (also referred to as Quality Adjusted Life Years (QALY))
RCT Stage - Secondary	To evaluate: • Overall survival • Anxiety/depression • Pain • Number of days spent in hospital/hospice • Use of medical interventions in last month of life • Intensive Therapy Unit (ITU) admission • Use of Cardio Pulmonary Resuscitation (CPR) • Quality of life • Cost-effectiveness • Resource use

Patient Population:	Feasibility stage: 60 patients with stage IV NSCLC	
	Randomised stage: 525 patients with stage IV NSCLC	
Main Eligibility Criteria:	Both Stages	
Inclusion	• Any adult (≥18 years) patient with newly diagnosed stage IV NSCLC, with histologically confirmed diagnosis • ECOG performance score 0-3	
Exclusion	• ECOG performance score 4 • Prognosis of ≤2 weeks • Participation in another local competing supportive or palliative care trial • Dementia, delirium or other lack of capacity or communication which renders the patient unable to participate in the trial • Any other psychological disorder which, in the view of the investigator, renders the patient unable to participate • Unable to communicate in English or with the use of an interpreter	
Research Design:		
Feasibility Stage	Observations will consist of the following assessments at specified time points: • SPARC assessment • Montreal Cognitive Assessment (MoCA) (optional) • Quality of life EQ-5D-5L • EORTC QLQ C30, L13 AND BM22 • Hospital Anxiety & Depression Scale (HADS) • Patient diary • Patient costs • Acceptability of randomisation questionnaire • Patient feedback questionnaire Carers will be asked to complete the following questionnaires at specified time points: • Health Survey SF-12 • FAMCARE-2 • Care of the Dying Evaluation (CODE) of experiences of care during end of life care Patients, carers and clinical staff interviews.	
RCT Stage	Arm A	Standard Care
	Arm B1	Early SPC referral
	Arm B2	Early SPC referral & SPARC assessment
Trial Duration:	5 years in total (including accrual and follow-up for both Feasibility Study and RCT)	

Contact Details:

SPECIAL Trial Office
Cancer Research UK Clinical Trials Unit (CRCTU)
School of Cancer Sciences
University of Birmingham
Birmingham, B15 2TT, UK
☎ +44 (0) 121 414 6372 🖷 +44 (0) 121 414 2230 ✉ SPECIAL@trials.bham.ac.uk

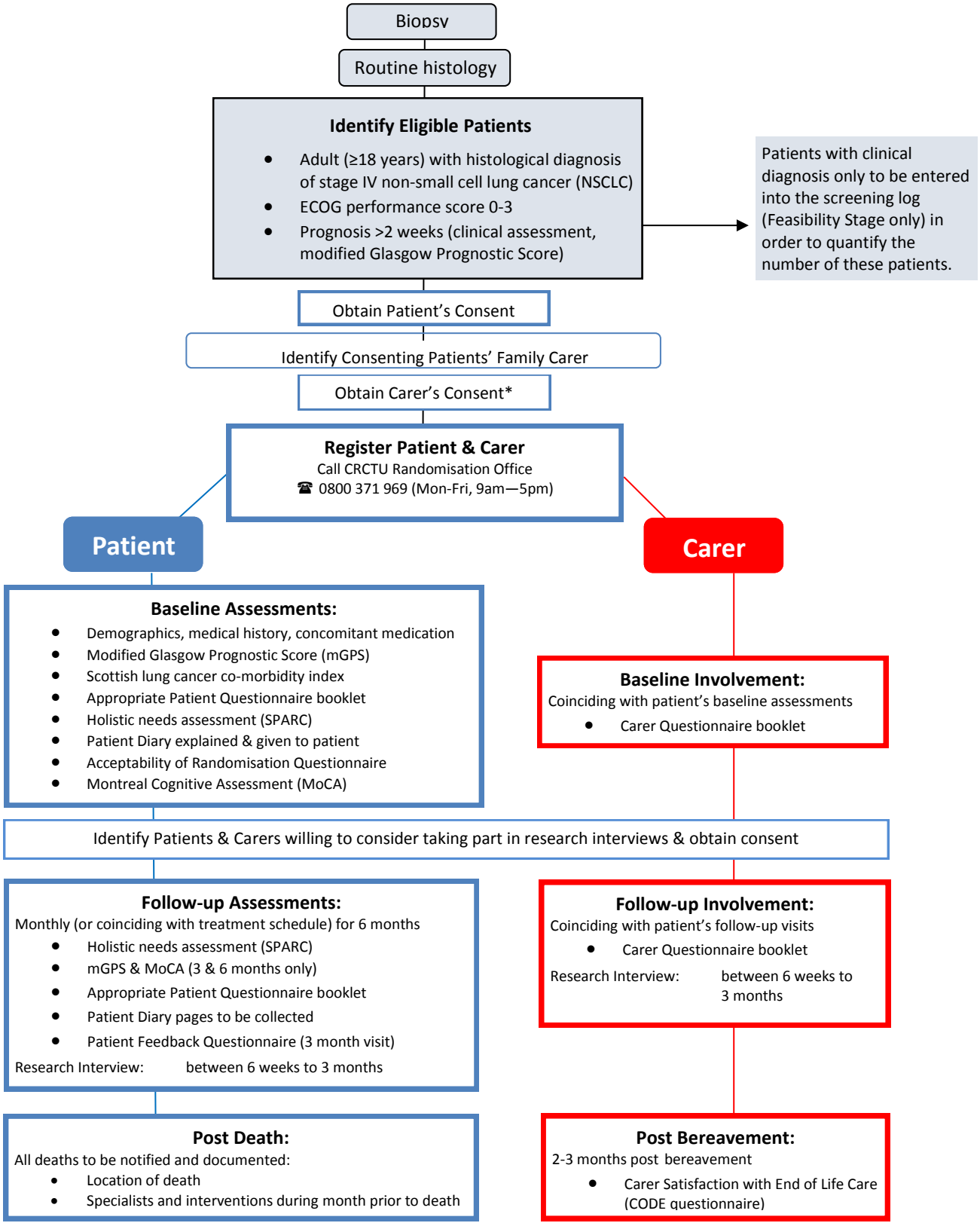

Figure 1: Schematic diagram of feasibility trial

* The patient's involvement in the trial is not dependent upon having a carer willing or able to take part in the trial. A carer's involvement is dependent upon their caring for a patient who is taking part in the trial.

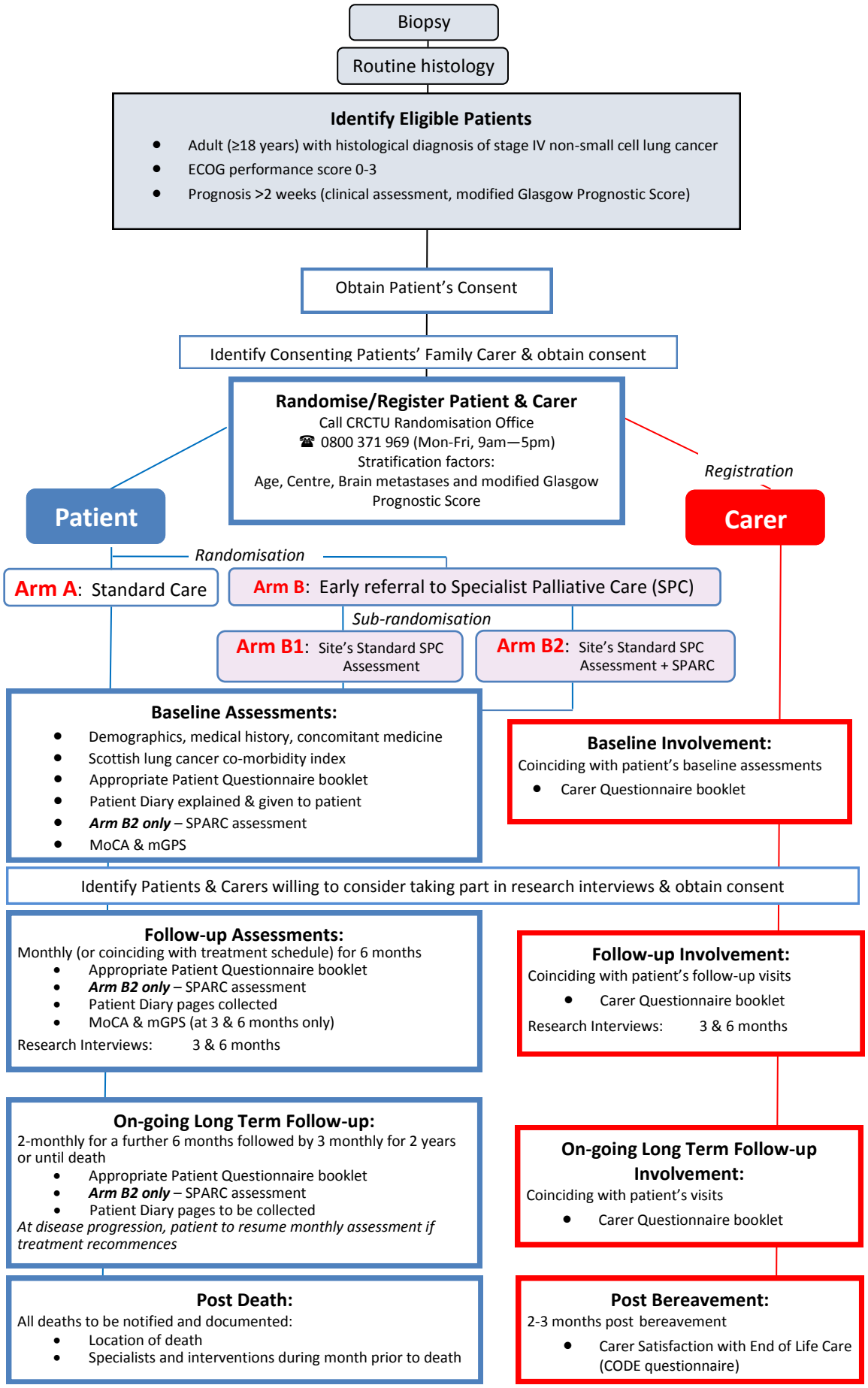

Figure 2: Schematics of Randomised Controlled Stage

* The patient's involvement in the trial is not dependent upon having a carer willing or able to take part in the trial. A carer's involvement is dependent upon their caring for a patient who is taking part in the trial.

Abbreviations

AE	Adverse Event
CI	Confidence Interval
CODE™	Care of the Dying Evaluation
CPR	Cardio-Pulmonary Resuscitation
CRCTU	Cancer Research UK Clinical Trials Unit (at the University of Birmingham)
CRF	Case Report Form
CRP	C-Reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
CV	Curriculum Vitae
DIRUM	Database of Instrument for Resource Use Measurement
DMC	Data Monitoring Committee
ECOG	Eastern Co-operative Oncology Group (performance status)
EORTC	European Organisation for Research and Treatment of Cancer
QLQ-C30	Generic cancer questionnaire
LC-13	Lung Cancer module
BM-22	Bone Metastases module
EQ-5D-5L	Simple, descriptive health status profile questionnaire.
FAMCARE2	A questionnaire tool used to measure family caregiver satisfaction with palliative care services
GCP	Good Clinical Practice
GHSS	Global Health Status Score
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
HNA	Holistic Needs Assessment
HTA (or NIHR HTA)	(National Institute of Health Research) Health Technology Assessment programme
ISF	Investigator Site File
ITU	Intensive Therapy Unit
MDT	Multi-Disciplinary Team
mGPS	Modified Glasgow Prognostic Score
MoCA	Montreal Cognitive Assessment
NIHR	National Institute of Health Research
NHS	National Health Service
NSCLC	Non-Small Cell Lung Cancer
PIS	Patient Information Sheet
QALY	Quality Adjusted Life Year
QAS	Quality Adjusted Survival time
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SD	Standard Deviation
SF-12®	Short Form health survey questionnaires
SPARC	Sheffield Profile for Assessment and Referral for Care
SPC	Specialised Palliative Care
TMG	Trial Management Group
TSC	Trial Steering Committee
WMA	World Medical Association

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1 BACKGROUND AND RATIONALE

1.1 Background

Lung cancer is the most common cancer in the UK, with approximately 25,000 new cases pa, of which 57.5% are men and 42.5% women[1]. Overall lung cancer has one of the worst survival probabilities and it is a major cause of death. There is a heavy burden of symptoms in lung cancer, especially in the advanced stages and the costs of managing these are significant to the National Health Service (NHS).

Non-small cell lung cancer (NSCLC) is the commonest type of lung cancer, and within that, stage IV (inoperable metastatic) NSCLC is the commonest subgroup (32%)[2]. This group also has the worst prognosis (median survival being 6.5 months) and its patients have a poor performance status and high levels of co-morbidity. Fortunately new therapies for managing lung cancer, including NSCLC, are rapidly developing. Whereas 10 years ago it was unusual to offer a patient with inoperable, advanced lung cancer any form of anti-cancer treatment other than palliative radiotherapy, now there are several options available. These include conventional cytotoxic chemotherapy regimens, including powerful but toxic drugs such as cisplatin, gemcitabine, taxanes and pemetrexed. Increasingly there are new biological 'targeted' therapies which generally do not cause such severe toxicities, can be taken orally, but are very expensive. These include erlotinib and other newly developed 'targeted' therapies. Taken collectively, the anti-cancer drugs can cause myelosuppression, constipation or diarrhoea, skin rashes and fatigue. These side effects impact severely on patients who already have pain, respiratory problems and systemic complications of cancer such as fatigue, loss of appetite (anorexia) and weight loss (cachexia).

Cancer patients are increasingly more knowledgeable about the disease and the current and emerging treatment options. Better healthcare information, the internet and media play their part in this. A consequence of this greater level of awareness and knowledge is that some patients want to have more choice and flexibility in accessing services, including complementary therapies, even while they are having anti-cancer treatment. At the same time, it is becoming clearer to patients that there are sometimes large variations in the availability of the supportive and palliative services, just as there are variations in access to the newer more expensive anti-cancer drugs.

As well as scheduling and addressing appropriate anti-cancer treatments, such as chemotherapy or radiotherapy, lung cancer treatment planning needs to take into account many other factors, such as social factors, which should not cause further burden to the patient. One way of ensuring that these needs are met is to refer the patients to specialist palliative care (SPC) services which can identify and deal with these issues. Often SPC allows patients to focus on their important priorities with advance care planning, helping them to know when to pursue or withdraw from anti-cancer treatments and what level of medical interventions they would like at the end of life.

A recent trial carried out in a single hospital in USA by Temel and team (2010)[3] showed that randomly allocating advanced NSCLC patients to standard care or earlier referral to palliative led to improved symptom control and psychological state in those having the palliative care, a reduced usage of invasive interventions including chemotherapy and attempts at resuscitation and, surprisingly, a longer survival. In the USA in general, palliative care is relatively under-developed and nearly always offered very near the end of their life.

Although SPC is much more developed in the UK and theoretically available to all who need it, regardless of nearness to death, in practice it varies because of local resources and also the knowledge and attitudes of cancer teams.

1.2 Trial Rationale

Traditionally palliative care services are largely provided in the UK by local and national independent, charitable organisations. Thus it is important for both the NHS and other providers to undertake research into new models of care in advanced cancer in which anticancer treatment and patient/family directed, supportive and palliative care services are simultaneously provided[4]. The National Cancer Action Team has recently recommended that all patients with cancer should receive Holistic Needs Assessment (HNA) at key points of their trajectory from diagnosis, after primary treatment, through continuing disease into end of life care or into survivorship[5].

As patients with advanced NSCLC often have a high symptom burden at diagnosis this patient group is in particular need of HNA at the point of diagnosis as well as through their ongoing care. Holistic needs include not only physical symptoms but also psychological, social, spiritual, financial issues; problems with independent living; concerns about treatments and side-effects; and information needs. Many services are not yet using any formal means of assessing holistic needs though there a range of HNA tools available with the Distress Thermometer/Concerns Checklist or the Sheffield Profile for Assessment and Referral for Care (SPARC) most commonly used in the UK[6].

The SPECIAL trial has been designed to address the question of whether early referral to palliative care services in the UK achieves the same range of benefits, including quality of life and survival, as those observed in the Temel *et al.* (2010)[3] US study, given that the provision of palliative care is so different in the two countries. It further asks the question whether a formal holistic needs assessment enhances the referral to palliative care.

2 AIMS, OBJECTIVES AND OUTCOME MEASURES

2.1 Aims and Objectives

The overall aim of the proposed research is to answer the question set by National Institute of Health Research Health (NIHR) Health Technology Assessment Programme (HTA), namely *"What is the clinical and cost-effectiveness of introducing specialist palliative care soon after diagnosis on quality of life and end-of-life care among patients with metastatic non-small-cell lung cancer?"*

This is a complex question in a very complex clinical and social scenario and therefore the trial addresses a number of specific research questions and objectives.

The specific objectives are set out here as a series of research questions:

2.1.1 Clinical

- Does earlier referral to SPC in advanced NSCLC bring benefits to patients in terms of better symptom palliation?
- What adverse consequences can arise from earlier referral to SPC, e.g. patient anxiety?
- Does a formal HNA soon after diagnosis improve the way that SPC services can respond to an early referral?
- Are carers' needs being recognised and adequately addressed?
- Is home and community based clinical care for advanced NSCLC patients and families enhanced or adversely affected by early referral to SPC?

- How can clinical lessons learnt from advanced NSCLC be applied elsewhere in cancer and chronic disease management?

2.1.2 Organisational

- What are the current services available to patients with newly diagnosed advanced NSCLC?
- What are the current levels of communication between cancer services and palliative care services and how can these be enhanced?
- How can transitions between anti-cancer treatment and palliative care be better managed?
- How can the interfaces between hospital/hospice/community-based services be improved?
- Do the current pathways for advanced NSCLC need to be revised?
- How can organisational lessons learnt from advanced NSCLC be applied elsewhere in cancer and chronic disease management?

2.1.3 Cost-effectiveness

- What are the current costs to the NHS in advanced NSCLC of anti-cancer treatments in hospital, for patients receiving SPC and for patients being managed at home by primary care?
- Does early referral to SPC lead to a shift in resource usage and costs from hospitals to other sectors and what are the overall savings to the NHS?
- Is early referral to SPC associated with a change in quality-adjusted life years (QALY) and is it cost-effective when compared with usual care?
- How can lessons about cost-effectiveness learnt from advanced NSCLC be applied elsewhere in cancer and chronic disease management?

2.2 Outcome Measures

2.2.1 Feasibility Outcome Measures

- The number of potentially eligible patients, the proportion consenting to registration and the proportion willing to be randomised.
    - Questionnaires collecting data on the number of eligible patients seen will be sent to potential recruiting centres
- Patient pathway planning and scoping for Randomised Controlled Trial (RCT) adaptation.
    - Time to specialist palliation, and the treatments delivered (including dose, where applicable) with intent (palliative or not) delivered will be recorded, and aid in defining the primary research question in the RCT.
    - Health service usage; impact on NHS.
- Feasibility of using quality of life (QoL) and resource use questionnaires.
    - Measured by return and completeness rates.
    - Patient opinion on the number of questionnaires and the time taken to complete will be recorded and used to select the best combination of questionnaires.
- To inform design for large scale RCT.
    - Overall survival will be assessed to validate the final sample size calculation for the RCT

2.2.2 Randomised Controlled Trial Outcome Measures

The primary objective is to compare the two treatment arms in terms of the two co-primary outcome measures:

(i) Global Health Status Score (GHSS) at three months post randomisation, and
(ii) Quality-Adjusted Survival time (QAS) over six months

Secondary outcome measures:

- Overall survival
- Anxiety/depression
- Pain
- Quality of Life
- Cost-effectiveness
- Resource use
    - Days spent in hospital/hospice
    - Admission to an Intensive Therapy Unit (ITU)
    - Use of medical interventions in last month of life (see Appendix 1 for definitions)
    - Use of cardio-pulmonary resuscitation (CPR)
- Compare the arms of SPARC sub-randomisation in the early palliative care group to see if HNA as an intervention is associated with better outcomes

The following will be measured from trial entry at each clinic visit the patient attends until the end of the trial or death:

- Health related quality of life using EQ-5D-5L and European Organisation for Research and Treatment of Cancer (EORTC) QLQ C30/LC13/BM22
- Hospital Anxiety and Depression Scale (HADS)
- HNA using SPARC (see Appendix 2)
- Modified Glasgow Prognostic Score (mGPS) (see Appendix 3)
- Nurse-rated and patient-rated ECOG
- Montreal Cognitive Assessment scale (MoCA) (see Appendix 4)

Additionally carers will receive:

- Short form-12® (SF-12®) health related quality of life questionnaire
- Family caregiver satisfaction of palliative care services questionnaire (FAMCARE-2)
- The CODE™ instrument

The modified Glasgow Prognostic Score will be used primarily as a prognostic and stratification measure at baseline. It will be repeated again at the key primary end-points of three months and six months to test for its utility as a prognostic score later in the disease [7],[8].

In order to control for effects of co-morbidity on patients' physical condition and holistic needs, the Scottish Lung Cancer Co-Morbidity Index (see Appendix 5) will also be used at baseline[9]. Neither this co-morbidity index nor the mGPS are outcome measures but do represent important potential antecedent variables which could influence symptoms and other holistic needs as well as survival, so will be used in the statistical analysis to help explain variations in the patients' outcomes.

3 TRIAL DESIGN

This will be a two stage project consisting of a feasibility stage followed by a RCT.

3.1 Feasibility Study

The first stage is a six month feasibility study in which key elements of the later randomised trial will be tested for relevance, acceptability and viability. There is no intervention in the feasibility study.

At three cancer centres, consecutive, newly diagnosed, stage IV NSCLC patients will be identified at weekly Lung Cancer multi-disciplinary team (MDT) meetings. Eligible patients will be approached to enter the feasibility study at the next clinic visit.

Patients will be reviewed in clinic every month (or alternatively every third week while receiving three-weekly treatment) for six months. Please note the timing of assessments while patients are undergoing treatment will coincide with clinic visits for example: chemotherapy three-weekly; targeted therapy four-weekly; radiotherapy four weekly.

Hospital records will also be checked weekly during the feasibility study recruitment phase to identify any patients coded with a diagnosis of lung cancer but who were not discussed at the Lung Cancer MDT meeting. Recruitment will either continue at each centre until at least 20 patients have entered the study or for a period of three months from opening to recruitment at each site.

3.1.1 Qualitative Research Interviews

Throughout the feasibility study the team will employ a nested approach, using qualitative methods, to assist in understanding the ways in which the trial is experienced by clinicians, managers, commissioners, patients and carers. Gathering these data will enable the trial team to plan more effectively for the RCT (see Section 10 for details). In particular, the nested qualitative trial can seek to explore the following:

- The clarity of trial purpose and the way this is understood by key stakeholders
- Issues relating to process and recruitment
- Attitudinal and cultural barriers which may inhibit trial effectiveness
- Informational needs of patients and carers
- Patient and carer experience of services
- Patient and carer experience/views of randomisation, follow up and assessment
- Unforeseen outcomes

The above list is not exhaustive and other areas relating to feasibility may become apparent during this stage of the trial.

The findings of the analysis of the feasibility study will be presented to the Data Monitoring Committee (DMC) who will make recommendations to the Trial Steering Committee (TSC). There may be minor amendments to the trial protocol which have implications for ethical permissions. Local groups, which will include patients, will also be asked to assess the lessons learnt from the feasibility study. On reviewing the data, the TSC will make recommendations to the NIHR HTA which will decide if the trial can proceed to the RCT stage.

3.2 Randomised Controlled Trial

Stage two will be a non-blinded, prospective randomised controlled interventional trial in which consenting patients with newly diagnosed stage IV NSCLC will be randomly allocated to either standard oncological/respiratory care alone, where the patient could be later referred to palliative care specialists, or early referral to local palliative care services (i.e. within two to four weeks of diagnosis) as well as local standard oncology/respiratory medical treatment and follow-up.

Patients randomised to the early SPC referral arm will be further randomised into two groups where half the patients will be asked to complete a SPARC questionnaire to assess their wider holistic needs.

Patients will be entered into the trial over a three year period and will be followed up for three years or until death.

3.2.1 Qualitative Research Interviews

A second nested trial will take place during the RCT. The RCT will seek to explore both the process and outcome of the intervention as experienced by patients allocated to SPC referral and the clinical staff looking after them. This nested trial will allow for exploration of the intervention above and beyond measurable outcomes. Important areas for exploration are anticipated to be:

- Acceptability of referral to both patients and carers
- The degree of understanding of the role of SPC at the point of referral
- The nature and scope of satisfaction with the intervention of SPC
- Unintended consequences of referral (particularly of a psychological, emotional or social nature)
- Adverse impacts upon home based care

See Section 10 for more information.

4 ELIGIBILITY

4.1 Inclusion Criteria

- Any adult (≥18 years) patient with newly diagnosed stage IV NSCLC, with histologically confirmed diagnosis
- ECOG performance score 0-3 (see Appendix 6)

4.2 Exclusion Criteria

- ECOG performance score 4
- Prognosis of two weeks or less†
- Considered eligible for, or current participation, in another local competing supportive or palliative care trial
- Dementia, delirium or other lack of capacity or communication which renders the patient unable to participate in the trial
- Any other psychological disorder which, in the view of the investigator, renders the patient unable to participate
- Unable to communicate in English or with the use of an interpreter

† An assessment of the patient's mGPS should be performed (see Appendix 3 and Section 7.3). This information will be required for randomisation into the RCT.

5 SCREENING AND CONSENT

5.1 Screening

Patients will be identified for both the feasibility study and RCT from newly diagnosed patients with stage IV (metastatic, inoperable) NSCLC (all histology subtypes) (see Appendix 7). Suitable patients will be identified during MDT meetings and will be approached at a subsequent clinic visit with their respiratory physician or oncologist, where the study and potential inclusion will be discussed.

Patients will be given a copy of the appropriate Patient Information Sheet (PIS) and a follow-up visit will be arranged to allow for patient questions and consent, should the patient so wish. Consent must be obtained within four weeks of diagnosis confirmation by the MDT, and ideally within two weeks. The feasibility study will address, confirm and inform the most appropriate time scales to be carried into the RCT.

The reason for screening failures should be captured on the Patient Screening/Enrolment Log which will be reviewed by the Trial Office in order to monitor uptake and identify issues with eligibility. Please note that for the feasibility study patients with clinical diagnosis only should also be included on the Log, so that the number of these patients can be quantified, these patients will not take part in the feasibility study. An Eligibility Checklist should be completed for each patient.

5.2 Informed Consent

It is the responsibility of the investigator to obtain written informed consent for each patient prior to performing any study or trial related procedure. Appropriate PIS (i.e. one for the feasibility study and one for the RCT) are provided to facilitate this process. Investigators must ensure that they adequately explain the aim, intervention, anticipated benefits and potential hazards of taking part in the study or trial (as appropriate) to the patient. The PIS will inform patients about the qualitative aspect of the research which includes an interview with a Qualitative Researcher from Sheffield.

The investigator should stress that the patient is completely free to refuse to take part or withdraw from the study or trial (as applicable) at any time. The patient should be given ample time (e.g. 24 hours) to read the appropriate PIS and to discuss their participation with others outside of the site research team. The patient must be given an opportunity to ask questions which should be answered to their satisfaction. The right of the patient to refuse to participate in the research without giving a reason must be respected.

If the patient expresses an interest in participating in the trial they will be asked to sign and date the latest version of the appropriate Patient Informed Consent Form. The investigator must then sign and date the form. A copy of the form will be given to the patient, a copy filed in the patient's medical records and the original placed in the Investigator Site File (ISF). Once the patient is entered into the trial the patient's registration number (feasibility study) or trial number (RCT) will be noted on their consent form, and the form filed in the ISF. In addition, if the patient has given explicit consent, a copy of their signed consent form must be sent in the post to the Trial Office for review. Patients agreeing to take part in the optional Qualitative Interviews will be asked to sign an additional consent form documenting this.

Once the patient has given consent the patient's primary carer will be informed about the trial, given the appropriate Carer's Information Sheet (i.e. for the feasibility study or RCT) and given time (e.g. 24 hours) to consider participating. The investigator should stress that the carer is completely free to refuse to take part or withdraw from the study or trial (as applicable) at any time. If they agree to participate they will be asked to sign and date the appropriate Carer's Informed Consent Form. This form should be countersigned by the investigator. The Carer's Informed Consent Form will be copied and filed as detailed above for the Patient Informed Consent Form, with a copy being sent to the Trial Office for in-house review if the carer has consented to this. Carers agreeing to take part in the optional Qualitative Interviews will be asked to sign an additional consent form documenting this.

Details of all of the informed consent discussions should be recorded in the patient's medical records, this should include date of, and information regarding, the initial discussion, the date consent was given, with the name of the trial and the version number of the Patient and Carer Information Sheets and Informed Consent Forms. Throughout the trial participants should have the opportunity to ask questions about the trial and any new information that may be relevant to their continued participation should be shared with them in a timely manner. On occasion it may be necessary to re-consent the participant in which case the process above should be followed and the patient's and or carer's right to withdraw from the trial respected.

Electronic copies of the Patient and Carer Information Sheets and Informed Consent Forms are available from the Trial Office and should be printed or photocopied onto the headed paper of the local institution.

6 TRIAL ENTRY

For both the feasibility study and the RCT written informed consent must be obtained prior to a patient's entry into the trial and recorded on the appropriate Informed Consent Form. An Eligibility Checklist should also be completed prior to registration or randomisation, as appropriate.

The name of the investigator directly responsible for the patient's care will be requested at registration/randomisation. Investigators must be registered with the Trial Office before they are permitted to register patients into the trial (see Section 17.1).

6.1 Feasibility Study - Registration

To register a patient into the trial complete the Registration Form and call Cancer Research UK Clinical Trials Unit (CRCTU) at the University of Birmingham on the number below:

☎ 0800 371 969

9.00 am till 5.00 pm Monday to Friday

The CRCTU Randomisation Office will be closed on Bank Holidays and University of Birmingham closed days. Sites will be informed of forthcoming closures in advance.

The following information should be provided:

- Name of site and investigator
- Patient's initials
- Date of birth
- Confirmation of eligibility
- Date of patient consent
- Whether the patient has consented to the optional aspects of the study. If the patient has consented to the Qualitative Interviews their full name and telephone number will be collected
- Details of carer consent including their initial's, whether they have consented to the qualitative interviews. If the patient has consented to the Qualitative Interviews their full name and telephone number will be collected)

The CRCTU will assign each feasibility study patient with a unique registration number that must be noted on the Registration Form, Informed Consent Form, as well as all subsequent Case Report Forms (CRFs). The completed Registration Form, Eligibility Checklist and a copy of the Informed Consent Form should to be sent to the Trial Office.

With the patient's prior consent their General Practitioner (GP) should also be informed that they are taking part in the trial. A feasibility study GP Letter is provided electronically for this purpose.

6.2 Randomised Controlled Trial - Randomisation

To randomise a patient into the RCT complete a Randomisation Form and call the CRCTU using the number below.

☎ 0800 371 969

9.00 am till 5.00 pm Monday to Friday

The CRCTU Randomisation Office will be closed on Bank Holidays and University of Birmingham closed days. Sites will be informed of forthcoming closures in advance.

The following information should be provided:

- Name of site and investigator
- Patient's initials
- Date of birth
- Confirmation of eligibility
- Date of patient consent
- Whether the patient has consented to the optional aspects of the study. If the patient has consented to the Qualitative Interviews their full name and telephone number will be collected)
- Details of carer consent including their initial's, whether they have consented to the qualitative interviews. If the patient has consented to the Qualitative Interviews their full name and telephone number will be collected)

Patients will be randomised using a computerised minimisation technique. Stratification variables include:

- Site
- Age (<50 years, ≥50 year)
- The presence or absence of brain metastases
- mGPS (scores 0, 1 or 2)

Patients will be randomised one-to-one to the following arms:

- Arm A: Standard Care
- Arm B: Early referral to SPC

Patients allocated to Arm B will undergo a second randomisation (1:1) to:

- Arm B1: Sites Standard SPC
- Arm B2: Sites Standard SPC + SPARC

Patients will be issued with a unique Trial Number which should be used on all correspondence with the Trial Office.

The completed Randomisation Form, Eligibility Checklist and a copy of the Informed Consent Form should be sent to the Trial Office.

With the patient's prior consent their GP should also be informed that they are taking part in the trial. A RCT GP Letter is provided electronically for this purpose.

7 ASSESSMENTS AND DELIVERY OF INTERVENTION

SPC will be delivered variably according to local service configuration. In some sites the service will be run within the NHS; in others it will be supplied from a local independent charitable hospice service. In essence, all SPC services are supplied by a combination of specialists trained in palliative medicine and nursing, and other clinical and allied health professionals who may have varying degrees of specialisation. Both stages of the study will describe and characterise which elements of these are applied, in what order and to what degree.

Sites in which all patients are referred early, i.e. within two to four weeks, to SPC will not be eligible to participate in this trial. In addition, in order to be able to participate as a site in the RCT trial, the SPC input should be offered by a palliative medicine doctor and nurse.

Health technologies which are used during the process of cancer care and symptom management for trial patients will also captured in both stages of the trial. These include:

- Radiotherapy including date of last dose in relation to time of death
- Cytotoxic chemotherapy including date of last dose in relation to time of death
- Targeted biological therapy including date of last dose in relation to time of death
- Other interventional health technologies (see Appendix 1 for details)
- Use of interventions around the end of life (see Appendix 1 for details)

7.1 Feasibility Study

Patients in the feasibility study will not receive any intervention and should be treated in accordance with the sites standard care pathway. The SPARC HNA tool will be piloted.

7.1.1 Feasibility Study Assessment Schedule

The patient visit schedule is summarised in Table 1.

Table 1: Patient Visit Schedule - Feasibility

Assessment	Screening/ Baseline	Follow-up Period	After Death
		Monthly, or to coincide with treatment schedule for 6 months	
Eligibility check	X		
ECOG Performance Status	X	X	
Patient's Informed Consent	X		
Carer's Informed Consent (once patient has consented)	X		
Patient Registration	X		
Demography, medical history	X		
Concomitant medication	X	X	
Modified Glasgow Prognosis Score (mGPS)	X	X*	
Scottish lung cancer co-morbidity index	X		
Patient Questionnaire Booklet (time-point specific)	X	X	
Sheffield Profile for Assessment and Referral for Care (SPARC) **ALL PATIENTS**	X	X	
Patient Acceptability of Randomisation Questionnaire	X		
Patient diary collected		X	
Montreal Cognitive Assessment scale (MoCA) (consenting participants only)	X	X*	
Carer Questionnaire Booklet	X	X	
Qualitative Interviews (consenting participants only)		X‡	
Patient Feedback Questionnaire		X†	
Recording of resource use		X	
Treatment details and measurement of response (as per local practice)		X	
Relapse/Progression		X	
Notification of death, location of death			X
Clinical Records Review: Interventions and Specialists seen during month leading up to death			X
CODE™ (consenting participating carers only; 2-3 months post-bereavement)			X

Notes

* mGPS & MoCA will be measured at 3 and 6 months during follow-up (see Section 7.3) ‡ Performed between 6 weeks and 3 months follow-up † Completed at the 3 month follow-up only

7.1.1.1 Baseline Assessments

Baseline assessments must be within two to four weeks of the patient being diagnosed and as soon as possible after feasibility study entry. The following assessments should be performed and will be captured on the CRF:

- mGPS (see Appendix 3 and Section 7.3)
- Demographics
- Medical history
- Scottish Lung Cancer Co-morbidity Index Score (see Appendix 5, for list of co-morbidities and scores)
- Current concomitant medications
- SPARC (see Appendix 2)
- ECOG (as per eligibility assessment; see Section 4.1 and Appendix 6)
- MoCA (see Appendix 4) only for those patients who consent to this optional measure of cognitive function

The patient should be asked to complete the following during the clinic appointment:

- Acceptability of Randomisation Questionnaire
- Baseline Patient Questionnaire Booklet

The carer should also be given the Carer Questionnaire Booklet if they have agreed to participate in the study.

Prior to completing the questionnaire a member of the site research team should discuss the questionnaires with the patient, and if applicable the carer, and answer any questions they may have. Once the questionnaires have been completed by the patient/carer the site research team should check to make sure that all of the questions have been completed and that, in particular, the date the questionnaires are completed and the patient's registration number has been accurately recorded.

The patient should also be given the Patient Diary (this will have sufficient diary sheets to last for six months). Completion of the diary should be explained to them and they should be asked to return completed sheets at their next appointment.

7.1.1.2 Follow-up Assessments

The patient should be followed-up at least once per month for six months. Patients being treated every third week (for example those receiving chemotherapy) will be seen every three weeks while on treatment. The patient's visits should be organised to correspond with their treatment visits where possible.

The following should be assessed at each visit (be that three weekly of four weekly):

- Disease status
- ECOG status (see Appendix 6)
- Concomitant medication

The patient should be asked to complete the following during the clinic appointment:

- Appropriate Follow-up Patient Questionnaire Booklet
- SPARC (see Appendix 2)

In addition to the above, at the **three and six month assessments**, the following must also be assessed:

- mGPS (see Appendix 3 and Section 7.3)
- MoCA (see Appendix 4) only for those patients who consent to this optional measure of cognitive function

The patient should be asked to complete the Patient Feedback Questionnaire at their 3 month follow-up assessment

The carer should be asked to complete the Carer Questionnaire Booklet. If the trial registered carer is not accompanying the patient, please send the carer questionnaire booklet home with patient so that the carer may complete and return it to the site research team at the next follow-up clinic visit.

Completed questionnaire booklets and forms should be returned to the Trial Office with the patient's completed diary sheets.

Please note: The patient may require a new Patient Diary after their six month assessment visit.
A larger format version of the diary is available (A4, larger font size) for patients who require large print.

The following information will be collected on the CRF at all follow-up visits:

- Disease status
- ECOG status (see Appendix 6)
- Concomitant medication
- Treatment details
- Response to treatment (determined as per local practice)
- Hospital admissions, including duration and reason for admission
- Details of relapse/progression
- Details of patient referral to the SPC team
- Resource use (see Appendix 1 for list of medical interventions)

7.1.2 Qualitative Research Interviews

Qualitative interviews will be performed for consenting patients at some point between six weeks and three months following registration. Patients and carers chosen for interview will be contacted directly by telephone by the Qualitative Research Team based at Sheffield to arrange a suitable time for the interview. The participant will be given the option of having a telephone interview, being interviewed at home, or being interviewed at the site, which ever option is most convenient for them.

Interviews will also be held with clinical staff, these will be organised by the Qualitative Research Team based at Sheffield on a mutually convenient date.

See Section 10 for more information.

7.1.3 Patient Death

As soon as possible following notification that a patient has died a Death Form should be completed and returned to the Trial Office. Every effort should be made to obtain the date and cause of death and the location of the patient at the time of death.

A clinical records review will be performed to determine what interventions the patient received and what specialists were seen during the month leading up to death. This data will be captured on the CRF.

The site's research team will contact consenting carers to ask them to complete the CODE™ questionnaire approximately three months post-bereavement. The carer will be instructed to return questionnaire to the Trial Office using the pre-paid envelope provided.

7.2 Randomised Controlled Trial

Patients entered into the RCT will be randomised to one of three groups:

- Arm A: Standard Care
- Arm B1: Early referral to SPC using Sites Standard SPC
- Arm B2: Early referral to SPC using Sites Standard SPC + SPARC

7.2.1 Description of Arms

7.2.1.1 Standard Care

Patients randomised to Standard Care will not receive any intervention and should be treated in accordance with the sites standard care pathway.

7.2.1.2 Early Referral to Special Palliative Care using Sites Standard Procedure

Patients randomised to early referral should immediately be referred to local SPC services as well as receiving standard oncology and/or respiratory medicine and follow-up.

Patients in Arm B1 should receive SPC in accordance with the sites usual process.

7.2.1.3 Early Referral to Special Palliative Care Using Sites Standard Procedure and Sheffield Profile for Assessment and Referral for Care (SPARC)

Patients in Arm B2 will receive the same intervention as those in Arm B1 and in addition should receive a HNA using SPARC (see Appendix 2) at the time points specified in the patient visit schedule. A copy of the patient's first SPARC form should be enclosed with the referral letter (see Section Appendix 2). The original form should be sent to the Trial Office and a copy filed in the ISF. Ideally the SPARC assessment form should be completed before any of the other trial questionnaires.

7.2.2 Randomised Controlled Trial Assessment Schedule

The patient visit schedule is summarised in Table 2.

Table 2: Patient Visit Schedule – Randomised Controlled Trial

Assessment	Screening/ Baseline	Follow-up Period	On-going Follow-up	After Death
		Monthly, or to coincide with treatment schedule for 6 months	2-monthly for 6 months then 3 monthly until death or further two years	
Eligibility check	X			
ECOG Performance Status	X	X	X	
Patient's Informed Consent	X			
Carer's Informed Consent (once patient has consented)	X			
Modified Glasgow Prognosis Score (mGPS)	X	X*		
Patient Randomisation	X			
Demography, medical history	X			
Concomitant medication	X	X	X	
Scottish lung cancer co-morbidity index	X			
Patient Questionnaire Booklet (randomisation and time-point specific)	X	X	X	
Patient diary collected		X	X	
Sheffield Profile for Assessment and Referral for Care (SPARC) **ONLY IF RANDOMISED TO ARM B2**†	X	X	X	
Montreal Cognitive Assessment scale (MoCA) (consenting participants only)	X	X*		
Carer Questionnaire Booklet	X	X	X	
Qualitative Interviews (consenting participants only)		X‡		
Recording of resource use		X	X	
Treatment details and measurement of response (as per local practice)		X	X	
Relapse/Progression		X	X	
Notification of death, location of death				X
Clinical Records Review: Interventions and Specialists seen during month leading up to death				X
CODE™ (consenting participating carers only; 2-3 months post-bereavement)				X

Notes

* mGPS & MoCA will be measured at 3 and 6 months during follow-up (see Section 7.3)

‡ Performed at approximately 3 and 6 months from trial entry

† A copy of SPARC should be provided to the patient's palliative care team after each assessment, the original should be returned to the Trial Office and a copy retained in the ISF

7.2.2.1 Baseline Assessments

Baseline assessments must be within two to four weeks of the patient being diagnosed and as soon as possible after entry into the trial. The following assessments should be performed and will be captured on the Baseline Form:

- mGPS* (see Appendix 3 and Section 7.3)
- Demographics
- Medical history
- Scottish Lung Cancer Co-morbidity Index Score (see Appendix 5, for list of co-morbidities and scores)
- Current concomitant medications
- ECOG (as per eligibility assessment; see section 4.1 and Appendix 6)
- An assessment of cognitive function should also be made using MoCA (see Appendix 4) for those patients who consented to the use of this optional measure

* **Please note:** mGPS must be performed prior to randomisation, as this is required to assess eligibility.

The patient should be asked to complete the:

- SPARC questionnaire (if randomised to Arm B2 only)†
- Baseline Patient Questionnaire Booklet

† **Please note:** A copy of SPARC should be sent to the patient's palliative care team with the referral letter, the original should be returned to the Trial Office and a copy retained in the ISF

The carer should also be given the Carer Questionnaire Booklet (if they have agreed to participate).

Prior to completing the questionnaire a member of the site research team should discuss the questionnaires with the patient, and if applicable the carer, and answer any questions they may have. Once the questionnaires have been completed by the patient/carer the site research team should check to make sure that all of the questions have been completed and that in particular that the date the questionnaires are completed has been accurately recorded.

The patient should also be given the Patient Diary (this will have sufficient diary sheets to last for 6 months). Completion of the diary should be explained to them and they should be asked to return completed sheets at their next appointment. A larger format version of the diary is available (A4, larger font size) for patients who require large print. Completed Patient Diary sheets will be collected at the next clinic visit.

7.2.2.2 Follow-up Assessments

The patient should be followed up at least once per month for six months. Patients being treated every third week (for example those receiving chemotherapy) will be seen every three weeks while on treatment. The patient's visits should be organised to correspond with their treatment visits where possible.

The following should be assessed at each visit (be that three weekly of four weekly):

- Disease status
- ECOG status (see Appendix 6)

- Concomitant medication review

The patient should be asked to complete the following during the clinic appointment:

- Appropriate Follow-up Patient Questionnaire Booklet
- SPARC questionnaire (only if randomised to Arm B2) †

† **Please note:** A copy of SPARC should be provided to the patient's palliative care team after each assessment, the original should be returned to the Trial Office and a copy retained in the ISF

In addition to the above, **at three and six month assessments**, the following must also be assessed:

- mGPS (see Appendix 3 and Section 7.3)
- MoCA (see Appendix 4)

The carer should be asked to complete the Carer Questionnaire Booklet *.

* **Please note:** If the trial registered carer is not accompanying the patient, please send the carer questionnaire booklet home with patient so that the carer may complete and return it to the site research team at the next follow-up clinic visit.

Completed questionnaires booklets and forms should be returned to the Trial Office with the patient's completed diary sheets.

Please note: The patient may require a new Patient Diary after their six month assessment visit.

The following information will be collected on the CRF at all follow-up visits:

- Treatment details
- Response to treatment (as per local practice)
- Details of relapse/progression
- Hospital admissions, including duration and reason for admission
- Details of patient referral to the SPC team
- Resource use (see Appendix 1 for list of medical interventions)

7.2.2.3 Long Term Follow-up Assessments

After the six month follow-up visit RCT patients will be followed up every two months for a further six months. Thereafter patients will be followed up three monthly until death or for a maximum of two years.

The patient should be asked to complete:

- SPARC questionnaire (only if randomised to Arm B2) †
- Long Term Follow-up Patient Questionnaire Booklet

† **Please note:** A copy of SPARC should be provided to the patient's palliative care team after each assessment, the original should be returned to the Trial Office and a copy retained in the ISF

The carer should be asked to complete the Carer Questionnaire Booklet*.

Completed questionnaires should be returned to the Trial Office with the patient's completed diary sheets.

***Please note:** If the trial registered carer is not accompanying the patient, please send the carer questionnaire booklet home with patient so that the carer may complete and return it to the site research team at the next follow-up clinic visit.

Survival data, including information on relapse and progression and on-going resource use will be collected on the CRF. If the patient receives additional treatment for relapse/progression they should resume monthly assessments (see Section 7.2.2.2).

7.2.3 Qualitative Research Interviews

Qualitative interviews will be performed for selected consenting patients and carers at approximately three and six months after randomisation. Patients/carers chosen for interview will be contacted directly by telephone by the Qualitative Research Team based at Sheffield to arrange a suitable time for the interview. The patient/carer will be given the option of having a telephone interview, being interviewed at home, or being interviewed at the site, which ever option is most convenient for them.

Interviews will also be held with clinical staff, these will be organised by the Qualitative Research Team based at Sheffield on a mutually convenient date.

See Section 10 for more information.

7.2.4 Patient Death

As soon as possible following notification that a patient has died a Death Form should be completed and returned to the Trial Office. Every effort should be made to obtain the date and cause of death and the location of the patient at the time of death.

A clinical records review will be performed to determine what medical interventions (see Appendix 1) the patient received and what specialists were seen during the month leading up to death. This data will be captured on the CRF.

The site's research team will contact consenting carers approximately three months post-bereavement to ask whether they would complete the CODE™ questionnaire. The carer will be instructed to return questionnaire to the Trial Office using the pre-paid envelope provided.

7.3 Clinical Tests

The only mandated clinical tests are:

- Albumin
- C-reactive protein (CRP)

These are to calculate mGPS for the patients at baseline and at the three and six month follow-up assessment (see Appendix 3).

7.4 Concomitant Medication

Details of all medications including planned and already commenced treatments will be collected at baseline and any changes to medication and treatments recorded during follow-up ad collected on the CRF.

No restrictions are placed on medications; this includes (using the cancer treatment example) challenges and re-challenges for chemotherapy, and all instances of radiotherapy administered to the patient throughout the duration of the trial; including all symptom control medications.

8 PATIENT REPORTED OUTCOMES

Patients will be asked to complete a number of questionnaire at different time points (as detailed in Table 1 and 2) that will document factors that may influence:

- Decision to continue to the RCT (feasibility only)
- Acceptability of the questionnaires (feasibility only)
- Psychological adjustment
- Quality of life
- Holistic needs
- Cognitive status
- Healthcare resource usage

The questionnaires are briefly described in Appendix 8.

Questionnaires should be completed in clinic and returned to the Trial Office by the site research team.

9 CARER REPORTED OUTCOMES

Dependent upon consent, patients' primary informal carers will be asked to complete carer-specific questionnaire booklets as detailed in Tables 1 and 2. A brief description of the questionnaires and booklet contents can be found in Appendix 9.

The questionnaires will be given to carers at baseline by the research staff in the clinic, and collected back on completion and returned to the Trial Office. If the carer wishes to complete the form at home, they may return the completed form directly to the Trial Office in the pre-paid envelope provided.

10 QUALITATIVE INTERVIEWS WITH PATIENTS AND CARERS

During the feasibility study a nested qualitative trial will be used to assist in the appropriate development of the RCT protocol (see Section 3.1.1). Patients and carers who choose to participate will be approached directly by the by the Qualitative Researchers in Sheffield as described in Section 7.1.2.

A mixture of face-to-face and telephone interviews will be undertaken. Face-to-face interviews will be used where possible, but in recognition that it may sometimes be difficult to organise these a telephone interview will be arranged if necessary. Interviews will be based upon a semi-structured approach. A total of 15 interviews (five patients, five carers and five clinical staff) at each site will be undertaken (n=45). Patients and carers will be interviewed between six weeks and three months from registration, clinician interviews will be carried out throughout the feasibility study.

A second nested trial will take place during the RCT (see Section 3.2.1). During the RCT, semi-structured face-to-face or telephone interviews will be undertaken with 45-50 patients and their carers where appropriate at approximately three and six months post randomisation. These interviews will be audio recorded. Four centres which form part of the RCT will be purposively sampled as the focus for the qualitative study; these four will include two rural and two urban settings. Patient/carer age (<50, 50+) and gender will be used as criteria for selection and at least three participants in each site will be recruited to each sub-group (12 per site selected for this part of the study n=48). Interviews will also be performed with clinical staff. In each of these four sites four clinical staff from each will be interviewed once during the study between three and four months after recruitment has begun, either face-to-face or over the telephone. These will be purposively sampled to ensure that medical and nursing staff are included. These interviews will be audio recorded.

Patients and carers will be sampled as above and approached by the site research team with a view to taking part in a qualitative interview. Those who express an interest will be provided with an information sheet and consented as detailed in Section 5.2. If appropriate a convenient appointment will be arranged by the Qualitative Researchers in Sheffield as described in Section 7.2.3.

The nature of the interview will be determined at the conclusion of the feasibility study although it is anticipated that interviews will initially be based on the topic guide included in Appendix 10.

Interviews will be transcribed verbatim. These data will be analysed using Framework Analysis[10] of which there are six stages:

1. Familiarisation: reading transcripts and fieldwork notes.
2. Identifying recurring themes: beginning to develop a working framework of the important themes and patterns within the data.
3. Indexing: applying a numerical code to each theme and using this to label transcripts. It may also be the case that amendments to the original framework are made at this stage.
4. Pilot charting: creating a chart/matrix using the framework and initial transcript data.
5. Charting: complete a matrix using full data set.
6. Interpreting: making use of the completed framework to understand and interpret patient and care experiences of early SPC referral.

11 HEALTH ECONOMICS

The feasibility study will measure the feasibility of collecting a range of data on resource usage in the three cohorts. The RCT will apply the acceptable measures at three to four weekly intervals.

11.1 Feasibility Study

We will use the feasibility study to pilot the Patient's Costs questionnaire which will be administered to patients and their carers. We have used the DIRUM database (Database of Instruments for Resource Use Measurement) and existing resource questionnaires to design a draft resource use questionnaire and this will be piloted for acceptability in the feasibility study[11]. As part of the piloting we will test the acceptable recall period for patients and the frequency of administration. Initially, the questionnaire will be administered at every assessment point and the change in resource use over time will be reviewed.

11.2 Randomised Controlled Trial

The primary analysis will present costs per QALY from an NHS and social care perspective in accordance with NICE guidelines[12]. Resource use on inpatient and out-patient hospital attendances, treatments and procedures will be collected from routine patient records. GP visits (home and surgery), district nurse visits and other specialist care received in primary care will be collected via the resource use questionnaire developed in the feasibility study. The questionnaire will also collect information on carers' time and loss of productivity which will be included in secondary analysis of costs per QALY to the NHS and society. Unit costs will be derived from appropriate national sources and will include; NHS reference costs, Personal Social Service Research Unit costs and the Office of National Statistics[13],[14],[15].

QALYs over six months will be calculated using the area under the curve formed by the longitudinal measures of the utility scores from EQ-5D-5L within six months, with all values from death onwards represented by '0' and imputation used to complete the curves where data are missing.

It is possible to derive utilities for the measurement of QALYs from both the EORTC [16] and the EQ-5D-5L. We will present costs per QALY results for the main analysis for EQ-5D-5L in accordance with NICE guidelines and present cost per QALY results using EORTC in sensitivity analysis. Results will be presented as incremental costs per QALY and will adjust for censoring using Lin's methods[17] for costs and QALY data, results will be presented in the net-benefit framework and will allow for uncertainty using bootstrapping and probabilistic sensitivity analysis.

12 PROTOCOL DEVIATIONS

The details of the protocol deviation (date, reason and type of deviation) should be clearly documented in the source data. A Deviation Form should be completed to notify the Trial Office of the deviation.

13 WITHDRAWAL OF CONSENT

Patients and/ or Carers may withdraw consent at any time during the trial.

The details of withdrawal (i.e. date, reason and type of withdrawal) should be clearly documented in the source data. A Patient/Carer Withdrawal Form should be completed to notify the Trial Office of the patient's or carer's withdrawal.

13.1 Patient

Three broad categories of withdrawal of consent are defined for the patient:

- Patient would like to withdraw from the feasibility study or the RCT (as applicable), but is willing to be followed up according to the trial schedule for survival analysis and resource usage (i.e. the patient has agreed that follow-up data can be collected and used in the trial analysis)
- Patient does not wish to attend the feasibility study or the RCT follow-up visits but is willing to be followed up at standard clinic visits for survival analysis (i.e. the patient has agreed that follow-up data can be collected at standard clinic visits and used in the trial analysis)*
- Patient is not willing to be followed up for protocol defined purposes at any further visits (i.e. the patient has agreed that any data collected prior to the withdrawal of consent can be used in the trial analysis)

* All patient data will be included in the analysis on an intent-to-treat basis.

13.2 Carer

The carer is free to stop completing the Carer Questionnaires at any time. Any data collected up until the point of withdrawal will be used in the analysis.

The withdrawal of the carer will not affect the patient's participation in the trial.

14 ADVERSE EVENT REPORTING

Adverse Events (AEs) are not expected in this study however the collection and reporting of AEs will be in accordance with the Research Governance Framework for Health and Social Care and the requirements of the National Research Ethics Service.

Definitions of different types of AE are listed in Appendix 11.

14.1 Reporting Requirements

14.1.1 Serious Adverse Events

Investigators should report AEs that meet the definition of an SAE (see Appendix 11) and that are thought to be attributable to the SPECIAL protocol (i.e. related) and are thought to be unexpected only. Please note the SPECIAL protocol does not determine patient treatment for their cancer and as such events linked to cancer treatment SHOULD NOT be reported as SAEs however details of all hospital admissions will be collected on the CRF to inform the health economic analysis.

14.1.2 Expected Serious Adverse Events

No SAEs are expected to occur as a result of participation in the SPECIAL trial.

14.1.3 Reporting Period

Details of all SAEs will be documented and reported from the date of entry until the six month follow up time point.

14.2 Reporting Procedure

14.2.1 Serious Adverse Events

For more detailed instructions on SAE reporting refer to the SAE Form Completion Guidelines contained in the ISF.

AEs defined as serious (and which are related and thought to be unexpected) require reporting as an SAE should be reported on an SAE Form. When completing the form, the investigator will be asked to define the causality and the severity of the AE which should be documented using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (see Appendix 11).

On becoming aware that a patient has experienced an SAE, the investigator (or delegate) must complete, date and sign an SAE Form. The form should be faxed together with a SAE Fax Cover Sheet to the Trial Office using one of the numbers listed below as soon as possible and no later than 24 hours after first becoming aware of the event:

To report an SAE, fax the SAE Form with an SAE Fax Cover Sheet to:

0121 414 2230 or 0121 414 7989

On receipt the Trial Office will allocate each SAE a unique reference number. This number will be transcribed onto the SAE Fax Cover Sheet which will then be faxed back to the site as proof of receipt. If confirmation of receipt is not received within 1 working day please contact the Trial Office. The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE. The SAE Fax Cover Sheet completed by the Trial Office should be filed with the SAE Form in the ISF.

For SAE Forms completed by someone other than the investigator the investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments. The form should then be returned to the Trial Office in the post and a copy kept in the ISF.

Investigators should also report SAEs to their own Trust in accordance with local practice.

14.2.2 Provision of Follow-up Information

Patients should be followed up until resolution or stabilisation of the event. Follow-up information should be provided on a new SAE Form (refer to the SAE Form Completion Guidelines for further information).

14.2.3 Trial Office

On receipt of an SAE Form seriousness and causality will be determined independently by a Clinical Coordinator. An SAE judged by the investigator or Clinical Coordinator to have a reasonable causal relationship with the trial protocol will be regarded as a related SAE. The Clinical Coordinator will also assess all related SAEs for expectedness. If the event is unexpected (i.e. is not defined in the protocol as an expected event) it will be classified as an unexpected and related SAE.

14.3 Reporting to the Research Ethics Committee

14.3.1 Unexpected and Related Serious Adverse Events

The Trial Office will report all events categorised as Unexpected and Related SAEs to the Research Ethics Committee (REC) within 15 days.

14.4 Reporting to the Principal Investigators

The Trial Office will report all Unexpected and Related SAEs to Principal Investigators.

15 DATA HANDLING AND RECORD KEEPING

15.1 Data Collection

CRFs must be completed, signed/dated and returned to the Trial Office by the investigator or an authorised member of the site research team (as delegated on the Site Signature and Delegation Log) within the specified time frame. The exception to this is the Withdrawal Form which must be co-signed by the investigator. Entries on the CRF should be made in ballpoint pen, in blue or black ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change.

Data reported on each form should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the form. All missing and ambiguous data will be queried. All sections are to be completed before returning.

Quality of Life, health economic and patient/carer reported data will be completed on paper forms by the participants and will be regarded as source data for the purposes of this trial. These questionnaires will be returned to the Trial Office and a copy will not be retained at site. Please note this does not include the SPARC.

In all cases it remains the responsibility of the investigator to ensure that the CRF has been completed correctly and that the data are accurate.

The completed originals should be sent to the Trial Office and a copy filed in the ISF. Trial forms may be amended by the Trial Office, as appropriate, throughout the duration of the trial. Whilst this will not constitute a protocol amendment, new versions of the form must be implemented by participating sites immediately on receipt.

The investigator should supply the Trial Office with any required source data (anonymised) on request.

16 ARCHIVING

It is the responsibility of the Principal Investigator to ensure that all essential trial documentation and source records (e.g. signed Informed Consent Forms, ISF, patients' medical records, copies of CRFs, etc.) at their site are securely retained for at least 5 years after the end of the trial. Do not destroy any documents without prior approval from the CRCTU Document Storage Manager.

17 QUALITY MANAGEMENT

The trial is being conducted under the auspices of the CRCTU according to the current guidelines for Good Clinical Practice (GCP). Participating sites will be monitored by CRCTU staff to confirm compliance with the protocol and the protection of patients' rights as detailed in the Declaration of Helsinki (Appendix 12).

17.1 Site Set-up and Initiation

All sites will be required to sign a Clinical Trial Site Agreement prior to participation. In addition all participating investigators will be asked to sign the necessary agreements including an Investigator Registration Form and supply a current *Curriculum Vitae* (CV) to the Trial Office. All members of the site research team will also be required to sign a Site Staff Registration Form and the Site Signature and Delegation Log, which should be returned to the Trial Office. Prior to commencing recruitment all sites will undergo a process of initiation. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, AE, and collection and reporting of data and record keeping.

Sites will be provided with an ISF containing essential documentation, instructions, and other documentation required for the conduct of the trial. The Trial Office must be informed immediately of any change in the site research team.

17.2 On-site Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the SPECIAL Quality Management Plan. Additional on-site monitoring visits may be triggered, for example by poor CRF return, poor data quality, excessive number of patient withdrawals or deviations. If a monitoring visit is required the Trial Office will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the SPECIAL trial staff access to source documents as requested.

17.3 Central Monitoring

Where patients and carers have given explicit consent sites are requested to send in copies of signed Informed Consent Forms for in-house review.

Trials staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Trials staff will check incoming CRF for compliance with the protocol, data consistency, missing data and timing. Sites will be sent Data Clarification Forms requesting missing data or clarification of inconsistencies or discrepancies.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to the Trial Management Group (TMG) and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol to the REC.

17.4 Audit and Inspection

The investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents.

Sites are also requested to notify the Trial Office of any audits or inspections.

17.5 Notification of Serious Breaches

The sponsor of the trial is responsible for notifying the REC in writing of any serious breach of:

- The conditions and principles of GCP in connection with that trial, or
- The protocol relating to that trial, within seven days of becoming aware of that breach.

For the purposes of this regulation, a “serious breach” is a breach which is likely to effect to a significant degree:

- The safety or physical or mental integrity of the subjects of the trial, or
- The scientific value of the trial,

Sites are therefore requested to notify the Trial Office of a suspected trial-related serious breach of GCP and/or the trial protocol. Where the Trial Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the Trial Office in providing sufficient information to report the breach to REC where required and in undertaking any corrective and/or preventive action.

18 END OF TRIAL DEFINITION

The end of the trial will be approximately six months after the final patient’s last visit. The Trial Office will notify the REC that the trial has ended and a summary of the clinical trial report will be provided within 12 months of the end of trial.

19 STATISTICAL CONSIDERATIONS

19.1 Feasibility Study

In the feasibility study no one outcome is considered primary. The feasibility of proceeding to an RCT shall be assessed through analysis of the criteria listed below. No formal stopping guidelines are proposed. The DMC shall advise the feasibility of proceeding to an RCT based on a review of all feasibility study data, with particular focus on recruitment.

19.1.1 Criteria for progression to Randomised Controlled Trial

The following targets are the key outcomes that will guide the decision to proceed to the RCT (discretion will be used and all outcomes will be viewed as a whole).

- Patients willing to be randomised
- Completion of baseline GHSS (90% of patients)
- Completion of GHSS at three month endpoint (80% of surviving patients)
- Completion of EQ-5D-5L at the six month end point (80% of surviving patients)

19.1.2 Definition of Outcome Measures

19.1.2.1 Patient pathway

- the number of screened and eligible patients identified
- the number of patients subsequently willing to be registered into the feasibility study
- the number of patients who find randomisation acceptable

Time to specialist palliative care, defined as the time spent on standard of care will be measured from the date of registration to:

- The date of referral to SPC
- The date of first visit for SPC
- Types of treatments given, eliciting
  - differences between standard and early palliative care
  - treatment resulting from SPARC and standard assessments (informing RCT sub-randomisation)
- Dose of chemo/radiotherapy received
- Treatment intent (palliative or other)

19.1.2.2 Questionnaire booklet completion

The following will be assessed for each questionnaire (each visit):

- Extent of missing data reported as the proportion of unanswered questions for each questionnaire
- The number of unreturned booklets
- Overall time taken to complete questionnaire booklet
- Patient opinion of:
  - number of questionnaires (classified as: too few, just right or too many)
  - appropriateness of each questionnaire/question

19.1.2.3 Overall survival

Overall survival is defined as the time from registration to death (due to any cause) or to date last known to be alive for those not known to have died.

19.1.3 Analysis of Outcome Measures

Full details will be specified in a Statistical Analysis Plan but an outline of the planned analyses is provided below.

Of the outcome measures assessed in the feasibility study some are qualitative and as such statistical analyses are not necessarily applicable. For quantitative measures the data will be reported through descriptive summary statistics and no hypothesis testing will be performed. Where appropriate, measures will be analysed by socio-economic status (English Indices of Deprivation 2010[18], Scottish Index of Multiple Deprivation 2012[19]).

Patient Pathway:

- For each participating site the number of eligible patients will be reported as a percentage of those screened, and the number of patients registered will be reported as a percentage of those eligible;
- The expected monthly recruitment rate for the RCT will be reported for each (potential) participating site and overall;
- A prediction of the consent rate will be calculated as the number of patients who are willing to be randomised out of the total number found to be eligible;
- Time to specialist palliative care referral, and to first treatment will be reported via the method of Kaplan and Meier, with median time to specialist palliative care (95% Confidence Interval (CI));
- A listing of the palliative measures defined above will be reported by site and sub-randomisation (standard assessment and SPARC). The details provided by the three participating sites will be compared to the information canvassed form the other sites.

Quality of life questionnaire completion:

The following measures will be reported by questionnaire and visit number, and will be compared to the results of a large Phase III late-stage lung cancer trial[20]. Where appropriate, measures will be assessed by patient and carer subgroups.

- The mean (standard deviation (sd)) proportion of unanswered questions for each questionnaire
- The number of booklets returned as a percentage of those expected
- The mean (sd) time taken to complete questionnaires

- The percentage of patients reporting the quantity of questionnaires to be: too few; just right; too many

The patient interviews will be reviewed and discussed to identify any questions and/or questionnaires deemed inappropriate.

To aid reporting in the RCT the treatments observed in the feasibility study will be used to define a 'drop-down list' and implemented on the trial database.

Overall survival:

A Kaplan Meier plot of overall survival will be reported. The six-month survival rate (95% CI) will be reported and the validity of the power calculation for the RCT will be assessed.

19.1.4 Planned Sub-group Analyses

Where appropriate outcome measures will be analysed by mGPS and ECOG performance score, accordingly.

19.1.5 Planned Final Analyses

The feasibility study will be closed once all patients have been followed for a minimum of three months. The data will be reported to the TSC and the feasibility of proceeding to the RCT shall be assessed.

19.1.6 Sample Size Justification

The feasibility study aims to register 60 patients over a three-month period. There is no statistical basis for this sample size; 60 was chosen as a logistically sensible number deemed sufficient to inform the RCT.

19.2 Randomised Controlled Trial

19.2.1 Definition of Outcome Measures

19.2.1.1 Primary outcome measures

The primary objective of the statistical analysis is to compare the two treatment arms in terms of the following co-primary outcome measures:

- GHSS from the EORTC QLQ C30 longitudinal questionnaire at three months post randomisation. GHSS is a descriptive measure of quality of life ranging from 0 (the worst score) to 100 (the best score)
- QAS over six months, combining the utility measure from the EQ5D questionnaire with survival time. QAS over six months will be calculated using the area under the curve formed by the longitudinal measures of the utility scores from EQ-5D-5L within six months, with all values from death onwards represented by 0 and imputation used to complete the curves where data are missing. Values will range from - 3.54 (the worst score, i.e. full survival at the worst QoL valued at -0.59) to 6.0 (the best score, i.e. full survival with perfect QoL).

19.2.1.2 Secondary outcome measures

A secondary objective will be to compare the arms of SPARC sub-randomisation in the early palliative care group to see if HNA as an intervention is associated with better outcomes.

Other secondary outcome measures are defined as:

Overall survival: defined as the time from randomisation to death (due to any cause) or to date last seen for those not known to have died.

Anxiety/depression: will be measured using the HADS questionnaire and scored as per the HADS algorithm.

Pain: based on the EORTC QLQ-C30 and -LC13 questionnaire pain domains.

Health Economics; Cost Effectiveness and Resource Use

- **Days spent in hospital/hospice:** obtained from patient records. Duration defined as time from admission to discharge.
- **Use, or not, of medical interventions in last month of life:** details of further interventions administered during the last month of life will be obtained from patient records**.** The patient subgroup will be defined as those for which death was observed.
- **ITU admission:** the number of patients admitted, the frequency and duration of visits will be obtained from patient records**.** Duration is defined as the time from admission to discharge from intensive treatment unit.
- **Use of CPR:** obtained from patient records**.**

QoL: Health related quality of life will be assessed using EQ-5D-5L and EORTC QLQ C30/LC13/BM22 instruments. The instruments will be scored as per the associated algorithm.

Memory and cognitive ability: will be assessed for consenting participants using administration of the MoCA. The instruments will be scored as per the associated algorithm.

mGPS: will be assessed at baseline, 3 and 6 months. The instruments will be scored as per the associated algorithm.

Secondary outcomes pertaining to family care-givers include:

Health Survey: assessed using the SF-12®. The instruments will be scored as per the associated algorithm.

Satisfaction with participant's end of life care: assessed using the CODE™ instrument and scored as per the associated algorithms.

19.2.2 Analysis of Outcome Measures

Full details will be specified in a Statistical Analysis Plan but an outline of the planned analyses is provided below.

19.2.2.1 Primary Outcome Measures

Global health status score: The two treatment groups will be compared in terms of this outcome measure at three months using a t-test. It is recognised that there will be some variation in the timing of the QoL assessments and a window of two weeks either side of the planned three month assessment will be acceptable. This part of the analysis will only be carried out in those patients who are alive and well enough to complete a questionnaire at three months (i.e. a complete case analysis) and therefore it is a conditional analysis but it will be intention-to-treat in the sense of including patients under their randomised allocation.

QAS time: Treatment groups will be compared using a t-test. The advantage of this analysis is that it is intention-to-treat, dealing with missing data due to death and dropout and therefore including all randomised patients in the analysis.

19.2.2.2 Secondary Outcome Measures

The following measures will be reported by treatment arm:

Overall survival: A Kaplan Meier plot of overall survival will be reported along with hazard ratio and median survival (both with 95% CI).

Anxiety/depression: The average change in HADS score from baseline to six months will be compared using a t-test (or non-parametric alternative). The mean area under curve will also be compared using a t-test.

Pain: The average change in pain domain score from baseline to six months will be compared using a t-test (or non-parametric alternative). The mean area under curve will also be compared using a t-test.

Cost Effectiveness:

- **Days spent in hospital/hospice -** Mean (95% CI) stay and overall stay duration and frequency of hospital/hospice say durations will be compared using a t-test (or non-parametric alternative). The number of patients admitted but not discharged will be reported. The proportion of patients spending time in hospital/hospice will be reported.
- **Use, or not, of medical interventions in last month of life -** A line-listing of medical interventions including, where applicable, intervention type, dose, duration and other pertinent metrics. The period over which these interventions are to be observed will also be reported (some may not have been followed for a month).

ITU admission: The number of ITU visits, and the number of patients making those visits along with the mean (95% CI) length of each visit, and the mean (95% CI) of patients overall ITU duration.

Use of CPR: The proportion of patients requiring CPR and the average number of resuscitations required per patient will be reported.

For each of the questionnaire based outcome measures the mean (sd) score will be reported by visit.

19.2.3 Planned Sub Group Analyses

No subgroup analyses are planned at present. The TMG and DMC will review the trial data and developments in treatment of this patient population and the protocol will be updated accordingly with details of subgroups of interest.

19.2.4 Planned Final Analyses

The planned final analysis will be determined once the feasibility study has been completed and the trial office is in receipt of all data to conduct such analysis. The DMC will inform of the result at the RCT stage.

The planned final analyses will be conducted for the RCT stage once all data pertaining to the last patients' visit six months after randomisation has been completed. The analysis of outcomes will be carried out once the data has been captured.

19.2.5 Sample Size Justification

The trial will recruit, at a minimum, a total of 525 patients to ensure 80% power for both primary outcome measures but if our recruitment rate allows then we will aim to recruit more patients within the recruitment period to improve the power, to a maximum of 700 patients for 90% power. The rationale behind these sample sizes is given below.

19.2.5.1 Global Health Status Score

Assuming a median survival time in these patients of six months and an exponential distribution, it is expected that 70% of randomised patients will be alive at three months. Experience in the BTOG2 trial shows that we would expect high compliance in these remaining patients, so we assume a further 5% dropout for reasons other than death, giving a total loss of 35% of randomised patients. From literature, GHSS in patients with metastatic NSCLC is 58.8 with standard deviation of 23 points and data from the stage IV patients in the BTOG2 trial shows similar values with a mean GHSS at baseline of 61.5 and standard deviation (SD) of 23. A difference of seven points between treatment groups at three months, which is a standardised effect size of 0.3, is considered to be realistic and clinically relevant. Assuming a 5% two-sided significance level and 80% power the analysis requires a total of 342 patients to detect this level of difference and thus 525 randomised patients. For 90% power the analysis requires a total of 456 patients and thus 700 randomised patients.

19.2.5.2 Quality adjusted survival

Assuming a standard deviation of two (which is a reasonable assumption given the likely range of values) and two-sided significance level of 5%, the trial needs 506 patients in the analysis to have 80% power to detect a difference of 0.5 of a quality-adjusted life month between the treatment groups. For 90% power 676 patients would be required. Since this analysis includes all patients in an intention-to-treat analysis, this represents the required number of randomised patients.

20 TRIAL ORGANISATIONAL STRUCTURE

20.1 Sponsor

The trial will be run by the University of Sheffield, in collaboration with Sheffield Teaching Hospitals NHS Foundation Trust who will act as governance sponsor.

20.2 Co-ordinating Centre

The trial is being conducted under the auspices of the CRCTU, University of Birmingham according to their local procedures.

20.3 Trial Management Group

The Chief Investigator, Co-investigators including the Trial Statistician, Trial Manager and Trial Coordinator will form the TMG. The TMG will be responsible for the day-to-day conduct of the trial, meeting at regular intervals (e.g. every 3 months), or as required, usually be teleconference. They will be responsible for the set-up, promotion, on-going management of the trial, the interpretation of the results and preparation and presentation of relevant publications.

20.4 Trial Steering Committee

An independent TSC has been set up to oversee the trial. Membership will be composed of selected TMG members, representatives from the funders and at least one patient advocate. The TSC will meet shortly before commencement of the trial and annually (usually by teleconference), they will supervise the conduct of the trial, monitoring progress including recruitment, data completeness, losses to follow-up, and deviations from the protocol. They will make recommendations about conduct and continuation of the trial.

20.5 Data Monitoring Committee

Data analyses will be supplied in confidence to an independent DMC, which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further patients. The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group.

The DMC will meet at the end of the feasibility study and make recommendations to the HTA via the TSC regarding the viability of the RCT. Specific progression criteria from the feasibility study to the RCT are outlined in Section 19.1.1.

The DMC is then scheduled to meet six months after the RCT opens to recruitment and then annually until last patient is recruited. Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the TSC via the Trial Office. The TSC will consider the DMCs findings and make recommendations to the TMG, HTA and sponsor. The DMC may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise patient safety.

21 FINANCE

This is an investigator-initiated and investigator-led trial funded by the NIHR HTA programme.

The sponsor will pay research costs, as defined in the Clinical Site Agreement, to participating sites.

The trial has been adopted by the NIHR Cancer Research Network Portfolio.

22 ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association (WMA) General Assembly, Helsinki, Finland, 1964, amended by the 48th WMA General Assembly, Somerset West, Republic of South Africa, 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html) (Appendix 12).

The trial will be conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the Data Protection Act 1998 and GCP. The protocol will be submitted to and approved by the REC prior to circulation.

Before any patients are enrolled into the trial, the Principal Investigator at each site is required to obtain local R&D approval. Sites will not be permitted to enrol patients until written confirmation of R&D approval is received by the Trial Office.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

23 CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 1998.

Full name and telephone number will be collected at trial entry for those patients and carers agreeing to participate in the Qualitative Interviews. This information will be shared via a secure method with the Qualitative Researchers in Sheffield. At the end of the study this information will be deleted from the trial database. If the patient or carer wishes to be interviewed at home the patient will also need to notify the Qualitative Researcher of their address. The interviews will be recorded by the Qualitative Researchers. These tapes will be transcribed and the transcriptions anonymised.

Initials date of birth, and hospital number will be collected for all patients and initials will also be collected for consenting carers. Patients will be identified using only their unique identifier, initials and date of birth on the CRF and correspondence between the Trial Office and the participating site. However patients and carers are asked to give permission for the Trial Office to be sent a copy of their signed Informed Consent Form(s) which will not be anonymised. This will be used to perform in-house monitoring of the consent process.

The investigator must maintain documents not for submission to the Trial Office (e.g. Patient Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that patient confidentiality is protected.

The Trial Office will maintain the confidentiality of all patients' and carers' data and will not disclose information by which these individuals may be identified to any third party. Representatives of the SPECIAL trial team may be required to have access to patient's medical records for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times.

24 INSURANCE AND INDEMNITY

This trial is an investigator-initiated and investigator-led trial sponsored by Sheffield Teaching Hospitals NHS Foundation Trust.

The University of Sheffield indemnifies the CRCTU and sponsor, their employees and agents involved in the trial, against any claims or proceedings in respect of personal injury made or brought against them by trial participants which are the result of a negligent error or omission in the protocol.

No provision has been made for indemnity in the event of a claim for non-negligent harm.

In terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial. Compensation is only available via NHS indemnity in the event of clinical negligence being proven.

The trial is coordinated by CRCTU at the University of Birmingham and its employees are indemnified by the University insurers for negligent harm caused by the co-ordination of the clinical trials they undertake whilst in the University's employment.

25 PUBLICATION POLICY

Results of this trial will be submitted for publication in a peer reviewed journal. The manuscripts and presentations will be prepared by the TMG and authorship will be determined by mutual agreement.

Any secondary publications and presentations prepared by investigators must be reviewed by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of Sheffield Teaching Hospitals NHS Trust. Intellectual property rights will be addressed in the Clinical Trial Site Agreement between sponsor and site.

26 REFERENCES

1. Khakwani, A., et al., *Lung cancer survival in England: trends in non-small-cell lung cancer survival over the duration of the National Lung Cancer Audit.* Br J Cancer, 2013. **109**(8): p. 2058-65.
2. Health & Social Care Information Centre, UK Government. *National Lung Cancer Audit for 2007.* 2009.
3. Temel, J.S., et al., *Early palliative care for patients with metastatic non-small-cell lung cancer.* N Engl J Med, 2010. **363**(8): p. 733-42.
4. Ahmedzai SH, W.D., *Palliative medicine and modern cancer care. .* Seminars in Oncology 2000. **27**(1): p. 1-6.
5. National Cancer Action Team, *Holistic needs assessment for people with cancer. A practical guide for healtcare professionals.* 2011.
6. Ahmedzai SH, K.G., Rogers E, Noble B, *SPARC: a holistic screening questionnaire for palliative and supportive care needs. .* J Palliat Care 2008. **24**(3): p. 194-195.
7. Leung EY, S.H., McMillan DC, *Clinical utility of the pretreatment glasgow prognostic score in patients with advanced inoperable non-small cell lung cancer.* J Thorac Oncol, 2012. **7**(4): p. 655-62.
8. Forrest, L.M., et al., *A prospective longitudinal study of performance status, an inflammation-based score (GPS) and survival in patients with inoperable non-small-cell lung cancer.* Br J Cancer, 2005. **92**(10): p. 1834-6.
9. Grose, D., et al., *Comorbidities in lung cancer: prevalence, severity and links with socioeconomic status and treatment.* Postgrad Med J, 2014. **90**(1064): p. 305-10.
10. Richie, J.S., E., *Qualitative Data Analysis for Applied Policy Research*, in *Analyzing Qualitative Data*, B.R. Bryman A, Editor. 1994, Sage: London. p. 173-194.
11. DIRUM. *Search Instruments*. [cited 2014 11 Nov]; Available from: http://www.dirum.org/instruments/search.
12. NICE, *Guide to the Methods of Technology Appraisal*, NICE, Editor 2008, www.nice.org.uk: London.
13. Payment by Results Team, *NHS Reference Costs 2010/11*, UK Government, Dept. of Health, 2011: London.
14. Curtis, L., *Unit Costs of Health and Social Care 2011*, 2011, University of Kent: Kent, UK.
15. Office of National Statistics, *2011 Annual Survey of Hours ad Earnings (SOC 2000)*, 2011: London.
16. Rowen, D., et al., *Deriving a preference-based measure for cancer using the EORTC QLQ-C30.* Value Health, 2011. **14**(5): p. 721-31.
17. Lin, D.Y., et al., *Estimating medical costs from incomplete follow-up data.* Biometrics, 1997. **53**(2): p. 419-34.
18. UK Government. *English Indices of Deprivation 2010*. 2010 [cited 2014 11 Nov]; Datasets Available from: http://data.gov.uk/dataset/index-of-multiple-deprivation.
19. The Scottish Government, *Scottish Index of Multiple Deprivation.* 2012.
20. Billingham LJ, G.P., Jarrett HW, Dunlop D, Thompson J, O'Byrne KJ, Kumar M, Skailes G, Nicolson M, Shah R, Leonard P, Chetiyawardana A, Wells P, Lewanski C, Woll P & Crosse B and D.F. M Hill. *Quality of life in advanced non-small cell lung cancer, effects of cisplatin dose and carboplatin in combination with gemcitabine: Results from BTOG2, a British Thoracic*

Oncology Group Phase III trial in 1363 patients. in *14th World Conference on Lung Cancer*. 2011. Amsterdam: group.bmj.com.

21. Nasreddine, Z.S., et al., *The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment.* J Am Geriatr Soc, 2005. **53**(4): p. 695-9.
22. Oken, M.M., et al., *Toxicity and response criteria of the Eastern Cooperative Oncology Group.* American Journal of Clinical Oncology, 1982. **5**(6): p. 649-55.
23. EuroQol. *How to use EQ-5D*. [cited 2014 11 Nov]; Available from: http://www.euroqol.org/about-eq-5d/how-to-use-eq-5d.html.
24. EORTC. *EORTC QLQ-C30*. [cited 2014 11 Nov]; Available from: http://groups.eortc.be/qol/eortc-qlq-c30.
25. Bergman, B., et al., *The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life.* Eur J Cancer, 1994. **30A**(5): p. 635-42.
26. Yeh, D.C., et al., *EORTC QLQ-BM22 quality of life evaluation and pain outcome in patients with bone metastases from breast cancer treated with zoledronic acid.* In Vivo, 2014. **28**(5): p. 1001-4.
27. Zigmond, A.S. and R.P. Snaith, *The hospital anxiety and depression scale.* Acta Psychiatr Scand, 1983. **67**(6): p. 361-70.
28. Penman, D.T., et al., *Informed consent for investigational chemotherapy: patients' and physicians' perceptions.* J Clin Oncol, 1984. **2**(7): p. 849-55.
29. Wilkinson, P.R., et al., *Longer term quality of life and outcome in stroke patients: is the Barthel index alone an adequate measure of outcome?* Qual Health Care, 1997. **6**(3): p. 125-30.
30. Aoun, S., et al., *Reliability testing of the FAMCARE-2 scale: measuring family carer satisfaction with palliative care.* Palliat Med, 2010. **24**(7): p. 674-81.
31. Kristjanson, L.J., *Validity and reliability testing of the FAMCARE Scale: measuring family satisfaction with advanced cancer care.* Soc Sci Med, 1993. **36**(5): p. 693-701.
32. Mayland, C.R., et al., *Caring for those who die at home: the use and validation of 'Care Of the Dying Evaluation' (CODE) with bereaved relatives.* BMJ Support Palliat Care, 2014.

APPENDIX 1 – MEDICAL INTERVENTIONS

Health technology resources used in cancer care and symptom management for trial patients to be captured on the CRF, include:

- Radiotherapy including date of last dose in relation to time of death
- Cytotoxic chemotherapy including date of last dose in relation to time of death
- Targeted biological therapy including date of last dose in relation to time of death
- Other interventional health technologies including:
    - Blood transfusion
    - Pleural aspiration
    - Airways stenting
    - Vascular stenting
    - Nerve blocks
    - Antibiotic courses for life-threatening infections or symptom relief

Use of interventions around the end of life, including:

- Terminal (palliative) sedation
- Medically assisted hydration and nutrition
- Attempts at resuscitation

APPENDIX 2 – SHEFFIELD PROFILE FOR ASSESSMENT AND REFERRAL FOR CARE (SPARC)

The SPARC[6] is a holistic screening questionnaire for supportive and palliative care needs. It is a multi-dimensional screening tool which gives a profile of needs to identify patients who may benefit from additional supportive or palliative care, regardless of diagnosis or stage of disease. SPARC is intended for use by primary care, hospital teams or other services to improve patient management, either by current professional carers or by referral to a specialist team. The patient-rated 45 item tool reflects nine dimensions of need and as such represents a comprehensive early HNA.

The SPARC tool should be used for all patients participating in the feasibility study and for those patients in the RCT randomised to Arm B2.

We would like to know a bit more about you and your concerns. Please fill in this questionnaire (with help from a relative or carer if needed) and return it to one of our research team. There are no "right" or "wrong" answers. If you are unsure of a question, please leave it blank.

COMMUNICATION AND INFORMATION ISSUES

1. Have you been able to talk to any of the following people about your condition?	**Yes**	**No**
a. Your doctor	☐	☐
b. Community nurse	☐	☐
c. Hospital nurse	☐	☐
d. Religious advisor	☐	☐
e. Social worker	☐	☐
f. Family	☐	☐
g. Other people (please state): _____		

PHYSICAL SYMPTOMS

Please circle one answer per line

In the past month, have you been distressed or bothered by:	**Not at all**	**A little**	**Quite a bit**	**Very much**
2. Pain?	0	1	2	3
3. Loss of memory?	0	1	2	3
4. Headache?	0	1	2	3
5. Dry mouth?	0	1	2	3
6. Sore mouth?	0	1	2	3
7. Shortness of breath?	0	1	2	3
8. Cough?	0	1	2	3
9. Feeling sick (nausea)?	0	1	2	3
10. Being sick (vomiting)?	0	1	2	3

PHYSICAL SYMPTOMS continued…

In the past month, have you been distressed or bothered by:		Not at all	A little	Quite a bit	Very much
11.	Bowel problems (e.g. constipation, diarrhoea, incontinence)?	0	1	2	3
12.	Bladder problems (urinary incontinence)?	0	1	2	3
13.	Feeling weak?	0	1	2	3
14.	Feeling tired?	0	1	2	3
15.	Problems sleeping at night?	0	1	2	3
16.	Feeling sleepy during the day?	0	1	2	3
17.	Loss of appetite?	0	1	2	3
18.	Changes in your weight?	0	1	2	3
19.	Problems with swallowing?	0	1	2	3
20.	Being concerned about changes in your appearance?	0	1	2	3
21.	Feeling restless and agitated?	0	1	2	3
22.	Feeling that your symptoms are not controlled?	0	1	2	3

PSYCHOLOGICAL ISSUES

Please circle one answer per line

In the past month, have you been distressed or bothered by:		Not at all	A little	Quite a bit	Very much
23.	Feeling anxious?	0	1	2	3
24.	Feeling as if you are in a low mood?	0	1	2	3
25.	Feeling confused?	0	1	2	3
26.	Feeling as if you are unable to concentrate?	0	1	2	3
27.	Feeling lonely?	0	1	2	3
28.	Feeling that everything is an effort?	0	1	2	3
29.	Feeling that life is not worth living?	0	1	2	3
30.	Thoughts about ending it all?	0	1	2	3
31.	The effect of your condition on your sexual life?	0	1	2	3

RELIGIOUS AND SPIRITUAL ISSUES		Please circle one answer per line			
In the past month, have you been distressed or bothered by:		**Not at all**	**A little**	**Quite a bit**	**Very much**
32.	Worrying thoughts about death or dying?	0	1	2	3
33.	Religious or spiritual needs not being met?	0	1	2	3

INDEPENDENCE AND ACTIVITY		Please circle one answer per line			
In the past month, have you been distressed or bothered by:		**Not at all**	**A little**	**Quite a bit**	**Very much**
34.	Losing your independence?	0	1	2	3
35.	Changes in your ability to carry out your usual daily activities such as washing, bathing or going to the toilet?	0	1	2	3
36.	Changes in your ability to carry out your usual household tasks such as cooking for yourself or cleaning the house?	0	1	2	3

FAMILY AND SOCIAL ISSUES		Please circle one answer per line			
In the past month, have you been distressed or bothered by:		**Not at all**	**A little**	**Quite a bit**	**Very much**
37.	Feeling that people do not understand what you want?	0	1	2	3
38.	Worrying about the effect that your illness is having on your family or other people?	0	1	2	3
39.	Lack of support from your family or other people?	0	1	2	3
40.	Needing more help than your family or other people could give?	0	1	2	3

TREATMENT ISSUES

Please circle one answer per line

In the past month, have you been distressed or bothered by:		Not at all	A little	Quite a bit	Very much
41.	Side effects from your treatment?	0	1	2	3
42.	Worrying about long term effects of your treatment?	0	1	2	3

PERSONAL ISSUES

		Yes	No
43.	Do you need any help with your personal affairs?	☐	☐
44.	Would you like to talk to another professional about your condition or treatment?	☐	☐
45.	**Would you like any more information about the following?**		
	a. Your condition	☐	☐
	b. Your care	☐	☐
	c. Your treatment	☐	☐
	d. Other types of support	☐	☐
	e. Financial issues	☐	☐
	f. Other (please state): _____		

Are there any other concerns that you would like us to know about?

Carry on over the page if needed

You can use this section to jot down any questions that you want to ask your doctors or other caring professionals

Question 1

Question 2

Question 3

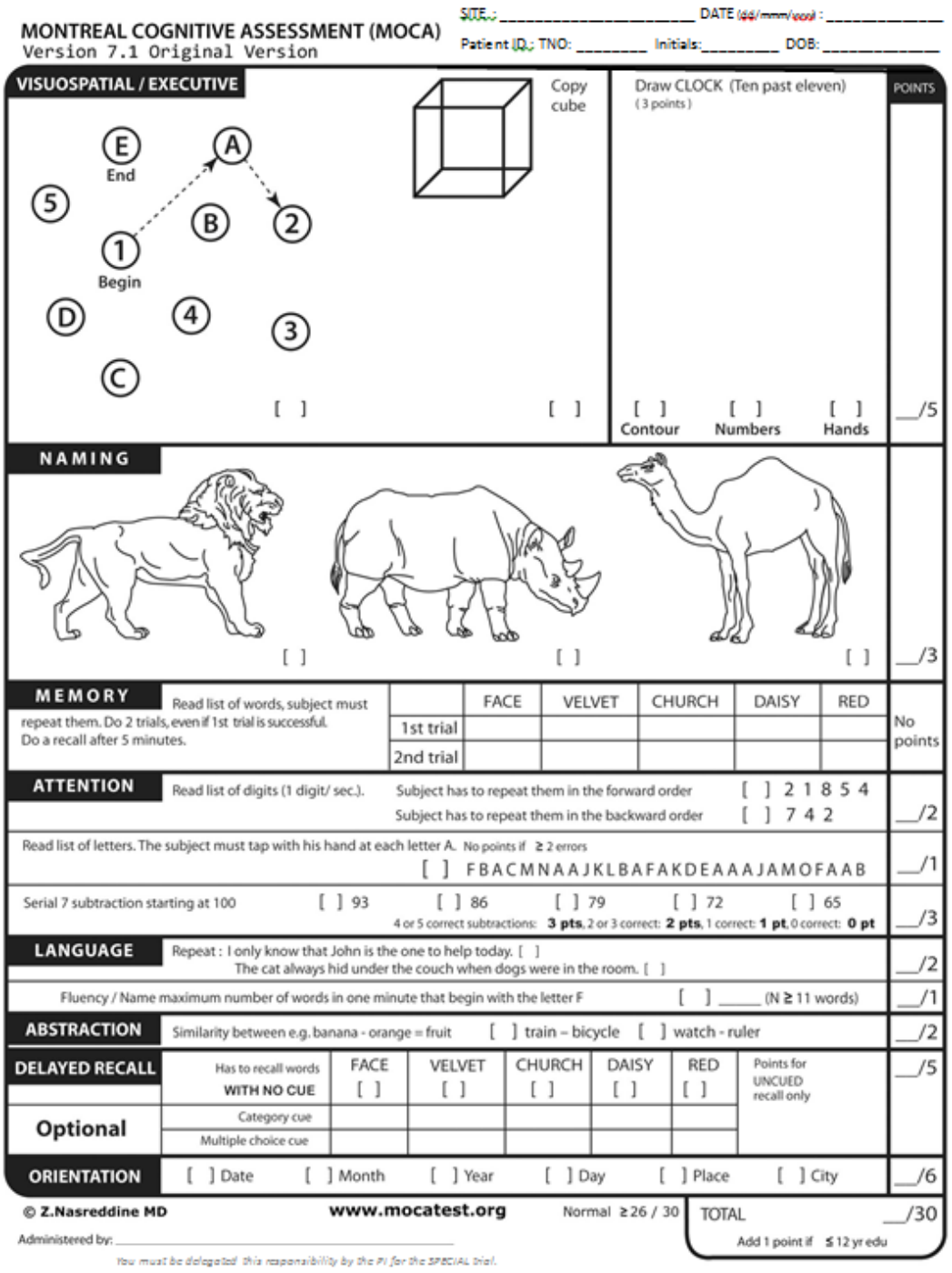
APPENDIX 3 – MODIFIED GLASGOW PROGNOSTIC SCORE (MGPS)[7, 8]

Modified Glasgow Prognostic Scores

	mGPS
CRP ≤10 mg/L and albumin ≥35 g/L	0
CRP ≤10 mg/L and albumin <35 g/L	0
CRP >10 mg/L	1
CRP >10 mg/L and albumin <35 g/L	2

APPENDIX 4 – MONTREAL COGNITIVE ASSESSMENT (MOCA)[21]

The Montreal Cognitive Assessment (MoCA)[21] is a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. The MoCA takes approximately 10 minutes to administer. Consent is optional and if the patient chooses not to participate then participation in the main trial will not be affected. Patients will be asked to complete a MoCA questionnaire at baseline, 3 months and then at 6 months.



MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

SITE : _____ DATE (dd/mmm/yyyy) : _____
Patient ID: TNO: _____ Initials: _____ DOB: _____

VISUOSPATIAL / EXECUTIVE — POINTS

Copy cube — [ ] [ ]

Draw CLOCK (Ten past eleven) (3 points) — [ ] Contour [ ] Numbers [ ] Hands — /5

NAMING — [ ] [ ] [ ] — /3

MEMORY — Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION — Read list of digits (1 digit/ sec.).
Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2 — /2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B — /1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** — /3

LANGUAGE — Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] — /2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words) — /1

ABSTRACTION — Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler — /2

DELAYED RECALL — /5

	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
Has to recall words WITH NO CUE	[ ]	[ ]	[ ]	[ ]	[ ]	
Optional: Category cue						
Optional: Multiple choice cue						

ORIENTATION — [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City — /6

© Z.Nasreddine MD www.mocatest.org Normal ≥ 26 / 30

TOTAL /30
Add 1 point if ≤ 12 yr edu

Administered by: _____
You must be delegated this responsibility by the PI for the SPECIAL trial.

APPENDIX 5 - SCOTTISH LUNG CANCER CO-MORBIDITY INDEX[9]

Co-morbidity	Severity scale	Severity Score			
		0	1	2	3
COPD	BTS/GOLD guidelines	No disease	FEV1 >60%	FEV1 40-60%	FEV1 <40%
Ischaemic heart disease	Canadian CV Society Classification	No disease	Angina with strenuous/ prolonged exertion	Angina after walking 200 hundred yards flat/flight stairs	Inability to carry out any level of exertion/angina at rest
Heart failure	NYHA classification	No disease	Slight limitation of physical activity due to dyspnoea	Comfortable at rest, less than ordinary activity causes dyspnoea	Dyspnoea at rest
Cerebrovascular disease	National Institutes of Health Stroke Scale	No detectable weakness/ sensory (incl visual/speech) impairment	Mild weakness/ deficit	Moderate weakness/ deficit	Severe weakness/ deficit
Dementia	Clinical Dementia Rating	No disease	Mild, able to carry out normal activity	Moderate, requires assistance in activities	Severe, unable to manage any activity. Full time care
Diabetes mellitus		No disease	HbA1C <7	HbA1C 7.1 - 10	HbA1C >10
Renal impairment		eGFR >90ml/min	eGFR 60-89 ml/min	eGFR 30-59 ml/min	eGFR <30ml/min or dialysis
Previous malignancy		No disease or Basal Cell Carcinoma	Previous cancer, no evidence active disease	Active, unlikely to cause death	Active, likely to cause death before lung cancer
Peripheral Vascular Disease		None	Claudication at >200 yards	Claudication at <200 yards	Rest pain
Alcohol		<25 Units/week	25-50 units/week	>50 units/week	Established alcohol related illness or end organ failure

APPENDIX 6 – EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS[22]

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

[22]

APPENDIX 7 – TUMOUR STAGING – TNM CLASSIFICATION

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American Joint Committee on Cancer

Lung Cancer Staging

7th EDITION

Definitions

Primary Tumor (T)

- **TX** Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
- **T0** No evidence of primary tumor
- **Tis** Carcinoma in situ
- **T1** Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (for example, not in the main bronchus)[1]
- **T1a** Tumor 2 cm or less in greatest dimension
- **T1b** Tumor more than 2 cm but 3 cm or less in greatest dimension
- **T2** Tumor more than 3 cm but 7 cm or less or tumor with any of the following features (T2 tumors with these features are classified T2a if 5 cm or less): involves main bronchus, 2 cm or more distal to the carina; invades visceral pleura (PL1 or PL2); associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
- **T2a** Tumor more than 3 cm but 5 cm or less in greatest dimension
- **T2b** Tumor more than 5 cm but 7 cm or less in greatest dimension
- **T3** Tumor more than 7 cm or one that directly invades any of the following: parietal pleural (PL3), chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina[2] but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe
- **T4** Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodule(s) in a different ipsilateral lobe

Distant Metastasis (M)

- **M0** No distant metastasis
- **M1** Distant metastasis
- **M1a** Separate tumor nodule(s) in a contralateral lobe, tumor with pleural nodules or malignant pleural (or pericardial) effusion[2]
- **M1b** Distant metastasis (in extrathoracic organs)

Notes

[1] The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.

[2] Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as M0.

ANATOMIC STAGE/PROGNOSTIC GROUPS			
Occult Carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
	T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T1a	N1	M0
	T1b	N1	M0
	T2a	N1	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a	N2	M0
	T1b	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T3	N2	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	T1a	N3	M0
	T1b	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N3	M0
	T4	N2	M0
	T4	N3	M0
Stage IV	Any T	Any N	M1a
	Any T	Any N	M1b

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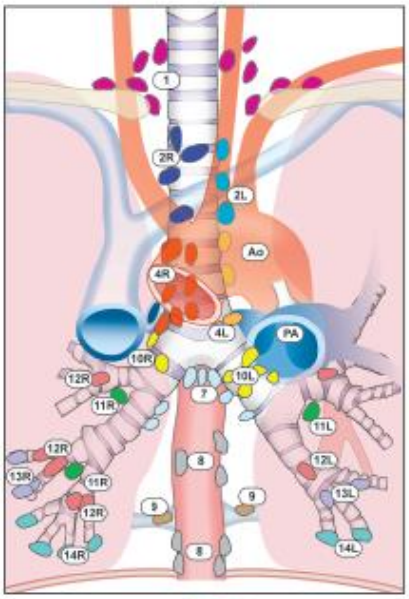
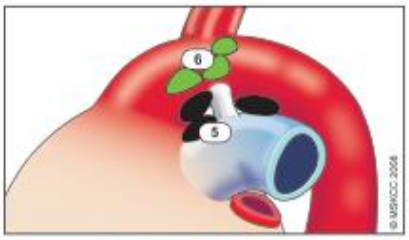
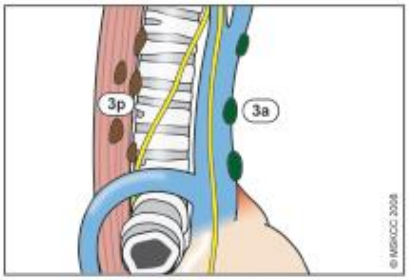
American Joint Committee on Cancer

Lung Cancer Staging

7th EDITION







Supraclavicular zone

- **1** Low cervical, supraclavicular, and sternal notch nodes

Superior Mediastinal Nodes

Upper zone

- **2R** Upper Paratracheal (right)
- **2L** Upper Paratracheal (left)
- **3a** Pre-vascular
- **3p** Retrotracheal
- **4R** Lower Paratracheal (right)
- **4L** Lower Paratracheal (left)

Aortic Nodes

AP zone

- **5** Subaortic
- **6** Para-aortic (ascending aorta or phrenic)

Inferior Mediastinal Nodes

Subcarinal zone

- **7** Subcarinal

Lower zone

- **8** Paraesophageal (below carina)
- **9** Pulmonary ligament

N_1 Nodes

Hilar/Interlobar zone

- **10** Hilar
- **11** Interlobar

Peripheral zone

- **12** Lobar
- **13** Segmental
- **14** Subsegmental

Regional Lymph Nodes (N)

- **NX** Regional lymph nodes cannot be assessed
- **N0** No regional lymph node metastases
- **N1** Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
- **N2** Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
- **N3** Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

ILLUSTRATION

The IASLC lymph node map shown with the proposed amalgamation of lymph into zones.

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APPENDIX 8 – PATIENT QUESTIONNAIRES

The following is a list of the questionnaires, presented in booklet format, which patients will be asked to complete. The contents of each booklet will be time-point specific.

Questionnaires Used in Patient Questionnaire Booklets

EuroQoL (EQ-5D-5L)

The EQ-5D-5L is a preference-based health related quality of life measure that can be used to obtain QALY in cost-effectiveness studies[23]. The EQ-5D-5L consists of five domains – mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each domain has five levels ranging from no problems to extreme problems. The EQ-5D-5L form will be presented in a booklet which will also contain the EORTC questionnaires; the booklet will take approximately 15 minutes to complete.

Quality of life using EORTC QLQ-C30, LC-13 and BM-22 module

The EORTC quality of life questionnaire is an integrated system for assessing the health-related quality of life of cancer patients participating in international clinical trials. The core questionnaire, the C30[24], is the product of more than a decade of collaborative research. Associated with the core C30 component will be the lung cancer specific and, if applicable, lung cancer and bone metastasis specific modules, LC-13[25] and BM-22[26], respectively. They are well-known, validated research clinical tools for evaluating health related quality of life, and are self-administered and have been used successfully in many cancer studies. The EORTC questionnaires will be presented as part of a booklet which will also contain the EQ-5D-5L questionnaire; the booklet will take approximately 15 minutes to complete.

Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS)[27], is a valid and reliable 14-item self-rating scale designed to assess anxiety and depression in both hospital and community settings. HADS is a psychological screening tool that gives clinically meaningful results, able to assess symptom severity and depression in patients with illness and the general population. The HADS questionnaire will be presented with the Quality of Life booklet at baseline, 3 month (12 weeks) and 6 month (24 weeks) follow-up visits. The HADS questionnaire will take approximately 5 minutes to complete.

Other Measures

Acceptability of Randomisation Questionnaire

Patients invited to participate in the feasibility study will be asked to complete a questionnaire on the acceptability of randomisation at baseline. The questionnaire will initially ask whether or not the patient would agree to participate in a randomised trial, followed by a 17 point list of reasons that patients are asked to rate on a five-point Likert scale to indicate to what extent they agree or disagree. These include factors that might have influenced their decision to either accept or decline and how they would feel if the timing of their referral to SPC was randomised.

The questionnaire was based on a design by Penman *et al.*[28] from previous research on the reasons patients gave for joining Phase III trials, which has been used in several other studies including the on-going PulMiCC (Pulmonary Metastasectomy in Colorectal Cancer, MREC ref 10/H0720/5) trial.

Patient Feedback Questionnaire

A short, seven-item questionnaire for patients to feedback their opinions on the questionnaires used in the feasibility study.

Patient Costs Record

An eight item disease-related expenses questionnaire to be completed by patients during their first follow-up visits. The questions asked are standard questions designed to provide a brief record of expenses incurred during the week prior to the clinic visit. The questionnaire will take approximately 5 minutes to complete.

Patient Diary

In order to capture SPC usage, patients will be given a diary into which all healthcare contacts, investigations and healthcare interventions are to be written. Appropriate social care contacts are also to be recorded in the diary. Health technologies which are used in the process of cancer care and symptom management for trial patients will also be captured.

Any supportive treatment given (interventional or holistic) will be collected in the Patient Diary along with recording on the CRF at the appropriate time point within the patient schedule (see Tables 1 and 2).

Table 3: Summary of Patient Questionnaire Booklet Content at Different Time Points

FEASIBILITY STUDY BOOKLETS	Content	Others
Baseline	EQ-5D-5L EORTC QLQ-C30 LC13 BM22 HADS	SPARC Assessment questionnaire Acceptability of Randomisation questionnaire MoCA (for consenting patients only) to be administered Patient Diary given and explained to patient
Follow-up	EQ-5D-5L EORTC QLQ-C30 LC13 BM22 Patient Costs	SPARC Assessment questionnaire ***All visits*** Collection of completed diary pages
3 and 6 month follow-up assessment	EQ-5D-5L EORTC QLQ-C30 LC13 BM22 HADS Patient Costs	SPARC Assessment questionnaire MoCA (for consenting patients only) to be administered at both visits Collection of completed diary pages ***At 3 month follow-up visit only*** Patient Feedback Questionnaire

RCT BOOKLETS	Content	Others
Baseline	EQ-5D-5L EORTC QLQ-C30 LC13 BM22 HADS	***Arm B2 only :*** SPARC Assessment questionnaire MoCA (for consenting patients only) to be administered Patient Diary given and explained to patient
Follow-up	EQ-5D-5L EORTC QLQ-C30 LC13 BM22 Patient Costs	***Arm B2 only :*** SPARC Assessment questionnaire Collection of completed diary pages
3 and 6 month follow-up assessment	EQ-5D-5L EORTC QLQ-C30 LC13 BM22 HADS Patient Costs	***Arm B2 only :*** SPARC Assessment questionnaire MoCA (for consenting patients only) to be administered at both visits Collection of completed diary pages
Longer term follow-up	EQ-5D-5L EORTC QLQ-C30 LC13 BM22	***Arm B2 only :*** SPARC Assessment questionnaire Another Patient Diary given Collection of completed diary pages

APPENDIX 9 – CARER QUESTIONNAIRES

The following SF12 and FAMCARE2 questionnaires may be completed either in the clinic when the patient attends for review or, if the carer wishes, at home and returned to the SPECIAL Trial Office in a freepost envelope provided.

SF-12® health survey

The SF-12® provides a measure of perceived health (health-related QoL) that describes the degree of general physical health status and mental health distress [29]. The format is given in 12 items, derived from the physical and mental domains of the Short Form Health Survey-36® (SF-36®).

Separate summary scores are obtained for each of the physical and mental domains by summing across all 12 items for each. The questionnaire will take approximately 3 minutes to complete.

FAMCARE-2

The FAMCARE-2 scale is used to measure family satisfaction with care of patients with advanced cancer [30]. The tool was originally developed for use on inpatient units, measuring different areas of care such as availability of care, physical patient care, psychosocial care and information giving. The original scale is a "20 item Likert-type scale measuring the degree to which family members are content with the health care provider behaviours directed toward the patient and themselves" [31]. The FAMCARE-2 Scale can be given to family members while a patient is receiving palliative care or at some point after a patient's death. Validity evidence for the tool has been gathered in a number of different settings, including inpatient units, outpatient cancer clinics and home care. It is used in such places as North America, Australia and Europe.

Care of the Dying Evaluation (CODE™) of experiences of care during end of life care

'Care Of the Dying Evaluation' (CODE™) is a 40-item self-completion post-bereavement questionnaire developed to assess the quality of care and the level of support provided to patients and their families during the last days of life [32]. The questionnaire asks about various aspects of care, including: communication, symptom control, provision of fluids, place of death and emotional and spiritual support.

The site's research team will contact consenting carers approximately three months post-bereavement to ask whether they would complete the CODE™ questionnaire. The CODE questionnaire will be sent out in an information pack by the site research team to the carer via the patient's home address approximately three months after the bereavement. The pack will contain a covering letter inviting the participating carer to complete and return the CODE questionnaire, carer information sheet, response form, copy of the CODE questionnaire and a freepost envelope for returning the questionnaire.

Table 4: Summary of Carer Questionnaire Booklet Content at Different Time Points

FEASIBILITY & RCT	Content	Others forms
All visits	Health Survey SF12 FAMCARE-2	CODE (3 months post-bereavement questionnaire) with *Freepost* addressed envelope to be return to SPECIAL Trial Office directly.

APPENDIX 10 – QUALITATIVE INTERVIEW QUESTIONS

Purpose:

To consider referral to specialised palliative care services from the perspective of trial participants. The emphasis of the interview is to explore the impact of early referral on the experiences of NSCLC patients and their caregivers. Interviews should last for around 30 minutes to one hour. Interviews will differ on each occasion to allow for emphasis on the most salient issues for participants.

The nature of the interview will be determined at the conclusion of the feasibility trial although it is anticipated that interviews will initially be based on the following example questions :

1. Can you recall being referred to SPC services and if so do you know why you were referred?
2. Can you tell me what you felt about being referred to SPC?
    - Explore- why do you think you might have felt this way? (*adverse consequences*)
3. What kind of information was given to you about referral?
4. At the time did you have any questions about being referred and were these questions answered satisfactorily?
5. What were you main concerns about treatment and care at the time of referral to SPC?
    - Explore- social, psychological, physical, financial, spiritual
6. How was SPC involved in your care and/or treatment?
7. Do you think that your involvement with SPC has benefited you in terms of care and treatment?
    - Explore- can you explain how SPC has helped?
8. Did you feel that there was anything that SPC provided which did not help you?
    - Explore- can you explain why these services were unhelpful?
9. Do you think carers needs have been taken into consideration?
    - Explore-why do you say this?
10. Has the involvement of SPC had any impact upon other services, such as those you receive at home?
11. Can you tell me about your current treatment regime, has this changed significantly since you were referred to SPC?
    - Explore- why has this changed? (where appropriate)
12. Is there anything that we have not discussed that you would like to say?

APPENDIX 11 – DEFINITION OF ADVERSE EVENTS

Adverse Event

Any untoward medical occurrence in a patient or clinical trial subject participating in the trial, which does not necessarily have a causal relationship with the treatment received.

Comment:

An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Related Event

An event which resulted from the administration of any of the research procedures.

Serious Adverse Event

An untoward occurrence that:

- Results in death unrelated to the original lung cancer diagnosis and treatment
- Is life-threatening*
- Requires hospitalisation** or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly/ birth defect
- Or is otherwise considered medically significant by the Investigator***

Comments:

The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on patients/event outcome or action criteria.

* Life threatening in the definition of an SAE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an unplanned, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. Thus, hospitalisation for protocol treatment (e.g. line insertion), elective procedures (unless brought forward because of worsening symptoms) or for social reasons (e.g. respite care) are not regarded as an SAE.

*** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.

Unexpected and Related Event

An event which meets the definition of both an Unexpected Event and a Related Event.

Unexpected Event

The type of event that is not listed in the protocol as an expected occurrence.

Common Toxicity Criteria Gradings

Toxicities will be recorded according to the CTCAE, version 4.0. The full CTCAE document is available on the National Cancer Institute website, the following address was correct when this version of the protocol was approved:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

APPENDIX 12 – WMA DECLARATION OF HELSINKI

Recommendations guiding physicians

in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964

and amended by the

29th World Medical Assembly, Tokyo, Japan, October 1975

35th World Medical Assembly, Venice, Italy, October 1983

41st World Medical Assembly, Hong Kong, September 1989

and the

48th General Assembly, Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The Health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the trial on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the trial and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the trial and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE

(Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical trial, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a trial must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN

SUBJECTS (Non-Clinical Biomedical Research)

7. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

8. The subject should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

9. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

10. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

TRIAL OFFICE

Cancer Research UK Clinical Trials Unit
School of Cancer Sciences
University of Birmingham
Edgbaston
Birmingham B15 2TT

☎ +44 (0) 121 414 6372

🖷 +44 (0) 121 414 2230

✉ SPECIAL@trials.bham.ac.uk

RANDOMISATION

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