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CLINICAL TRIAL PROTOCOL

Short Title: Anticoagulation Length in Cancer Associated Thrombosis

Full Title: A feasibility study to inform the design of a randomised controlled trial to identify the most clinically and cost effective length of **A**nticoagulation with **L**ow molecular weight heparin **I**n the treatment of **C**ancer **A**ssociated **T**hrombosis

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Name of Sponsor:	**Cardiff University**

Authorised by:

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Signature:		Date:	21/3/13

Developed on behalf of the NCRI Palliative and Supportive Care Clinical Studies Group

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WCTU WALES CANCER TRIALS UNIT / UNED YMCHWIL CANSER CYMRU
Marie Curie Palliative Care Research Centre CARDIFF
NCRI National Cancer Research Institute / NCRN National Cancer Research Network
NHS National Institute for Health Research

General Information

This protocol describes the ALICAT clinical trial, and provides information about the procedures for entering participants into the trial. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other patients. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial, but sites entering patients for the first time are advised to contact the Wales Cancer Trials Unit (WCTU) in Cardiff to confirm that they have the most up-to-date version of the protocol in their possession. Problems relating to the trial should be referred, in the first instance, to the WCTU.

Compliance

This trial will adhere to the conditions and principles which apply to all clinical trials as outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 1031), as amended, EU Directive 2001/20/EC, and EU Directive 2005/28/EC. It will be conducted in compliance with the protocol, the Declaration of Helsinki (South Africa, 1996), the Research Governance Framework for Health and Social Care (Welsh Assembly Government 2009 and Department of Health 2005), the Data Protection Act 1998, and other regulatory requirements as appropriate.

Funding

The ALICAT trial is being funded by the Health Technology Assessment (HTA) programme on behalf of the National Institute for Health Research (NIHR) and is thus part of the NCRN/NCRI portfolio of clinical trials.

This trial is supported by Cancer Research UK (CR UK) core funding at the WCTU.

WCTU Registration/Randomisation line:
029 2064 5500
(Open Monday – Friday, 9am – 5pm)

N.B. This telephone number is strictly for randomisation/enrolment and should not be used for general queries.

Serious Adverse Event (SAE) Fax Number:
029 2064 4488

Trial Co-ordination

The ALICAT trial is being coordinated by the WCTU, a National Cancer Research Institute (NCRI) accredited, and United Kingdom Clinical Research Collaboration (UKCRC) registered trials unit.

This protocol has been developed by the ALICAT Trial Management Group (TMG) on behalf of the NCRI Palliative and Supportive Care Clinical Studies Group.

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Abbreviations and Glossary

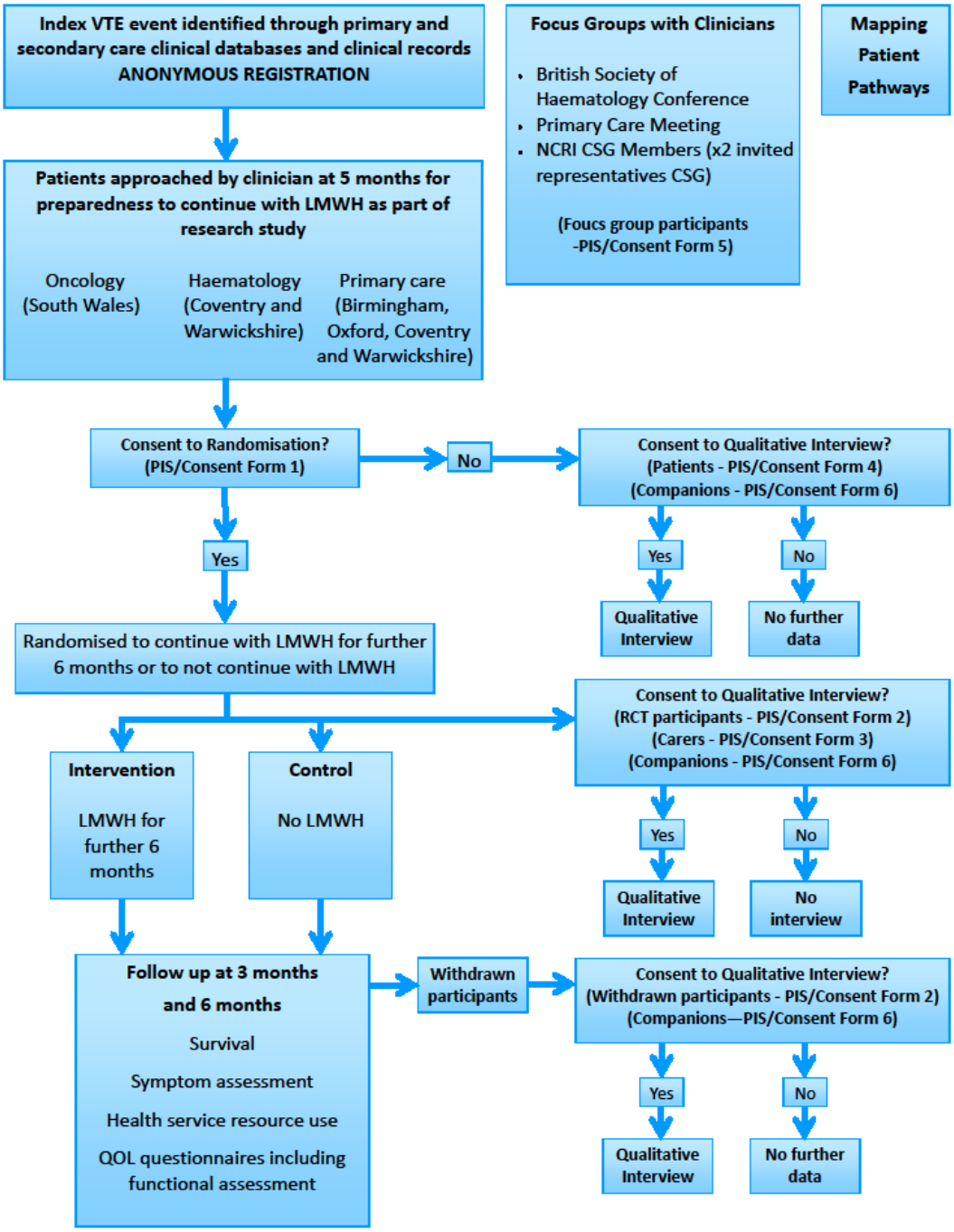
ALICAT	A feasibility study to inform the design of a randomised controlled trial to identify the most clinically and cost effective length of Anticoagulation with Low molecular weight heparin In the treatment of Cancer Associated Thrombosis (ALICAT).
ABPI	Association of the British Pharmaceutical Industry
ACCP	American College of Clinical Pharmacy
ACCO	American College of Clinical Pharmacology
AE	Adverse Event
ALT	Alanine Transaminase
ANC	Absolute neutrophil count
AR	Adverse Reaction
ASCO	American Society of Clinical Oncology
ASR	Annual Safety Report
AST	Aspartate aminotransferase
BSH	British Society for Haematology
CAT	Cancer Associated Thrombosis
CCG	Clinical Commissioning Group
CSG	Clinical Studies Group
CI	Chief Investigator
CPAS	Chemotherapy and Pharmacy Advisory Service
CRF	Case Report Form
CR-UK	Cancer Research UK
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CTIMP	Clinical Trial of an Investigational Medicinal Product. A clinical trial that is within the scope of the UK Medicines for Human Use (Clinical Trials) Regulations 2004.
CTPA	Computerised tomography pulmonary angiogram
DVT	Deep Vein Thrombus
DSUR	Development Safety Update Report
ECOG	Eastern Cooperative Oncology Group

EQ-5D-5L	A standardised instrument for use as a measure of health outcome
ESAS-r	Edmonton Symptom Assessment System (revised version)
ESMO	European Society for Medical Oncology
EudraCT	European Union Drug Regulatory Agency Clinical Trial
GCP	Good Clinical Practice
GP	General Practitioner
HIT	Heparin induced thrombocytopenia
IB	Investigator's Brochure
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product. A pharmaceutical form of an active substance or placebo being tested or used in a clinical trial, including products already with a marketing authorisation, but used or assembled (formulated or packaged) in a way different to the authorised form, or when used for an unauthorised indication, or when used to gain more information about the authorised form.
INR	International Normalised Ratio
ISR	Investigator Safety Report
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
LMWH	Low Molecular Weight Heparin
MHRA	Medicines and Healthcare products Regulatory Agency
MidRec	Midland Research Practices Consortium
NCRI	National Cancer Research Institute
NCRI CSG	National Cancer Research Institute Clinical Studies Group
NCRN	National Cancer Research Network
NHS	National Health Service
NHSIC	National Health Service Information Centre (formerly the Office for National Statistics)
NICE	National Institute for Health and Clinical Excellence
NIHR CSP	National Institute for Health Research Co-ordinated System for Gaining NHS Permission. This system defines and carries out checks that only need to be done once, and those that are required for each NHS location/organisation
NIHR HTA	National Institute for Health Research Health Health Technology Assessment programme

NIMP	Non-Investigational Medicinal Product. Medicinal products that are not the object of investigation (i.e. other than the tested product, placebo or active comparator) supplied to the patients participating in the trial and used in accordance with the protocol. E.g. background treatment, rescue medication.
NSAID	Non steroidal anti-inflammatory drug
Patient	A patient under care who may be eligible for the trial but has not yet consented to participate in any trial related activities.
Participant	An individual who has given written informed consent and is participating in trial related activities
PCRN-CE	Primary Care Research Network for Central England
PCT	Primary Care Trust
PE	Pulmonary Embolus
PI	Principal Investigator
PIS	Participant Information Sheet
QLQ-C30	EORTC quality of life questionnaire for assessing health related quality of life of cancer patients
QoL	Quality of Life
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SEWTU	South East Wales Trials Unit
SOP	Standard Operating Procedure
Sponsor	The primary organisation that oversees and is responsible for the clinical trial
SPC	Summary of Product Characteristics
SSA	Site-Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
TSF	Trial Site File
UK	United Kingdom

UKCRC	United Kingdom Clinical Research Collaboration
VTE	Venous Thromboembolism
WBC	White blood cell
WCTU	Wales Cancer Trials Unit

1.0 Trial schema



2.0 Trial synopsis

Study title	A feasibility study to inform the design of a randomised controlled trial to identify the most clinically and cost effective length of **A**nticoagulation with **L**ow molecular weight heparin **I**n the treatment of **C**ancer **A**ssociated **T**hrombosis				
Study acronym	ALICAT				
Short title	Anticoagulation Length in Cancer Associated Thrombosis				
Funder	NIHR HTA	**Funder's No**	10/145/01		
Chief Investigator	Dr Simon Noble				
Sponsor	Cardiff University	**Sponsor No**	SPON1037-11		
Study period	2 years	**Phase**	II	**Number of arms**	2
Number of participants	200 patients anonymously registered, 60 patients randomised				
Investigational Medicinal Products(s) (IMP)	Low Molecular Weight Heparin (LMWH)				

Objectives

To explore the feasibility of conducting a randomised controlled trial to identify the use of low molecular weight heparin in the treatment of cancer associated thrombosis (CAT) in patients with locally advanced or metastatic cancer following an initial six months of anticoagulation.

To do this we will:

- Identify the number of eligible patients willing to be recruited to the study over 12 months (target recruitment rate of 30% of eligible patients);
- Assess the proportion of participants who experience recurrent VTE during the follow-up period;
- Explore the feasibility of completing study measures;
- Assess quality of life during participation in the study;
- Assess symptoms during the study;
- Explore the barriers to progressing to a full randomised control trial
- Explore the attitudes of clinicians regarding equipoise, and willingness to recruit to the trial;
- Explore the attitudes and views of participating patients regarding equipoise and acceptability of the intervention;
- Explore the attitudes and views of patients who are not willing to consent to the study, or who withdraw after randomisation;

- Identify key cost drivers;
- Explore the spread of recruitment in different recruitment environments;
- Assess the safety of prolonged treatment of cancer associated thrombosis through safety reporting.

Main inclusion criteria

- Receiving LMWH for treatment of CAT for approximately five months;
- Locally advanced or metastatic cancer;
- Able to self-administer LMWH, or have LMWH administered by a carer;
- Able to give informed consent;
- Age ≥16 years.

See Section 6.3 for full inclusion criteria.

Main exclusion criteria

- Receiving drug other than LMWH for CAT;
- Contraindication to continuing anticoagulation;
- Confirmed recurrent VTE whilst receiving anticoagulation;
- Fitted with a prosthetic heart valve;
- Pregnant and/or lactating females.

See Section 6.4 for full exclusion criteria.

Treatments

Arm A - Continue LMWH at treatment dose according to body weight for further six months

Arm B - Discontinue LMWH once patient has received six months treatment following index VTE case

Trial assessments

Screening assessments for all patients

- Confirmation of disease stage
- Confirmation of CAT and treatment with LMWH

Baseline assessments for randomised patients

- Disease history
- Cancer treatment history
- History of index VTE
- VTE treatment history
- Physical assessment

- Current disease status
- Haematology
- Urea and electrolytes
- Liver function test
- Bone profile
- Comorbidities (baseline toxicity)
- Concomitant medication
- Use of NHS resources in previous 3 months
- Quality of life questionnaires:
    - EORTC QLQ-C30 Version 3.0
    - EQ-5D-5L
    - ESAS-r

Week 12 and week 26 assessments for randomised patients

- VTE treatment and compliance
- Physical assessment
- Haematology
- Urea and Electrolytes
- Liver Function test
- Bone profile
- Toxicities
- Concomitant medications
- Use of NHS resources (Hospital admissions, GP visits, etc.)
- Quality of life questionnaires:
    - EORTC QLQ-C30 Version 3.0
    - EQ5D-5L
    - ESAS-r

Unscheduled Events - Any time from randomisation until 6 month follow-up for randomised patients

- Serious Adverse Events (SAEs)
- Bleeding events
- VTE events
- Withdrawals

- Death

Endpoints:

Primary outcome measure:

- Number of eligible patients over 12 months
- Number of recruited patients over 12 months (target recruitment rate of 30% of eligible patients)
- Proportion of participants with recurrent VTEs during follow-up.

Secondary outcome measures:

- Completion of trial protocol
- Costs
- Quality of life
- Symptom assessment
- Attitudes of clinicians and patients

2.1 Lay summary

Venous thromboembolism (VTE) is a term to describe blood clots in the legs, known as a deep vein thrombus (DVT), or in the lung, known as a pulmonary embolus (PE). It is a common condition, which causes many symptoms and at its most serious may lead to sudden collapse and death. It is particularly common in cancer patients and its treatment requires three to six month's blood thinning medicine known as an anticoagulant. For most patients, a tablet called warfarin is used, but this is a potentially risky treatment in cancer patients because it may increase the risk of bleeding and VTE reoccurs in a fifth of patients.
Low molecular weight heparin (LMWH) is better than warfarin at treating VTE in cancer patients, decreasing the chance of VTE coming back by half. Although given as an injection once a day, studies have shown it is acceptable to patients and, for some, preferable to warfarin.

It is recommended that patients receive LMWH for six months only. However, if someone still has a cancer after six months of treatment with LMWH, there is still a chance that the VTE could come back because the cancer, which is causing the blood clots, has not gone away.

Theoretically, patients might benefit from taking LMWH for longer than six months but this has not been demonstrated in clinical trials. Furthermore, we do not know whether prolonged LMWH treatment will improve the patients' quality of life, help prevent death, or be cost-effective to the National Health Service (NHS).

In this clinical trial, we would like to compare the effect of continuing with LMWH for an extra six months with the effects of not continuing LMWH. Because this has not been done before, we need to determine if it would be feasible to carry out a full clinical trial with these patients by assessing whether we would be able to recruit enough patients and whether people would be interested in taking part in the study.

Patients with advanced or metastatic cancer, who have been taking LMWH for five months for VTE, will be asked if they would be willing to continue with LMWH for a further six months as part of a research study. If they say yes, then they will be chosen at random to either receive the LMWH for a further six months (intervention group), or to stop LMWH at six months following standard practice (control group). We will follow up patients for six months from recruitment and ask them to complete questionnaires at three monthly intervals. These questionnaires will ask about their symptoms and quality of life.

We will interview patients who do not wish to consent to the study to explore their reasons for this decision. We will also interview patients who do participate in the trial to explore their reasons and experiences of participating in the trial. We will also interview participants who do consent to the study, but who later withdraw from the study, to explore their experiences and reasons for withdrawal. We will also explore the views clinicians have towards the trial through focus groups.

This information will help us decide whether or not it is possible to successfully conduct a full clinical trial in this important area of patient care.

3.0 Background, rationale and objectives

Venous thromboembolism (VTE) is the formation of a blood clot (thrombus) in a vein, which may displace from its original site and form an embolus. Most thrombi occur in the deep veins of the legs and are known as deep vein thromboses (DVTs). Symptoms vary from leg pain and swelling, to chest pain and breathlessness, and sudden collapse and death due to embolism in the lungs. A DVT also causes long-term swelling and ulceration of the legs, known as post-thrombotic syndrome, in a third of people. The total cost to the NHS of managing VTE is estimated at £640 million per year (1). VTE occurs in 1 in 1000 patients and annually affects 6.5 million people worldwide. The rate is higher in the cancer population; in the UK over 250,000 people a year are diagnosed with cancer, up to 18 per cent of whom will develop VTE (2). The standard treatment of VTE is well established, consisting of five days anticoagulation with low molecular weight heparin (LMWH), followed by three to six months of warfarin (3). However, the management of cancer associated thrombosis (CAT) presents several challenges with a higher rate of both re-thrombosis and bleeding amongst cancer patients compared to those with non-malignant disease (4).

The impact of VTE on the cancer patient is substantial; conferring a worse prognosis compared with similar stage cancer patients without VTE (5, 6). Furthermore, anti-coagulation with warfarin is complicated by drug-drug interactions, variable drug absorption, and changing nutritional status (7). This inevitably has a practical impact on the delivery of anti-cancer therapies. Maintaining stable coagulation with warfarin is difficult and requires more frequent monitoring with blood tests, which adversely affects patients' quality of life (8). Current evidence based guidelines recommend 6-months LMWH as first-line therapy for CAT due to greater efficacy (4, 9, 10). However, patients with ongoing cancer remain at risk of VTE recurrence beyond six months and may therefore benefit from indefinite anticoagulation. To date, there is no evidence that this is appropriate or cost effective.

3.1 Summary of current evidence

Evidence for the use of LMWH is summarised in table 1, below. Based on these data, guidelines from professional organisations (which include the American College of Clinical Pharmacy (ACCP), American Society of Clinical Oncology (ASCO), British Society for Haematology (BSH), and European Society for Medical Oncology (ESMO)) recommend LMWH for the treatment of CAT. However, there are important gaps in the current evidence base. In patients with CAT and ongoing cancer, anticoagulation brings even more challenges than the treated general cancer population. As the cancer progresses, so does the thrombotic tendency; due to increased tumour burden releasing procoagulants, reduced mobility and, in pelvic cancers, additional stasis due to local vessel occlusion (11). Consensus recommends consideration of continuing anticoagulation indefinitely in this patient group although the evidence supporting this is limited to case series and has not been

economically evaluated (12). As the thrombotic tendency increases with disease progression so does the risk of bleeding associated with anticoagulation (13), therefore the choice of anticoagulant for indefinite anticoagulation in CAT will need to carefully balance efficacy and safety.

The past five years has seen the introduction of new oral anticoagulants including direct Xa inhibitors (rivaroxaban, apixaban) and direct thrombin inhibitors (dabigatran etexilate). Both dabigatran etexilate and rivaroxaban have been evaluated in the treatment of DVT and PE showing non-inferiority to warfarin with respect to recurrent VTE and bleeding profile (14, 15). Furthermore, the use of dabigatran and rivaroxaban has been cautioned in high-risk groups such as cancer patients until studies with representative numbers of cancer patients are available (16-18). However, only 5% and 6.8% of patients respectively had cancer and these agents are yet to demonstrate non-inferiority, in this setting, to the current gold standard (LMWH). Since advanced cancer patients are at particular risk of recurrent thrombosis and bleeding, the use of the new oral anticoagulants in this study would be hard to justify ethically without convincing safety and efficacy data in this patient group. In addition, by using a novel agent, we may risk introducing poorly understood variables that will cloud the issue; something that can be prevented by using the current gold standard which has a well documented efficacy and safety profile.

Table 1: Summary for the use of LMWH

Study	Design	Bleeding Warfarin: LMWH	Recurrent VTE Warfarin: LMWH
Meyer et al, 2002	Patients with cancer and VTE randomised to 3 months of treatment with either LMWH enoxaparin (1mg/kg) or warfarin	Major: 12/75 (16%): 5/71 (7%)	3/75 (4%): 2/71 (2.8%) (calculated from combined endpoint minus bleeding)
CLOT Lee et al, 2003	Patients with active cancer presenting with acute VTE randomised to receive LMWH dalteparin or oral anticoagulant therapy	Major: 12/335 (4%): 19/335 (6%) (p=0.27) Any bleeding: 13.6%: 18.5% (p=0.09)	53/336 (15.8%): 27/336 (8%)
LITE Hull et al, 2006	Patients with acute VTE and cancer randomised to receive either unfractioned heparin followed by warfarin for 84 days at a targeted INR of 2.5, or	At 3 months: 24/100 (24%): 27/100(27%)	At 3 months: 10/100 (10%): 6/100 (6%) At 1 year:

	LMWH tinzaparin (175 International Units/kg) for 85 days		16/100 (16%): 7/100 (7%) (p=0.044)

Therefore, to ensure the safety of this patient group, we propose to test the feasibility of extending the use of the gold standard treatment, LMWH.

3.2 Research objectives

The purpose of this study is to address a specific gap in the evidence base for the management of cancer associated VTE in patients with ongoing malignant disease. To address this evidence gap, a sufficiently powered randomised controlled trial (RCT) is needed, to gain information relating to the sample group, which entails a vulnerable adult population, of uncertain number, prognosis, and with uncertainty around willingness to recruitment or likely attrition. Therefore, a trial is proposed specifically to look at the feasibility of progression to a phase 3 RCT, the primary outcome of which would be to determine the proportion of recurrent symptomatic VTE in cancer patients receiving an additional six months LMWH.

The overarching aims of this study are to:

- **To identify practicalities of conducting a full RCT with regard to recruitment, retention and outcome measurement**

  This will ensure all flagging and recruitment processes are running effectively, identify the number of eligible patients that can be recruited in a one year timeframe, identify the dropout rate, and assess the practical utility of measuring primary outcome measures, reporting processes, and assessment tools within the context of a full RCT. Through the proposed scoping exercise, we will be able to identify the likely spread of potential recruitment environments and thus gauge the degree of support a full RCT would attract.

- **To explore the barriers to progressing to a full RCT**

  In the event of sufficient numbers of patients being eligible for inclusion in the study, the barriers to recruitment are most likely to be logistical or attitudinal. The logistical challenges, such as how and where to identify patients for recruitment, will be addressed through the pragmatic conduct of the feasibility study and scoping exercise. The attitudinal barriers that need to be explored lie with the attitudes of clinicians and the cancer associated thrombosis (CAT) patients being invited to participate. Without the support of clinicians to recruit to a full RCT, it would be impossible to conduct the study. Since consensus recommendations advocate the continuation of LMWH anticoagulation beyond six months in patients with CAT and ongoing cancer, it is possible that clinicians will be unwilling to enter such patients into a trial due to a belief

that current practice, (despite lack of evidence) is correct. However, the necessity of continuation of anticoagulation is yet to be established and the economic implications remain to be determined. The views of patients who either do not consent to the study, or who withdraw from the study post-randomisation, need to be explored in order to understand any reasons why they may be unwilling to take part. Whilst a qualitative study has suggested LMWH is an acceptable intervention in the treatment of CAT (8), this study only interviewed patients receiving LMWH for four weeks and their views may not reflect those of a patient who has been self-injecting for six months. Neither does it offer insight into whether these patients would be willing to self-inject for a further six months. The corollary is that patients may be reluctant to stop a drug that has been used to treat a previously experienced condition and would not consent to a trial if there was a chance the LMWH would be stopped.

Finally, we have carefully considered the selection of anticoagulant to be used for extended treatment. This is discussed in more detail in the summary of clinical evidence. Several systematic reviews and international guidelines recommend LMWH as the treatment of choice when compared to warfarin in the treatment of CAT. Warfarin has already been demonstrated as inferior to LMWH in treatment of CAT for the first six months. The bleeding rate has been demonstrated to be greater in CAT patients receiving warfarin as the disease progresses (13). This does not appear to be dependent on the International Normalised Ratio (INR) (19).

3.3 Primary Outcomes:

(i) Number of eligible patients over 12 months

A screening log will be kept in each recruitment site to identify patients potentially meeting the inclusion criteria. Eligible patients who are approached about the trial and given the participant information sheet (PIS) will be anonymously registered on a central database. This will help to inform the design of a Phase III study.

(ii) Number of recruited patients over 12 months (target recruitment rate of 30% of eligible patients)

Patients meeting the inclusion criteria will be invited to participate in the study as outlined. The number of eligible participants consenting to randomisation shall be recorded.

(iii) Proportion of randomised participants with recurrent VTEs during follow-up

The number of randomised patients experiencing recurrent symptomatic VTE shall be recorded and used to inform the sample size required for a full RCT. VTE will be objectively confirmed through radiological investigation. DVT will be confirmed through Doppler ultrasonography or venography. PE shall be confirmed through computerised tomography pulmonary angiogram(CTPA).

3.4 Secondary Outcomes:

(i) Completion of trial protocol

This will be assessed six months after randomisation to ascertain the attrition rate due to death during the study period or patient choice. Participants choosing to withdraw from either arm of the study protocol will be invited to participate in a qualitative interview to explore the reasons for withdrawal.

(ii) Costs

The feasibility study will identify key cost drivers to inform the design of a future definitive trial, which will include a cost utility study.

(iii) Quality of life

Participants' quality of life will be measured using the EORTC QLQ-C30 Version 3.0 and EQ-5D-5L at three monthly intervals for six months. The EORTC QLQ–C30 Version 3.0 has become a benchmark measure of quality of life (QoL) in cancer patients. It contains five functional scales: physical, role, cognitive, emotional and social; three symptom scales: pain, nausea/vomiting and fatigue, global health and quality of life scales and several other single items. The EQ-5D-5L is a short QoL tool, designed to complement other QoL measures and is recommended by National Institute for Health and Clinical Excellence (NICE) for use in economic analyses.

(iv) Symptom assessment

Symptoms will be assessed using the Edmonton Symptom Assessment System Revised (ESAS-r) at three monthly intervals for six months. The ESAS-r is used to capture participants' perspective on their symptoms, providing an indication of symptom severity of nine symptoms: pain, tiredness, drowsiness, nausea, lack of appetite, depression, anxiety, shortness of breath, wellbeing (20, 21). In addition, we will look for symptoms likely to be specifically due to VTE; new or worse leg swelling/pain, new or worse breathlessness, and pleuritic chest pain.

(v) Attitudes of clinicians and patients

The qualitative components of the trial will provide rich data in relation to the attitudes of clinicians recruiting to the study and to patient motivation to participate in the trial, perceived benefits and burdens, and reasons for withdrawal from the trial.

There will be two qualitative components in total; focus groups with clinicians and patient interviews.

4.0 Study design

This is a mixed methods study involving the following four components:

Randomised controlled trial comparing ongoing LMWH treatment for CAT vs. cessation of LMWH at six months treatment (current licensed practice) in patients with locally advanced or metastatic cancer. Patients will be recruited in two stages. Stage 1 will be considered complete once 62 patients have been registered. If at least 15 out of these 62 participants accept randomisation, then we will continue recruitment in stage 2 of the trial, until 200 patients have been registered in total.

Nested qualitative study to explore attitudes towards participating in the study; potential barriers and concerns to participation; factors influencing compliance with self-injecting (where appropriate). Interviews shall be held with:

- Patients who do not wish to continue with LMWH;
- Trial participants in the intervention arm;
- Trial participants in the control arm;
- Carers of trial participants;
- Participants who withdraw from the study.

Focus groups with clinicians from oncology, haematology and primary care will explore attitudes to recruiting to the study, to identify the challenges of progressing to a full RCT.

A **UK wide survey exercise** to develop a classification and enumeration system for the CAT models and pathways of care.

This trial has been categorised by the Sponsor as risk assessment Type A, i.e. comparable to the risk of standard medical care, under the MRC/DH/MHRA Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products.

5.0 Participating site selection

This study will be carried out at three types of participating sites within the United Kingdom (UK). All sites who are interested in participating in the trial will be required to complete a registration form to confirm that they have adequate resources and experience to conduct the trial.

The key clinician managing the long-term anticoagulation of CAT in this patient group varies across the United Kingdom; with responsibility, and thus recruitment setting, differing between primary care, haematology and the oncology clinic. In order to assess the feasibility of recruiting sufficient numbers to inform a full RCT, three recruitment settings will be evaluated:

- Oncology outpatients will be recruited at two hospital sites: Velindre Cancer Centre, Velindre NHS Trust (catchment population 1.5 million) and Aneurin Bevan CAT Clinic, Aneurin Bevan Health Board (catchment population 639,000);
- Haematology outpatients will be recruited at Warwick Hospital (South Warwickshire NHS Foundation Trust) and George Eliot Hospital (George Eliot Hospital NHS Trust) both of which fall under the remit of the the Arden Cancer Research Network (catchment population 1,000,000), and Worcester Royal Hospital (Worcester Acute Hospitals NHS Trust);
- Primary Care; research networks (Primary Care Research Network for Central England (PCRN-CE) and The Midland Research Practices Consortium (MidReC)), using approximately 15 practices recruited from the following Clinical Commissioning Groups (CCGs) each in:
    - NHS Birmingham South Central CCG (catchment population 383,000);
    - NHS Coventry & Rugby CCG, NHS Warwickshire North CCG and NHS South Warwickshire CCG, all which fall under the remit of the Arden Cluster (Coventry & Warwickshire) (catchment population 914,008);
    - Oxfordshire CCG (catchment population 689,500).

A different member of the TMG will act as the Principal Investigator (PI) within each recruitment setting:

- Oncology outpatients – Dr Simon Noble;
- Haematology outpatients – Dr Peter Rose;
- Primary care - Dr David Fitzmaurice.

The following documentation must be completed and received by the WCTU in order for a site to begin recruitment:

- Confirmation of local R&D approval;
- Favourable opinion of host care organisation/Principal Investigator from Research Ethics Committee (REC);
- Signed partnership agreement between the host care organisation and Sponsor;
- Current Curriculum Vitae (CV) and Good Clinical Practice (GCP) training certificate of the PI;
- A copy of the most recent approved version of the Participant Information Sheet(s) and Consent Form(s) on host care organisation headed paper;
- A copy of the most recent approved GP or Oncologist letter on host care organisation headed paper;
- A copy of the most recent Pregnancy Information Sheet(s) and Consent Form(s) on host care organisation headed paper;
- Completed Delegation Log (signature list and delegation of responsibilities);
- Full contact details for all host care organisation personnel, indicating preferred contact;
- A set of laboratory normal ranges and laboratory certification/accreditation from the host care organisation laboratory being used for analyses .

Once all the documentation has been received at the WCTU, confirmation of site approval will be sent by the WCTU to the site PI.

All documentation must be stored in the Investigator Site File (ISF) at the site and in the Trial Site File (TSF) at the WCTU. The WCTU must be notified immediately of any changes to the trial personnel and their responsibilities during the running of the trial and the respective trial files must contain this up-to-date information.

Site initiation will be by attendance at an ALICAT launch meeting or by teleconference/one-to-one meetings if attendance of key personnel is unfeasible.

The WCTU will not provide GCP training for participating sites. However, the Dr David Fitzmaurice will provide trial-specific GCP training for Primary Care sites where appropriate and necessary.

6.0 Participant eligibility

Any queries about whether a patient is eligible to enter the trial should be discussed with the WCTU before randomisation. Any issues will then be raised with the CI or one of the clinical Co-Investigators in the CI's absence.

Patients are eligible for the trial if all the inclusion criteria (Section 6.2) are met and none of the exclusion criteria (Section 6.3) apply.

6.1 Screening procedures

Index VTE events shall be identified through primary and secondary care clinical databases and clinical records.

Oncology and Haematology outpatient settings:

Potential participants will already be attending outpatients for management of their cancer or CAT. Potential participants will be screened by a NISCHR (Welsh sites) or NIHR NCRN (English sites) researcher and flagged up to the local PI.

Primary Care setting:

Potential participants will be screened by a dedicated full time Trial Manager/Researcher in the Primary Care Clinical Research & Trials Unit (PC-CRTU) at the University of Birmingham. Patients who meet the eligibility criteria will be invited to the participating practice to consider participating in the study. The search will be repeated on a monthly basis in order to identify incident cases.

Before any trial related procedures are undertaken, the patient's written informed consent must be obtained. The patient should be given adequate time after the initial invitation to participate before being asked to sign the consent form.

6.2 Inclusion criteria

Patients meeting any of the following criteria may be included in the trial:

1. Receiving LMWH for treatment of CAT for approximatly five months;
2. Locally advanced or metastatic cancer;
3. Able to self-administer LMWH, or have LMWH administered by a carer*;
4. Able to give informed consent;
5. Age ≥16 years.

* Routine administration of LMWH by a District Nurse is <u>not</u> permissible.

The PI must confirm the eligibility of a patient in the patient's medical notes prior to randomisation.

6.3 Exclusion criteria

If any of the following criteria apply, patients cannot be included in the trial:

1. Receiving drug other than LMWH for CAT;
2. Contraindication to continuing anticoagulation;
    a. known allergies to LMWHs, heparin, sulfites or benzyl alcohol;
    b. active major bleeding,
    c. history of heparin-induced thrombocytopenia,
    d. known poor compliance with LMWH;
3. Confirmed recurrent VTE whilst receiving anticoagulation;
4. Fitted with a prosthetic heart valve;
5. Pregnant and/or lactating females.

6.4 Completion of screening logs

Information on all eligible patients should be recorded on the ALICAT screening log. The log should record whether or not patients were eligible for the trial and if they were approached about the trial. It should also record if they agreed to randomisation or were approached about taking part in a qualitative interview. Where possible, information on why the patient was not approached, randomised or approached for the qualitative interview should also be recorded.

Screening logs should be stored at the site until the end of the trial, but may also be requested periodically by the WCTU.

6.5 Patient registration

Eligible patients should be approached by the investigator and invited to take part in the ALICAT trial when they are approaching the completion of their first 5 months treatment with LMWH for CAT. The eligible patients should be posted ALICAT PIS and Consent Form 1, which explains the rationale behind randomisation and what will happen if the patient takes part in the trial, with their 5 month clinical appointment.

Prior to obtaining participant consent, the clinical trials nurse should telephone the WCTU randomisation line to register that a patient has been approached and given the ALICAT PIS and Consent Form 1. A unique Patient Registration Number will be given to the caller, and this should be recorded on the ALICAT screening log. At this stage, no patient information or identifiers will be collected and complete patient anonymity will be maintained.

To register a patient, please call:

WCTU Registration/Randomisation line:
029 2064 5500
(Open Monday – Friday, 9am – 5pm)

N.B. This telephone number is strictly for registration/randomisation and should not be used for general queries.

6.6 Informed consent

The ALICAT trial involves six different PIS and Consent Forms. It is important that the correct documents are used for each part of the trial (randomised controlled trial, qualitative interviews and clinician focus group). Please refer to Section 1.0 Trial Schema which defines when each document should be used and for which type of trial participant. Under the circumstances that a potential participant does not have a good understanding of spoken and written English, an impartial interpreter will be made available at a specified outpatient clinic appointment for that particular participant as per local practice. The use of an interpreter will be at the discretion of the site Principal Investigator. Under the circumstances that a Welsh speaking patient requests a PIS and Consent Form to be translated into Welsh under the principles of the Welsh Language Act, the site will contact the WCTU to make further arrangements.

6.6.1 Consent for the randomised controlled trial component of the trial

Registered patients should be asked if they consent to be randomised into the trial. The patient's written informed consent must be obtained using the ALICAT trial PIS and Consent Form 1. Only when written informed consent has been obtained from the patient and they have been randomised into the trial can they be considered a trial participant.

Patients will also be asked to consent having their NHS number collected and to be registered with NHS Information Centre (NHS IC) Flagging so that the date and cause of death can be collected without longer-term follow-up. This will be optional and additional to the standard informed consent.

Where patients are recruited in primary care, their consent will be sought to notify their Oncologist. Where patients are recruited in secondary care, their consent will be sought to notify their General Practitioner (GP) of their involvement in the trial.

The patient's consent to participate in the trial should be obtained after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment. All patients must be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which they may be exposed. They will be informed of the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorised individuals other than their treating physician.

Patients should be given a minimum of 24 hours after being given PIS and Consent Form 1 to consider and discuss participation in the trial with friends and family. A contact number for someone at the site should be given to the patient should they wish to discuss any aspect of the trial. Following this, the randomising investigator should determine that the patient is fully informed of the trial and their participation, in accordance with the principles of GCP.

Patients should always be asked to sign a consent form. The person taking consent must be appropriately trained and named on the trial delegation log. The person taking consent, and the PI, must both sign the consent form. One copy should be given to the participant. The original copy should be kept in the investigator site file. A further copy should be kept with the participant's medical record (GP or hospital depending on the location of recruitment). A photocopy should be sent to the WCTU for compliance monitoring purposes.

The right of the patient to refuse to participate in the trial without giving reasons must be respected. After the patient has entered the trial, the investigator must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the participant. However, the reason for doing so should be recorded in the CRF and the participant will remain within the trial for the purpose of follow up and data analysis according to the treatment option to which he/she has been allocated. Similarly, the participant must remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing his/her further treatment.

For those consenting to be randomised into the study; neither the participants nor their physicians will be able to choose the participant's treatment. Treatment will be allocated randomly using a computer-based algorithm. This is to ensure that the groups of participants receiving each of the different treatments are similar.

6.6.2 Informed consent for qualitative interviews

Patients will also be asked if they would consider taking part in an optional qualitative sub-study, which is designed to explore their reasons for, and experiences of, taking part in the trial. If they agree to be contacted by a Qualitative Researcher to discuss taking part in an interview they will be asked to initial the relevant boxes on the main trial consent form. They will then be given an additional PIS, which explains the qualitative sub-study and the next steps, and consent form to sign (refer to Section 1.0 Trial Schema for which patients should be given which PIS). Consent Forms should be distributed and filed as described above in Section 6.6.

7.0 Randomisation

Participant randomisation will be performed centrally by the WCTU. Randomisation can only be performed once the participant has signed the Consent Form 1.

The randomisation form should be completed and the WCTU contacted on the following telephone number:

WCTU Randomisation:
029 2064 5500
(Open Monday – Friday, 9am – 5pm)

N.B. This telephone number is strictly for randomisation/registration and should not be used for general queries.

Participants will be randomised to a trial arm using random blocks.

At randomisation, the participant will be given a unique participant trial number and the treatment allocation. These details should be recorded on the participant enrolment case report form (CRF) and the top copy returned to the WCTU within four weeks.

If the patient consents to a copy of the consent from being sent to the WCTU (this is a separate question on the consent form), please also fax a copy of the signed Participant Consent Form 1 to the WCTU at 029 2068 7501. The randomiser will check this consent form during the randomisation as part of the central monitoring of consent for this trial.

After randomisation, the WCTU will fax confirmation to the Research Nurse/GP at the participating site.

The participant's GP or Oncologist (as appropriate) will be informed by the site of the participant's randomisation, if the participant gives consent to do so.

Participants randomised to the intervention arm of the trial will be given a Participant Trial Card and asked to carry it with them at all times, and to show it to their Research Nurse/Clinician/GP at each visit. They will also be given a participant diary card to record their trial medication (prescriptions and LMWH injections), concomitant medication, symptoms, and use of healthcare facilities. Participants randomised to the control arm of the trial will also be given a participant diary card, but only need to complete the symptom and use of healthcare facilities sections.

It may be possible for participants to be recruited into other clinical trials, but this should be discussed with the ALICAT CI via the WCTU before this is considered.

8.0 Trial treatments

Currently, dalteparin (Fragmin®) is the only LMWH licensed specifically for the long-term treatment of CAT. However, enoxaparin (Clexane®) and tinzaparin (Innohep®) are still used in some practices for the treatment of CAT and these three LMWHs are the trial IMPs in ALICAT.

As this is a pragmatic feasibility study, participating clinicians' treatment practices will not alter. The type of LMWH used will be recorded. Switching from one protocol IMP to another protocol IMP during the trial treatment period is allowed if deemed necessary by the treating clinician, and must be documented on the treatment CRFs.

As a guide, the recommended doses of each LMWH as per their Summary of Product Characteristics (SPCs) are given below. Current SPCs can be found at www.medicines.org.uk/emc/. Since this is a pragmatic trial, they are documented for guidance. However, it is recognised that dose alterations may occur over time as per the clinician's judgement.

LMWH	Month 1	Month 2-6	Entry to ALICAT
dalteparin (Fragmin®)	200 International Units/kg total body weight, once daily	150 International Units/kg total body weight, once daily	Dose as detailed at month 6
tinzaparin (Innohep®)	175 International Units/kg total body weight, once daily	175 International Units/kg total body weight, once daily	Dose as detailed at month 6
enoxaparin (Clexane®)	1.5 mg/kg (150 International Units/kg) total body weight, once daily	1.5 mg/kg (150 International Units/kg) total body weight, once daily	Dose as detailed at month 6

Within current practice, the dose of LMWH may be altered at the discretion of the supervising clinician for the following reasons:

- **Reason for increasing dose of LMWH:**

  Recurrence of symptomatic VTE despite administration of weight adjusted dose as per SPC. Some clinicians may use measurements of anti-Xa levels to guide LMWH dosing in this situation.

- **Reason for decreasing dose:**

  Sometimes patients may experience minor bleeding which will resolve on decreasing the dose of LMWH. This is a clinical decision of the supervising clinician that will be made

based on balancing the perceived risks of recurrent VTE should LMWH be stopped or major bleeding should LMWH be continued.

- **Dose for obese patients:**

  In the case of dosing obese patient, follow the SPC or local clinical practice.

- **Dose for renal impairment:**

  In the case of renal impairment, follow the SPC. Renally impaired patients should have dose adjustment depending on creatinine clearance/anti factor Xa levels according to local policy.

8.1 Trial Arm A - Continue LMWH

Participants randomised to this trial arm will have already received LMWH at treatment dose for six months and should continue the same drug at the same dose for a further six months. No dose alterations are required unless clinically indicated (see Section 8.1.2).

LMWH is an anticoagulant (given daily as a subcutaneous injection) used in the prevention and treatment of VTE. It has a documented safety profile and very few significant drug-drug interactions (see 8.1.4).

8.1.1 Scheduling

The LMWH shall be given as a daily subcutaneous dose at the same time as previously administered over the previous six months.

8.1.2 Dose delays and modifications

The LMWH shall be administered as per normal CAT treatment practice and as such, there will not be any anticipated dose delays or alterations.

As this is a pragmatic feasibility study, dose modifications should be based on the clinical opinion of the physician responsible for the anticoagulation as per usual practice. In the event of an SAE, the treating clinician should make the decision as to whether to continue or discontinue LMWH treatment.

Such examples may include:

- Dose increase for recurrent VTE;
- Dose reduction for bleeding complications.

Any alteration of LMWH administration or dose will be documented in the patient diary booklets and in the treatment and compliance CRF.

Episodes of bleeding or recurrent VTE shall be documented as per the VTE event CRF.

8.1.3 Measures of compliance / adherence

Compliance shall be monitored through review of participant diary cards during trial visits and as part of the qualitative interview study. Information from diary cards will be transferred to the treatment CRF by the research nurse. The WCTU will then review compliance through central monitoring.

8.1.4 Concomitant medications / procedures

Participants randomised to trial arm A will have been receiving LMWH for six months when randomised, during which time permitted procedures and concomitant medications will have been observed according to local policies. These policies should be followed for the ongoing trial. Participants will be asked to record their medications in the participant diary booklets.

The use of concomitant medicines shall be at the discretion of the local PI but must be documented in the CRFs.

- **Permitted concomitant medications / procedures**
  As per local policy for patients receiving LMWH for CAT.
- **Medications permitted with caution / procedures**
  As per local policy for patients receiving LMWH for CAT.
- **Non-permitted concomitant medications / procedures**
  As per local policy for patients receiving LMWH for CAT. However, non-steroidal anti-inflammatory drugs (NSAIDs) (e.g. ketorolac (toradol®, dextran, and clopidogrel) have a well-documented risk of causing increased bleeding when given with LMWH, and are specifically contraindicated.

8.1.5 Drug supply, distribution and storage

Participants randomised to trial arm A shall continue receiving the LMWH they have been receiving for the previous six months.

It is not the intention that the ALICAT trial will change the way the LMWH is normally prescribed, and we have sought consent from the MHRA for a clinical trial labelling exemption, because a requirement for labelling could affect the results of the trial. The ALICAT trial will be fully exempt from the UK Statutory Instrument The Medicines for Human Use (Clinical Trials) Regulations 2004 No. 1031 Part 7 Regulation 46 with respect to IMP labelling and dispensing.

IMP shall be prescribed by the participant's GP, oncologist or haematologist according to pre-existing local arrangements. A trial-specific prescription form will not be provided. All sites should use their local prescription form and standard local prescription procedure.

The drug shall be dispensed from commercial stock through local hospital pharmacies (NHS Trust/Health Board sites) or high street pharmacies (GP Practice sites).

Trial-specific IMP labels will not be provided by the WCTU. Prior to dispensing IMP to trial arm A participants, pharmacies should label the IMP with their local label prior following standard local practice.

It is anticipated that excess treatment costs will only be incurred for participants allocated to the treatment arm at participating sites where currently it is not common practice to extend LMWH treatment for CAT beyond six months. Excess treatment costs will not be incurred for participants allocated to the control arm of the trial, irrespective of the local policy for extended LMWH treatment.

The LMWH should be stored as per local policy.

Returned IMP should be disposed of according to local policy.

8.1.6 Drug interactions

LMWHs have an increased bleeding risk with the following medicines:

- Aspirin
- Warfarin
- Rivaroxaban
- Dabigatran
- Apixaban
- Ketorolac

Treatment with aspirin is allowed if the patient has already been receiving aspirin during the first 5 months of LMWH treatment without any problems. If a patient is switched to any of the anticoagulant treatments warfarin, rivaroxaban, dabigatran or apixaban, then they should be withdrawn from ALICAT trial treatment. Keterolac is also not allowed within this trial.

8.2 Discontinue LMWH (trial arm B)

Participants randomised to arm B shall stop LMWH once a total of six months drug has been administered from the initial diagnosis of VTE. Participants will be given a diary booklet to record any other medications prescribed during the trial period.

8.3 Drug accountability

There is no requirement for sites to complete trial specific drug accountability forms. Details of drugs administered (e.g. prescriptions, patient compliance, and any alterations to IMP formulations) will be captured in the CRF, with the aide of the patient diary booklet.

9.0 Trial assessments for participants randomised to trial arms A and B

9.1 Baseline assessments

- Confirmation of consent
- Disease history – diagnosis details of primary tumour
- Cancer treatment history – details of surgery, radiotherapy and/or chemotherapy
- History of index VTE – site of VTE and date diagnosed
- VTE treatment history – type of LMWH, dosage, details of whether LMWH is self-administered or carer-administered, details of other VTE treatments, e.g. stent
- Physical assessment – ECOG performance status, weight
- Current disease status – details of local recurrence, nodal and metastatic disease sites
- Haematology – WBC, haemoglobin, ANC, platelets
- Urea and Electrolytes – urea, sodium, potassium, creatinine and urea
- Liver Function test – albumin, ALT/AST, ALP and total bilirubin
- Bone profile – calcium and phosphate
- Comorbidities (baseline toxicity) – any pre-existing conditions and current CTCAE grade V4.03
- Concomitant medication – all non-LMWH medication should be recorded
- Use of NHS resources in previous 3 months (hospital admissions, GP visits, nurse visits, etc.). Details to be taken from patient diary booklet and patient notes.
- Quality of life questionnaires:
    - EORTC QLQ-C30 Version 3.0
    - EQ-5D-5L
    - ESAS-r

Trial participants will be given a diary booklet at the baseline visit to record details of trial and non-trial medications and to any side-effects and adverse events.

9.2 Assessments during study

When arranging trial visits, please request that the participant brings their diary booklet along to clinic. Patients will return for two scheduled trial visits at week 12 and 26, but if the patient experiences a serious adverse event (SAE), a bleeding event, or a recurrent VTE event, these can be reported at any time until 30 days after the completion of the ALICAT trial.

9.2.1 Assessments to be undertaken at week 12

- VTE treatment and compliance – current dose of LMWH, details of missed doses and dose modifications to be taken from patient diary booklet.
- Physical assessment – performance status ECOG, weight
- Haematology* – as above
- Urea and Electrolytes* – as above
- Liver Function test* – as above
- Bone profile* – as above
- Toxicities – all side-effects and adverse events should be recorded on the CRF. Any SAEs (see section 10.0 for a definition) not already identified and reported to WCTU, should additionally be reported on a separate SAE form. Note that heparin induced thrombocytopenia (HIT) must be reported as an SAE.
- Concomitant medications – all non-LMWH medication should be recorded
- Use of NHS resources – as above
- Quality of life questionnaires:
    - EORTC QLQ-C30 Version 3.0
    - EQ5D-5L
    - ESAS-r

***No extra blood tests are required for the study, use latest routine blood test results**

9.2.2 End of treatment assessments at week 26

- VTE treatment and compliance – as above
- Physical assessment – as above
- Haematology* – as above
- Urea and Electrolytes* – as above
- Liver Function test* – as above
- Bone profile* – as above
- Toxicities – as above
- Concomitant medications – as above
- Use of NHS resources – as above
- Quality of life questionnaires:
    - EORTC QLQ-C30 Version 3.0
    - EQ5D-5L

- ESAS-r

***No extra blood tests are required for the study, use latest routine blood test results**

9.3 Unscheduled events

These events may be reported at any time from randomisation until four weeks after the end of the 26 week trial treatment phase (week 30). Separate CRF booklets are available to record each of these events. Some bleeding and VTE events may also fit the criteria for an SAE, in which case, both types of form should be submitted for the same event.

9.3.1 Serious Adverse Events

SAEs should be reported during the treatment period, and up to 30 days after the last treatment date, using the SAE CRF. Sites will be supplied with one SAE CRF booklet per site. See Section 10.0 for guidance on reporting SAEs. Note that planned hospital visits for cancer treatment should not be classed as SAEs and should be recorded on the CRF in the use of NHS resources section.

9.3.2 Bleeding events

The following details of bleeding events will be recorded on the bleeding events CRF. Sites will be supplied one bleeding event CRF booklet per site.

- Date of bleed;
- Site of bleed;
- Severity according to CTCAE V4.03 haemorrhage grading scale;
- Severity (major or minor) according to the classification used in the CLOT study (26). A bleeding event will be classified as major if it is associated with death, occurred at a critical site (intracranial, intraspinal, intraocular, retroperitoneal, or pericardial area), resulted in a need for a transfusion of at least two units of blood, or led to a drop in hemoglobin of at least 2.0 g per decilitre.
- Number and type of blood transfusions;
- Outcome.

9.3.3 VTE events

The following details of VTE events will be recorded on the VTE events CRF. Sites will be supplied one VTE events CRF booklet per site.

- Date of VTE;
- Site of VTE;

- Method of confirmation. DVT will be confirmed through doppler or venography, PE shall be confirmed through CTPA.

9.3.4 Withdrawal

Participants are free to withdraw from the main trial and/or qualitative interview (as appropriate) at any time. Participants who are withdrawing from treatment will be encouraged to continue with trial follow-up visits and assessments. The following information will be collected on the withdrawal form.

- Date of withdrawal;
- Level of withdrawal;
- Reason for withdrawal.

Please refer to Section 11.3.2 for further information about withdrawal from qualitative interviews.

9.3.5 Death

The following information will be collected in the event of death:

- Date of death;
- Cause of death, disease progression, bleeding event, VTE event, or other reason.

9.4 Completion of CRFs

The top copy of each completed CRF should be returned to the WCTU for data entry **within four weeks of the scheduled visit**, or as soon as possible after any of the unscheduled events listed above. The remaining copy is to be retained at the local site. Ensure that the CRF is as complete as possible before submitting to WCTU.

CRF pages and data received by the WCTU from participating trial sites will be checked for missing, illegible or unusual values (range checks) and consistency over time.

The PI is responsible for ensuring the accuracy, completeness, legibility and timeliness of data reported on CRFs.

If missing or questionable data are identified, a data query will be raised on a data clarification form. The data clarification form will be sent to the relevant participating site. The site shall be requested to answer the data query or correct data on the data clarification form. **The case report form pages should not be altered.**

All answered data queries and corrections should be signed off and dated by a delegated member of staff at the relevant participating site. The completed data clarification form

should be returned to the WCTU and a copy retained at the site along with the participants' CRFs.

The WCTU will send regular reminders for any overdue CRFs and/or data. It is the site's responsibility to submit complete and accurate data in timely manner.

9.5 Schedule of trial assessments

Procedure / Assessment	Trial visit				
	Baseline	Week 12	Week 26	Any time until week 30	Week 26 onwards
Confirmation of consent	X				
Provision/review of diary cards	X	X	X		
Disease history	X				
Cancer treatment history	X				
History of index VTE	X				
VTE treatment history	X				
VTE treatment and compliance		X	X		
Physical assessment	X	X	X		
Current disease status	X				
Haematology	X	X	X		
Urea and Electrolytes	X	X	X		
Liver function test	X	X	X		
Bone profile	X	X	X		
Toxicity (comorbidities)	X	X	X		
Concomitant medication	X	X	X		
Use of NHS resources	X	X	X		
EORTC QLQ-C30 Version 3.0	X	X	X		
EQ-5D-5L	X	X	X		
ESAR-r	X	X	X		
SAEs				X	
Bleeding events				X	
VTE events				X	
Withdrawal				X	
Death				X	
Qualitative Interviews (optional)					X

10.0 Safety reporting and pharmacovigilance

The following definitions are in accordance with both the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031), as amended.

Adverse Event (AE): Any untoward medical occurrence in a clinical trial participant to whom an IMP has been administered and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory finding), symptom, or disease. All AEs should be recorded in the toxicities section of the CRF whether considered minor or serious, drug related or not.

Adverse Reaction (AR): Any noxious and unintended response in a clinical trial participant to whom an investigational medicinal product has been administered, which is related to any dose administered. A "response" to a medicinal product means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

All AEs and ARs should be recorded in the toxicities section of the CRF.

Serious Adverse Event (SAE):

Any adverse event that:

- Results in death
- Is life-threatening*
- Required hospitalisation or prolongation of existing hospitalisation**
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Other medically important condition***

***Note:** The term "life-threatening" in the definition of serious 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 which hypothetically might have caused death if it were more severe.

****Note:** Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure, for continued observation. Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened, or elective procedures, does not constitute an SAE. Pre-planned admission for cancer treatment does not constitute an SAE.

*****Note:** other events that may not result in death, are not life-threatening, or do not require hospitalisation, may be considered as a SAE when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

In addition, for the purposes of this trial the following events will also be considered SAEs and must be captured on the SAE form.

Heparin induced thrombocytopenia (HIT)

Serious Adverse Reactions (SARs): Any SAE occurring in a clinical trial participant for which there is a reasonable possibility that it is related to the IMP at any dose administered (possibly, probably or definitely related to the IMP).

Suspected Unexpected Serious Adverse Reactions (SUSAR): These are SARs which are classified as 'unexpected' i.e. an AR, the nature and severity of which is not consistent with the information about the medicinal product outlined in the summary of product characteristics (SPC) for that product. The current SPC can be accessed at **www.emc.medicines.org.uk** and a copy will be kept in each site's trial site file. Expectedness decisions must be based on the content of the SPC; other factors such as participant population and participant history should not be taken into account.

Please see Table 1. for a list of reported side effects with LMWH. Please note that although this list was exhaustive at the time of authorisation of this protocol, the SPC may have been updated and we encourage you to consult the most recent version for the treatment(s) in question when assessing the expectedness of an adverse reaction. The current SPC can be accessed via www.emc.medicines.org.uk.

Table 2. Reported side effects with LMWH as specified in SPCs

	Frequency
Blood and Lymphatic system disorders	
Thrombocytosis	Rare
Reversible Mild nonimmunologically-mediated thrombocytopenia (type I)	Common
Immunologically-mediated heparin-induced thrombocytopenia (HIT)	Rare
Immune system disorders	
Allergic reactions	Rare
Endocrine disorders	
Hyperkalaemia	Uncommon
Hypoaldosteronism	Uncommon
Metabolic acidosis	Uncommon
Cardiac disorders	
Prosthetic cardiac valve thrombosis	Rare
Vascular disorders	
Haemorrhage (bleeding at any site)	Common
Hepatic and biliary disorders	
Transient elevation of liver transaminases	Common
Raised gamma-GT	Rare
Skin and subcutaneous tissue disorders	
Rash, Urticaria, pruritus	Uncommon
Skin necrosis, transient alopecia	Rare
Pain at injection site	Common
Subcutaneous haematoma at injection site	Common
Gastrointestinal disorders	
Retroperitoneal bleeds	Not known
Injury, poisoning and procedural complications	
Spinal or epidural haematoma	Not known
Nervous system disorders	
Headache	Uncommon
Musculoskeletal and connective tissue disorders	
Osteoporosis has been reported in connection with long-term treatment with heparin	Not known
Reproductive system and breast disorders	
Priaprism	Not known

Adverse events (AE) should be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (Appendix 1). The toxicity grades should be recorded on the toxicity part of the CRF.

An SAE form is not considered as complete unless the following details are provided:

- Full participant trial number
- An AE /AR
- A completed assessment of the seriousness, causality and expectedness as performed by the PI or another appropriately qualified clinician registered on the delegation log

If any of these details are missing, the site will be contacted and the information must be provided by the site to the WCTU as soon as it becomes available.

10.1 SAE reporting exceptions

For the purposes of this trial the following events do not require immediate reporting:

Death due to disease progression Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened, or elective procedures Pre-planned admission for cancer treatment

These should be completed on the relevant CRF page and forwarded to the WCTU in the normal timeframes for CRFs.

10.2 Pregnancy reporting whilst participating in the ALICAT trial

Pregnancy, or the pregnancy of a partner occurring whilst participating in ALICAT trial, although not considered an SAE, must be notified to the WCTU within the same timelines as an SAE (i.e. during the trial treatment period and up to 30 days after the last date of treatment). In the event of a pregnancy, if the participant or the female partner of a male participant have read the Pregnancy Information Sheet, and signed the Pregnancy Consent Form, the WCTU must be contacted immediately to request a Pregnancy Report Form. The Pregnancy Report Form should be completed and returned to the WCTU to capture all the relevant information required for the expedited reporting of these events. The outcome of a pregnancy should be followed up carefully and any abnormal outcome of the mother or the foetus should be reported. This also applies to pregnancies following the administration of the investigational medicinal product to the father prior to sexual intercourse.

10.3 Participating site responsibilities

All SAEs must be reported immediately by the PI at the participating site to the WCTU unless the SAE is specified as not requiring immediate reporting (see above). This includes SAEs related to IMPs. All other AEs should be reported on the CRF following the CRF procedure described in Section 12.1. The PI should assess the SAE to determine the likely causality with the trial treatment (graded as definitely, probably, possibly, unlikely or not related) and the expectedness (unexpected or expected). The PI should sign and date the SAE CRF to acknowledge that he/she has performed this assessment. A completed SAE form for all events requiring immediate reporting should be faxed to the WCTU within 24 hours of knowledge of the event. A separate form must be used to report each event, irrespective of whether or not the events had the same date of onset.

Serious Adverse Event (SAE) Fax Number:

029 2064 4488

It is also required that sites respond to and clarify any queries raised on any reported SAEs and report any additional information as and when it becomes available through to the resolution of the event.

Serious adverse events should continue to be reported until 30 days after the participant receives their last dose of the investigational medicinal product. Serious adverse reactions should continue to be reported until the end of follow up.

10.4 The WCTU responsibilities

Following the initial report, all SAEs should be followed up to resolution wherever possible, and further information may be requested by the WCTU. The participant will be identified only by trial number, date of birth and initials. The participant's name should not be used on any correspondence.

Cardiff University is undertaking the duties of trial Sponsor and has delegated to the WCTU the responsibility for reporting SUSARs and other SARs to the regulatory authorities (MHRA and relevant ethics committees) as follows:

SUSARs which are fatal or life-threatening must be reported no later than seven days after the Sponsor is first aware of the event. Any additional, relevant information must be reported within a further eight days.

SUSARs that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming aware of the reaction.

A list of all SARs (expected and unexpected) will be reported annually to the MHRA and REC in a Development Safety Update Report (DSUR). The DSUR must be submitted within 60 days of the anniversary of the MHRA CTA approval date.

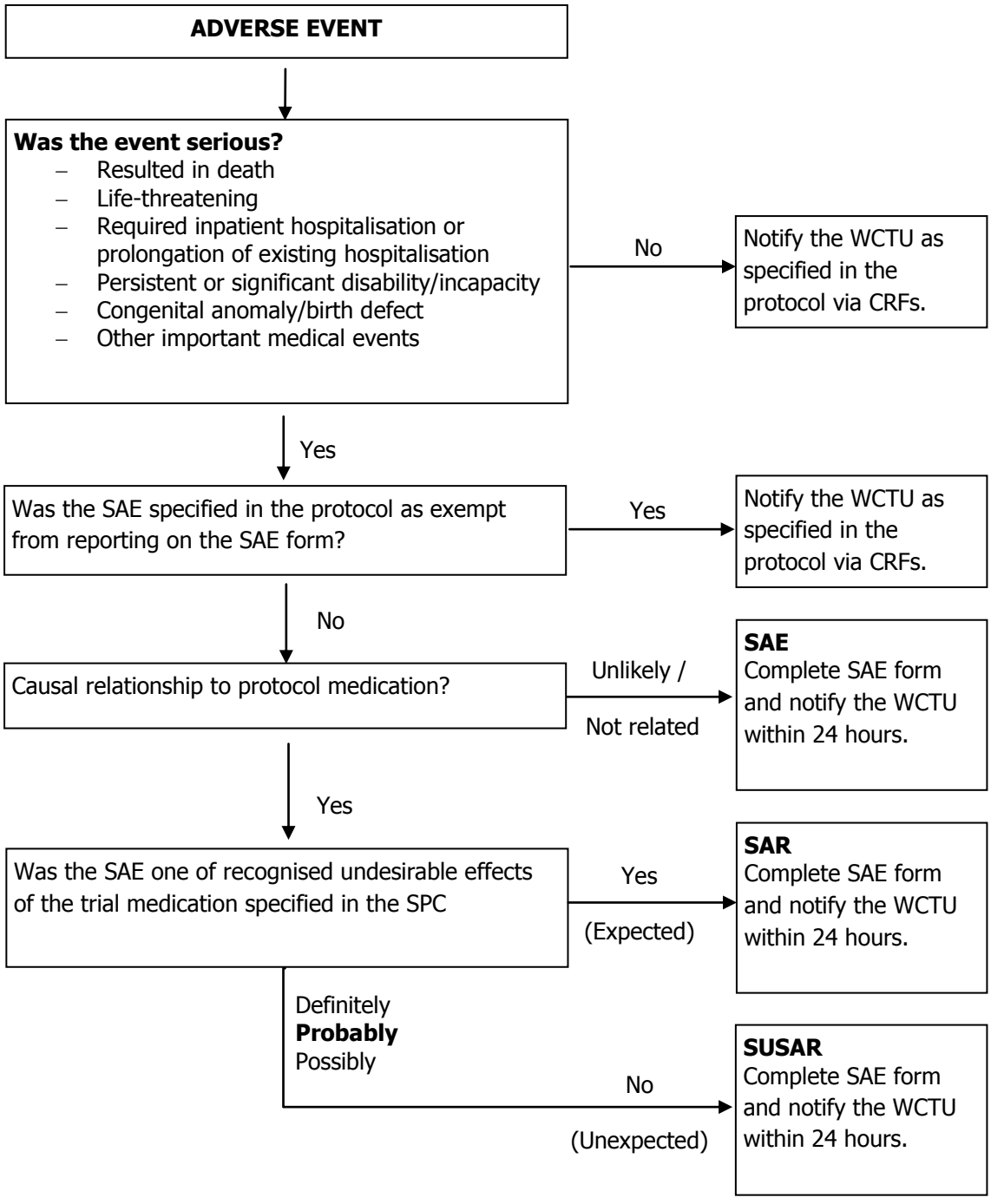
The WCTU will report a list of all SARs (expected and unexpected), and any other safety recommendations, to all the REC and PIs every year throughout the course of the trial via an Investigator Safety Report (ISR). This frequency may be reviewed and amended as necessary.

The WCTU should continue reporting SAEs until 30 days after the participant receives their last dose of the IMP. Serious adverse reactions should continue to be reported until 30 days after the end of trial treatment.

Once an SAE is received at the WCTU, it will be evaluated by staff at the WCTU and the CI (or their delegate) for seriousness, expectedness and causality. Investigator reports of suspected SARs will be reviewed immediately and those that are SUSARs identified and reported to the MHRA, and REC.

The causality and expectedness assessment given by the PI cannot be downgraded by the CI (or their delegate) and in the case of disagreement; both opinions will be provided with the report.

10.5 Flowchart for Serious Adverse Event reporting



CRF Case Report Form
SAE Serious Adverse Event
SAR Serious Adverse Reaction
SUSAR Suspected Unexpected Serious Adverse Reaction
SPC Summary of Product Characteristics
WCTU Wales Cancer Trials Unit

11.0 Trial management

11.1 Trial committees and trial management

The conduct of the trial is being overseen by the following committees:

- **The Trial Management Group (TMG)** will be responsible for the day-to-day running of the trial and will meet at least once every six months. The TMG members will include the Chief Investigator, other active trial investigators, WCTU representatives, and specialist advisors (e.g. Pharmacist, Statistician, consumer representative).

- A data management plan will be developed. The data will be reviewed (approximately six monthly) by an **Independent Data Monitoring Committee** (IDMC), consisting of at least two Clinicians (not entering patients into the trial) and an independent Statistician. An interim IDMC meeting will be held at the end of stage 1 of the trial, i.e. when 62 patients have been randomised. At this meeting the IDMC will review sufficient participants have accepted randomisation to merit continuation of recruitment into stage 2 of the trial. At the following meetings, the IDMC will be asked to recommend whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients. A decision to discontinue recruitment, in all patients or in selected subgroups, will be made only if the result is likely to convince a broad range of Clinicians including PIs in the trial and the general clinical community. If a decision is made to continue, the IDMC will advise on the frequency of future reviews of the data on the basis of accrual and event rates. The IDMC will make confidential recommendations to the Trial Steering Committee (TSC).

- **Independent Trial Steering Committee (TSC)** will be a committee of independent members that provides overall supervision of the trial. The role of the TSC is to act on behalf of the sponsor, to provide overall supervision for the trial, to ensure that it is conducted in accordance with GCP, and to provide advice through its independent chairman. The TSC will review the recommendations from the IDMC and will decide on continuing or stopping the trial, or modifying the protocol. It will meet at least annually when it will consider each report of the IDMC, as well as results of other trials and new information which has arisen, and recommend appropriate action.

- Clinicians from all collaborating sites will be invited to investigator meetings during the trial to review progress.

11.2 Monitoring

The clinical trial risk assessment has been used to determine the intensity and focus of monitoring activity in the ALICAT trial. Low intensity monitoring levels will be employed and fully documented in the monitoring plan.

A monitoring plan will be developed. Central monitoring of trial data from all trial sites will be performed regularly to assess form return rate and the completeness and quality of trial data returned from each participating site. If any major concerns are raised regarding patient safety and/or the quality and timeliness of the data from a particular site are raised, then an on-site monitoring visit may be triggered, where the trial site file will be monitored and source data verification will be performed.

11.3 Participant withdrawal

In consenting to the trial, participants are consenting to LMWH, trial follow-up and data collection. Patients may also optionally consent to a qualitative interview and NHS IC flagging.

Participants may withdraw from the trial at any time. Withdrawal for any reason requires a completed withdrawal CRF to be faxed to the WCTU with the hard copy to follow soon after. Participants do not have to give a reason for their withdrawal but sites should make a reasonable attempt to find out why.

11.3.1 Participant withdrawal for the main RCT

Participants may withdraw from the main RCT at the following levels:

Level 1: Withdraw from trial treatment – participants stop trial treatment but remain in follow-up.
Level 2: Complete withdrawal from the trial – participants stop trial treatment and do not remain in follow-up.

If a participant wishes to withdraw from trial treatment, participating sites should nevertheless explain the importance of remaining on trial follow up for the purposes of data capture only. If the participant explicitly states their wish not to contribute further data to the trial, the WCTU should be informed. Data collected prior to participant withdrawal at any of the two levels indicated above will be collected and used for trial analysis by the WCTU. Participants who initially consented to be registered with the NHSIC or equivalent will remain on the system so that important research information on date and cause of death can be requested from NHSIC by the WCTU.

A participant may withdraw, or be withdrawn, from trial treatment for the following reasons:

- Intolerance to treatment (including SAEs and toxicities)
- Participant choice

- Clinician's decision
- Non-concordance with protocol treatment (N.B. switiching to a different LMWH does not constitute non-concordance with protocol treatment)
- Other reasons including deterioration in clinical condition

11.3.2 Participant withdrawal for qualitative interviews

Participants are free to withdraw from the focus groups or qualitative interviews, at any time, either before, during or after the focus group/interview. Withdrawing interviewees who are taking part in the randomised controlled part of the trial may remain in the randomised controlled part of the trial if they wish. Participants do not have to give a reason for withdrawing from the qualitative sub-study if they do not wish to do so.

Level A: Withdraw from qualitative interview – still agree to the research team using their data.
Level B: Complete withdrawal from interview – does not agree to their data being used. The transcripts and recorded data will be edited or deleted accordingly.

11.4 Lost to follow-up

If a participant is lost to follow up the WCTU will contact the participant's GP to obtain information on the participant's status. Participants have the option to consent to NHS IC Flagging. This will entail completion of a separate consent form which will contain the participant name and will therefore be kept separate from the other data, and securely locked away. This will enable the WCTU to trace the participant cause and date of death.

11.5 The end of the trial

For the purposes of regulatory requirements the end of the trial is defined as the date of the final data capture to meet the trial endpoints, i.e. whichever of the following data capture events is the later:

- last participant completed schedule week 26 visit;
- last participant unscheduled event occurring up until week 30;
- last participant qualitative interview;
- last clinician focus group;
- last web survey data entry.

11.6 Archiving

The TMF and ISF containing essential documents will be archived at an approved external storage facility for a minimum of 15 years. The WCTU will archive the TMF and TSFs on

behalf of the Sponsor. The Principal Investigator is responsible for archival of the ISF at site for a minimum of 15 years. Essential documents pertaining to the trial shall not be destroyed without permission from the Sponsor.

12.0 Statistical considerations

12.1 Randomisation

Randomisation will take place after confirmation of eligibility by a telephone call to the WCTU. Patients will be randomised using block randomisation with varying block sizes. Randomisation will use a 1:1 allocation ratio.

12.2 Outcome measures

12.2.1 Primary outcome measure

(i) Number of eligible patients over 12 months

A screening log will be kept in each recruitment site to identify patients meeting the inclusion criteria. This will help to inform the design of a phase 3 RCT study.

(ii) Number of recruited patients over 12 months (target recruitment rate of 30% of eligible patients)

Patients meeting the inclusion criteria will be invited to participate in the study as outlined. The number of eligible patients consenting to randomisation shall be recorded.

(iii) Proportion of participants with recurrent VTEs during follow-up (weeks 1-30).

The number of patients experiencing recurrent symptomatic VTE shall be recorded and used to inform the sample size required for a full RCT. VTE will be objectively confirmed through radiological investigation. DVT will be confirmed through Doppler ultrasonography or venography. PE shall be confirmed through CTPA.

12.2.2 Secondary outcome measures

(i) Completion of trial protocol:

Will be assessed six months after randomisation to ascertain the attrition rate due to death during the study period or patient choice. Participants choosing to withdraw from either arm of the study protocol will be invited to participate in a qualitative interview to explore the reasons for withdrawal.

(ii) Quality of life:

Will be measured using the EORTC QLQ-C30 Version 3.0 (Appendix 2) and EQ-5D-5L (Appendix 3) at three monthly intervals for six months. The EORTC QLQ –C30 Version 3.0 has become a benchmark measure of QoL in cancer patients. It contains five functional scales: physical, role, cognitive, emotional and social; three symptom scales: pain, nausea/vomiting and fatigue, global health and quality of life scales and several other single items. The EQ-5D-5L is a short QoL tool, designed to complement other QoL measures and is recommended by NICE for use in economic analyses (see below).

(iii) Symptom assessment:

Will be measured using the Edmonton Symptom Assessment System Revised (ESAS-r; Appendix 4)) at three monthly intervals for six months. The ESAS-r is used to capture patients' perspective on their symptoms, providing an indication of symptom severity of nine symptoms: pain; tiredness; drowsiness; nausea; lack of appetite; depression; anxiety; shortness of breath; wellbeing (20, 21). In addition, we will look for symptoms likely to be specifically due to VTE: new or worse leg swelling/pain; new or worse breathlessness; pleuritic chest pain.

(iv) Attitudes of clinicians and patients

The qualitative components of the trial will provide rich data in relation to the attitudes of clinicians recruiting to the study and to patient motivation to participate in the trial, perceived benefits and burdens, and reasons for withdrawal from the trial. There will be two qualitative components in total: a) Focus groups with clinicians; b) Patient interviews (See 13.0)

12.3 Sample size calculation

We aim to assess the feasibility of randomisation by determining if at least 30% of potential patients will agree to randomization. We will document the proportion of patients with confirmed recurrent VTEs during follow-up. This will inform the design and sample size of the powered phase 3 RCT trial.

12.3.1 Expected numbers of eligible patients available:

We anticipate there being at least 200 eligible patients per year in total from all three recruitment settings:

i) Oncology (Velindre Cancer Centre and Aneurin Bevan Bevan CAT Clinic): last year 343 cancer patients at Velindre Cancer Centre received LMWH for CAT, of which 140 would have met the inclusion criteria;

ii) Haematology (University Hospitals Coventry and Warwickshire NHS Trust): last year there were 230 patients with CAT of which 92 would have met the inclusion criteria;

iii) Primary Care (PCRN-CE and MidReC): anticipate there being five patients recruited from each PCT (Birmingham, Warwickshire and Oxfordshire) participating practice.

12.3.2 Anticipated sample size needed for a phase 3 trial

Not all patients who have been injecting LMWH for five months will be happy to continue injecting for a further six months. We are not sure what proportion of patients will be

willing to be randomised, but we consider that at least 30% need to agree in order to make a phase 3 RCT trial worthwhile. This study will aim to assess the feasibility of randomisation by determining if at least 30% of potential patients will agree to randomisation. We will then calculate the precision of this proportion with a 95% confidence interval. We will also estimate the proportion of patients who experience recurrent VTEs during follow-up, which will inform the design of the phase 3 RCT trial.

We expect there to be around 140 patients being treated with LMWH at Velindre every year. At the anticoagulation clinical in Warwick, around 230 patients have cancer associated VTE per year, and of these, around 92 have locally advanced or metastatic cancer. It is not known how many eligible patients will be found at primary care clinics; we anticipate there being up to 10 eligible patients per primary care practice, out of which we would expect to recruit 5 patients. In total then, we could assume that we would have at least 200 eligible patients per year in total across three sites.

12.3.2.1 Sample size needed to assess the feasibility of randomisation

If less than 15% of eligible patients agree to take part in the trial, then we would be concerned that a phase 3 RCT trial may not be suitable because we may not recruit suitable numbers, considering that a larger phase 3 RCT trial could have more stringent eligibility criteria as a result of this feasibility study. If at least 30% agree to take part then we would consider that randomising patients to a larger phase 3 trial would be feasible. Using a Fleming's single stage design, setting p1 to 0.15 and p2 to 0.3, and with 5% significance and 90% power, then we will need to approach 62 eligible participants with details of the trial. This design requires that at least 15 out of 62 participants consent to the trial. We therefore propose a 2-stage sample size. If at least 15 out of the first 62 participants recruited to the trial accept randomisation, then we will continue recruitment into stage 2. If fewer than 15 agree, we will determine at this stage that randomisation within this population is not feasible.

12.3.2.2 Sample size needed to accurately estimate the proportion agreeing to randomisation and to estimate the outcome measures for the phase 3 trial

If we expect that 200 will be the maximum potential number of eligible patients, then we can expect to be able to produce a confidence interval for the proportion willing to be randomised of width 0.137 or less. For example, if the percentage is 50%, then we could expect the confidence interval to be 6.85% either side of the point estimate. If the percentage is 30% we can expect a slightly smaller confidence interval of 6.3% either side. If only 150 patients are deemed eligible, then we can expect to calculate a 95% confidence interval for the proportion with a maximum width of 0.158.

Our target registration number for this feasibility trial is therefore 200 patients, of which we hope that at least 60 patients will be randomised into the two groups. 30 patients per arm

will provide enough power to create a 95% confidence interval around the risk of VTE recurrence, which would have a width of 0.34 or less. As an example, if we found that the risk of VTE occurrence was 50% in the arm that stopped, we would be able to estimate a confidence interval of approximately 33% to 67% or smaller. If the risk of VTE was 8.8% the confidence interval would be 0 to 19%. If we were able to recruit 120 participants in this study, we could estimate our outcomes in each arm with a confidence interval width of 0.246 or less. If we randomised 200 patients we would have a confidence interval width of 0.126 or less.

12.4 Statistical analyses

A full statistical analysis plan will be defined before the first interim analysis of the trial.

12.5 Sub-group analyses

No formal subgroup analyses are planned. However, if any treatment effect is found we will investigate whether it is consistent across participant subgroups (defined by all pre-treatment factors collected) although this analysis will be exploratory in nature. Exploratory analyses may be conducted to aid hypothesis generation if a phase III RCT trial is subsequently developed.

13.0 Qualitative research

The qualitative components of the trial will provide rich data in relation to the attitudes of clinicians recruiting to the study and to patient motivation to participate in the trial, perceived benefits and burdens, and reasons for withdrawal from the trial. There will be two qualitative components in total: a) focus groups with clinicians; b) patient interviews.

13.1 Clinician focus groups

Focus groups with clinicians from oncology, haematology and primary care (two groups per setting; six groups in total) will explore:

- attitudes to recruiting to the study to identify the challenges of progressing to a full RCT;
- assessment of equipoise and acceptability of intervention;
- what evidence would be needed, if at all, to convince them to alter their practice in prescribing LMWH;
- whether they would continue a patient on LMWH after six months;
- views on the appropriate outcome measures for the RCT;
- pathways they follow.

Six to ten clinicians will be recruited per group. Recruitment will be via email. Where feasible focus groups will be held at national meetings and educational events (e.g. NCRI annual meeting, British Society of Haematology Conference, and Society for Academic Primary Care conferences).

13.2 Patient interviews

Semi-structured interviews will be held with:

- Patients who do not wish to continue with LMWH (non-consenters);
- Trial participants in the intervention arm;
- Trial participants in the control arm;
- Carers of trial participants randomised to the intervention or control arm (e.g. partner/relative/friend);
- Participants who withdraw from the intervention or control arm.

Interviews will explore: attitudes towards participating in the study; potential barriers and concerns to participation; factors influencing compliance with self-injecting (where appropriate).

Patients who take part in the intervention or control arms of the trial will be interviewed to explore: their reasons for, and experiences of, participating in the trial; their views and

attitudes towards equipoise; and in the case of the intervention participants, the acceptability of LMWH.

Patients that refuse consent to the trial will be interviewed to explore their understanding of trial processes, their experiences within the first five months of VTE treatment off-trial and reasons for non-consent.

Participants withdrawing from the study will be interviewed to explore reasons for their withdrawal, to identify potential strategies and support necessary to minimise attrition. Recruitment to trials in patients with advanced cancer is known to be difficult (23) and patient reported data in the qualitative arm of this study will inform strategies for recruitment in a full phase 3 RCT.

Carers of patients who take part in the intervention or control arms of the trial will be interviewed to explore their experiences of caring for someone taking part in the ALICAT trial.

In terms of the acceptance of randomisation to an intervention for symptom palliation/survival benefit, patients' decision making is strongly influenced by good communication. For the purposes of the trial, the PIS and delivery of information by research staff will be essential to the integrity and equipoise of the trial (24).

Sampling strategy: Fifty to seventy patients will be recruited in total (10 to 15 per group):

	Non-Consenters	**Trial Participants (Intervention)**	**Trial Participants (Control)**	**Carers of Trial Participants**	**Withdrawn Participants**	**Total No. Interviews**
No. Semi-Structured Interviews	**10-15**	**10-15**	**10-15**	**10-15**	**10-15**	**50-75**

Consent: Potential interviewees will be consented following the process described in Section 1.0 Trial Schema and Section 6.0 Participant Eligibility.

Timing of interviews: Non-consenters will be interviewed as soon as possible after they have been approached to participate in the trial. Trial participants and their carers will be interviewed after they have completed the treatment phase of the trial, i.e. approximately 3 12 weeks after the 26 week treatment date. Participants withdrawing from the intervention or control arm of the trial will be offered the opportunity to participate at the point of withdrawal.

Approaching patients: All eligible patients will be approached until enough have been recruited to represent all groups. In the first instance, participants will be approached by research practitioners at the recruiting site who will notify patients of the interview study. When signing the Main Trial Consent Form 1, patients will be able to indicate if they consent to being contacted by the Qualitative Researcher to discuss being interviewed. The name, telephone number and email address of patients who consent to be contacted by the qualitative researcher will be passed to the researcher verbally via telephone to ensure adequate data protection. The Qualitative Researcher will then contact participants to discuss the interview study, and if the patient agrees, arrange a convenient time and location for interview. The patient's address will not be recorded unless the patient verbally agrees to be interviewed. The qualitative researcher will then take written informed consent immediately prior to the interview where appropriate. The Qualitative Researcher will obtain a Research Passport, including an enhanced CRB check, where appropriate.

The interviews: Participants will be interviewed at home or in a quiet clinic location, according to participant preference. In previous studies, our experience indicates that the home setting is usually the preferred option. Interviews will usually be 30 – 60 minutes in length and will be terminated earlier if the participant is thought to be fatigued or becomes unwell.

13.3 Data management

The focus groups and patient interviews will be audio recorded and field-notes will be made to record any instances of non-verbal communication or reactions to any of the discussions. The digital media files will be uploaded onto a secure computer at the Marie Curie Palliative Care Research Centre (MCPRC), stored on a secure server and labelled with a unique identifier.

Personal data will be stored securely for a maximum of 6-12 months from the date of collection and destroyed immediately after the interview, following the date of collection and destroyed immediately after the interview, following WCTU/MCRPRC SOPs.

Digital recordings may contain identifiable data. Digital recordings will be transcribed in full and verbatim by a transcription secretary at the MCPRC and following an SOP to ensure data protection and confidentiality. Transcripts will be anonymised and stored securely at WCTU. Transcripts will be uploaded onto QSR NVivo 10 qualitative software programme for efficient data management and analysed using framework analysis (22) (see below).

Participants will be asked to consent to the use of their anonymised extracts of talk in the study report and future publications.

All digital recordings of voice data will be deleted at the end of the study (i.e. once the funders report has been accepted). However, anonymised transcripts and analysis data will be stored securely for 15 years, after which it will be destroyed according to the WCTU and Sponsor data protection and archiving SOPs.

13.4 Framework Analysis

Analytic framework:

The qualitative component of this trial aims to describe the attitudes of patients and to identify barriers to recruitment and retention. Data will be analysed to identify problems with systems and procedures that need addressing as well as patient attitudes and experiences. Framework analysis is selected as the most appropriate analytic method to achieve this for both the focus group and interview data (22).

Framework analysis was developed for use in applied policy research where objectives are clearly set and shaped by specific outcome needs with the intention of developing actionable outcomes and providing answers. The approach develops a hierarchical thematic framework that is used to classify and organize data according to key themes, concepts and emergent categories (25). It 'involves a systematic process of sifting, charting and sorting material according to key issues and themes.' (22). The analysis is driven by the original accounts of the participants; it is systematic but dynamic, open to change and amendment throughout the process. It allows a full review of all material collected and easy retrieval of that material, comparisons between cases and review of overall views of particular themes (22). The analytic process is transparent and others can easily view the interpretations derived from it.

Framework analysis will be carried out in line with Ritchie and Spencer's five interconnected steps (22):

- **Familiarisation with data** – Interview recordings will be listened to and transcripts and field notes read. The researcher will list key ideas and recurrent themes. Transcripts will be annotated in the right hand margin;
- **Identifying a thematic framework** – An index of themes will be created. This was will be informed by the original research aims to understand issues around recruitment and retention and introduced during the interviews by the questions asked, but also by issues raised by the participants in the data. A common index will be used to enable identification of common and divergent themes;
- **Indexing the data** – The index will be systematically applied to each transcript by annotating them with the codes from the thematic framework. During this process, the framework may be adjusted, adding new themes and subthemes as they

emerge. The adjusted framework will then be applied to subsequent transcripts and reapplied to existing transcripts to ensure all data is appropriately coded;

- **Charting** – Data will be lifted from the transcripts and arranged according to thematic references;
- **Mapping and interpretation** – Charts and research notes will be reviewed to find associations between themes. Relationships will be described on hierarchical diagrams and then described in written form.

13.5 Presentation of results and dissemination

The anonymised data will be represented by selected extracts in a narrative format with a thematic structure. The results will be discussed with data extracts used in support of claims made. The TMG will analyse the results to assess potential alterations to trial design, and will include the qualitative analysis to complement the reporting of the full trial, where appropriate.

Potential publications resulting from the embedded qualitative study will not be reported before the completion of the main trial if any aspect of this will cause a negative affect or compromise the trial in any way. The decision to publish results arising from the qualitative study before the end of the main trial, or not, will be made by the TMG and the IDMC.

13.6 Withdrawal

Please refer to Section 11.3.2.

14.0 Identification of patient pathways

Responsibility for the management of patients with ongoing malignancy post VTE varies.

Data from the clinician focus groups (Section 13.1) will be used to map/model the patient management pathways.

The South East Wales Trials Unit (SEWTU) will undertake a UK wide survey exercise with relevant stakeholders from primary and secondary care. This will be in the form of a telephone/web survey and will allow a classification and enumeration of the models of care. This will also be triangulated with available documentary evidence on pathways of care. The survey will sample oncology, haematology and primary care.

The survey will be structured around the patient pathway from identification of a VTE, early management and late management developed from the focus groups. A particular focus will be on the management of transition points between settings and how continuities in care are assured. Respondents will be encouraged to submit any local documents they use on care pathways.

A sampling framework will be developed from the clinician focus group. Analysis will consist of a mapping exercise based on the framework maps developed from the focus groups. This mapping will draw in data from the focus groups, survey, patient interviews and resource usage reported from trial participants. These will then be grouped into similar models to create a taxonomy. This classification will be initially verified in the TMG.

The survey, sampling framework, analysis and associated site document and data storage will be planned and conducted following SEWTU and Sponsor local policies and SOPs.

15.0 Health Economics

The feasibility study will identify key cost drivers to inform the design of a future definitive trial, which will include a cost utility study. Orders of magnitude of differences in costs and outcomes identified in the EQ-5D-5L (Appendix 4.) will help estimation of anticipated effect sizes for the full trial. Health Economic data will be collected by the WCTU on standard CRFs, and analysed by Prof David Cohen.

16.0 Publication policy

Data from all sites will be analysed together and published as soon as possible. Individual participating PIs may not publish data concerning their participants that are directly relevant to questions posed by the trial until the TMG has published its report. The TMG will form the basis of the writing committee and advise on the nature of publications, subject to the Sponsor's requirements.

All publications should include a list of participating PIs, and if there are named authors, these should include the CI, Co-Investigators, Trial Manager, and Statistician(s) involved in the trial. If there are no named authors then a writing committee will be identified.

17.0 Ethical and regulatory considerations, and Informed Consent

17.1 Ethical approval

This protocol will be submitted to a Multi-centre Research Ethics Committee (REC) that is legally "recognised" by the United Kingdom Ethics Committee Authority for review and approval. The approval of the REC must be obtained before the start of a clinical trial or any trial procedures are conducted.

17.2 Clinical Trial Authorisation (CTA)

The trial is being performed under a Clinical Trial Authorisation (CTA) from the MHRA. CTA approval must be obtained before the start of the trial in accordance with Part 3, Regulation 12 of The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031). The trial has been classified as risk type A (no higher than the risk of standard medical care) using the MHRA risk-adapted approach to the management of clinical trials of IMPs. The trial also meets the requirements for full exemption for IMP labelling as specified in Part 7, Section 46 of the aforementioned UK statutory instrument. Therefore, there are no trial-specific IMP labelling requirements for this trial.

17.3 Regulatory Considerations

All substantial amendments to this Protocol must be approved by the REC responsible for the study and MHRA, before the implementation of the amendments. Minor amendments will not require prior approval by the REC and MHRA.

If the trial is temporarily halted it will not be recommenced without reference to the REC responsible for the study and the MHRA.

The REC and MHRA will be notified within 90 days of trial completion. If the trial is terminated early, the REC and MHRA will be notified of this within 15 days.

A summary of the clinical trial report will be submitted to the REC responsible for the study and MHRA within one year of the completion of the last participant's final trial procedure.

17.4 Research Governance approval

This trial protocol will be submitted through the Research Governance process of the host care organisation for review and approval. The Research Governance approval of the host care organisation must be obtained before recruitment of participants within that host care organisation.

17.5 Sponsorship

The ALICAT trial is being sponsored by Cardiff University. Cardiff University shall be responsible for ensuring that the trial is performed in accordance with the following:

- The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031) and subsequent amendments;
- GCP;
- Declaration of Helsinki (1996) Research Governance Framework for Health and Social Care (Welsh Assembly Government 2009 and Department of Health 2nd July 2005);
- The Data Protection Act 1998.

Cardiff University has delegated the following responsibilities to the WCTU and Chief Investigator:

- Obtaining a Clinical Trial Authorisation (CTA) and subsequent amendments;
- Obtaining favourable ethics committee opinion and subsequent amendments;
- Selection of investigators and ensuring each site has full trial documentation;
- Giving notice to the REC and MHRA when the trial has ended or if the trial is suspended to recruitment or terminated early;
- Keeping records of all AEs reported by PIs;
- Ensuring recording and prompt reporting of SARs to the CI;
- Reporting to the MHRA and REC any SUSARs within specified timeframes;
- Ensuring PIs are informed of SUSARs;
- Providing annual listing of all SARs to the MHRA, investigators, IDMC and REC using the Annual Safety Report, Development Update Safety Report or Investigator Safety Report;
- Reporting urgent safety measures to REC/MHRA within 3 days of initial notification;
- Reporting serious breaches of GCP or trial protocol within 7 days of initial notification;
- Having quality control systems in place to ensure that the study is conducted according to GCP at all participating sites;
- Monitoring of the study;
- Analysis of the main trial and qualitative sub-study data.

The following responsibilities are delegated to SEWTU:

- Trial design;

- Development, conduct and analysis of a UK wide web based survey to identify patient pathways.

The following responsibilities are delegated to the individual participating sites:

- Have in place arrangements to adhere to GCP;
- Keep a copy of all essential documents (as defined in GCP) and ensure appropriate archiving and destruction once the study has ended;
- Take appropriate urgent safety measures;
- Report urgent safety measures to the WCTU immediately and no later than 24 hours;
- Report serious breaches of GCP or trial protocol to the WCTU immediately and no later than 24 hours.

The following responsibilities are delegated to the University of Birmingham:

- Trial design;
- Review of data;
- Appointment of a Trial Manager/Researcher at the Primary Care Clinical Research & Trials Unit (PC-CRTU) to coordinate the conduct of the trial at primary care sites.

The following responsibilities are delegated to the University of Glamorgan:

- Trial design;
- Analysis of health economics data.

The following responsibilities are delegated to the University of Hull:

- Trial design;
- Review of clinical data;
- Evaluation of data within the context of future trial design.

The following responsibilities are delegated to the Cambridge University Hospitals NHS Foundation Trust:

- Trial design;
- Review of data;
- Evaluation of data in the context of future trial design.

The following responsibilities are delegated to the King's College Hospital NHS Trust:

- Trial design;
- Review of data;
- Evaluation of data in the context of future trial design.

17.6 Indemnity

- Non-negligent harm: This trial is an academic, investigator-led and designed trial, coordinated by the WCTU. The CI, local Investigators and coordinating site do not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. The Association of the British Pharmaceutical Industry (ABPI) guidelines will not apply.
- Negligent harm: Where studies are carried out in a hospital, the hospital continues to have a duty of care to a patient being treated within the hospital, whether or not the patient is participating in this trial. Cardiff University does not accept liability for any breach in the other hospital's duty of care, or any negligence on the part of employees of hospitals. This applies whether the hospital is an NHS Trust or not. The Sponsor shall indemnify the site against claims arising from the negligent acts and/or omissions of the Sponsor or its employees in connection with the Clinical Trial (including the design of the Protocol to the extent that the Protocol was designed solely by the Sponsor and the Site has adhered to the approved version of the Protocol) save to the extent that any such claim is the result of negligence on the part of the Site or its employees.

17.7 Data protection

The WCTU will act to preserve patient confidentiality and will not disclose or reproduce any information by which participants could be identified (except where participants are registered with the National Health Service Information Centre (NHSIC; formerly the Office for National Statistics) or traced via the NHS Central Register, which requires separate consent). Data will be stored in a secure manner and will be registered in accordance with the Data Protection Act 1998. The data custodian for this trial is the Scientific Director of the WCTU.

17.8 Finance

The WCTU is core funded by CR-UK and these core resources will be used to support this trial. This study is funded by the National Institute for Health Research Health Technology Assessment funding number 10/145/01. The trial is in the National Cancer Research Network (NCRN) and National Institute for Health (NIHR) portfolio. Local NCRN/WCTN/SCRN support should be available at each site taking part to support entry of participants into this trial.

18.0 References

1. Report of the independent expert working group on the prevention of venous thromboembolism in hospitalised patients. London: Department of Health; 2007. 70 p. p.
2. Noble S, Pasi J. Epidemiology and pathophysiology of cancer-associated thrombosis. Br J Cancer. 2010 Apr 13;102 Suppl 1:S2-9. PubMed PMID: 20386546. Epub 2010/04/23. eng.
3. Keeling D, Baglin T, Tait C, Watson H, Perry D, Baglin C, et al. Guidelines on oral anticoagulation with warfarin - fourth edition. Br J Haematol. 2011 Aug;154(3):311-24. PubMed PMID: 21671894. Epub 2011/06/16. eng.
4. Noble SI, Shelley MD, Coles B, Williams SM, Wilcock A, Johnson MJ. Management of venous thromboembolism in patients with advanced cancer: a systematic review and meta-analysis. Lancet Oncol. 2008 Jun;9(6):577-84. PubMed PMID: 18510989. Epub 2008/05/31. eng.
5. Levitan N, Dowlati A, Remick SC, Tahsildar HI, Sivinski LD, Beyth R, et al. Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy. Risk analysis using Medicare claims data. Medicine (Baltimore). 1999 Sep;78(5):285-91. PubMed PMID: 10499070. Epub 1999/09/28. eng.
6. Sorensen HT, Mellemkjaer L, Olsen JH, Baron JA. Prognosis of cancers associated with venous thromboembolism. N Engl J Med. 2000 Dec 21;343(25):1846-50. PubMed PMID: 11117976. Epub 2000/12/16. eng.
7. Noble S. The challenges of managing cancer related venous thromboembolism in the palliative care setting. Postgrad Med J. 2007 Nov;83(985):671-4. PubMed PMID: 17989265. Pubmed Central PMCID: 2659959. Epub 2007/11/09. eng.
8. Noble SI, Finlay IG. Is long-term low-molecular-weight heparin acceptable to palliative care patients in the treatment of cancer related venous thromboembolism? A qualitative study. Palliat Med. 2005 Apr;19(3):197-201. PubMed PMID: 15920933. Epub 2005/06/01. eng.
9. Khorana AA, Streiff MB, Farge D, Mandala M, Debourdeau P, Cajfinger F, et al. Venous thromboembolism prophylaxis and treatment in cancer: a consensus statement of major guidelines panels and call to action. J Clin Oncol. 2009 Oct 10;27(29):4919-26. PubMed PMID: 19720907. Pubmed Central PMCID: 2799060. Epub 2009/09/02. eng.
10. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008 Jun;133(6 Suppl):454S-545S. PubMed PMID: 18574272. Epub 2008/07/24. eng.
11. Johnson MJ, Sproule MW, Paul J. The prevalence and associated variables of deep venous thrombosis in patients with advanced cancer. Clin Oncol (R Coll Radiol). 1999;11(2):105-10. PubMed PMID: 10378636. Epub 1999/06/23. eng.
12. Noble SI, Hood K, Finlay IG. The use of long-term low-molecular weight heparin for the treatment of venous thromboembolism in palliative care patients with advanced cancer: a case series of sixty two patients. Palliat Med. 2007 Sep;21(6):473-6. PubMed PMID: 17846086. Epub 2007/09/12. eng.
13. Prandoni P, Lensing AW, Piccioli A, Bernardi E, Simioni P, Girolami B, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood. 2002 Nov 15;100(10):3484-8. PubMed PMID: 12393647. Epub 2002/10/24. eng.
14. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med. 2009 Dec 10;361(24):2342-52. PubMed PMID: 19966341. Epub 2009/12/08. eng.
15. Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010 Dec 23;363(26):2499-510. PubMed PMID: 21128814. Epub 2010/12/07. eng.
16. Peetz D, Lackner KJ. Dabigatran versus warfarin for venous thromboembolism. N Engl J Med. 2010 Mar 18;362(11):1050; author reply -1. PubMed PMID: 20237354. Epub 2010/03/20. eng.
17. Teachey DT. Dabigatran versus warfarin for venous thromboembolism. N Engl J Med. 2010 Mar 18;362(11):1050; author reply -1. PubMed PMID: 20301800. Epub 2010/03/20. eng.
18. Romualdi E, Donadini MP, Ageno W. Oral rivaroxaban after symptomatic venous thromboembolism: the continued treatment study (EINSTEIN-Extension study). Expert Rev Cardiovasc Ther. 2011 Jul;9(7):841-4. PubMed PMID: 21809964. Epub 2011/08/04. eng.
19. Hutten BA, Prins MH, Gent M, Ginsberg J, Tijssen JG, Buller HR. Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation

to both malignancy and achieved international normalized ratio: a retrospective analysis. J Clin Oncol. 2000 Sep;18(17):3078-83. PubMed PMID: 10963635. Epub 2000/08/30. eng.
20. Bruera E, Kuehn N, Miller MJ, Selmser P, Macmillan K. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. J Palliat Care. 1991 Summer;7(2):6-9. PubMed PMID: 1714502. Epub 1991/01/01. eng.
21. Watanabe SM, Nekolaichuk C, Beaumont C, Johnson L, Myers J, Strasser F. A multicenter study comparing two numerical versions of the Edmonton Symptom Assessment System in palliative care patients. J Pain Symptom Manage. 2011 Feb;41(2):456-68. PubMed PMID: 20832987. Epub 2010/09/14. eng.
22. Ritchie JS, L., editor. Qualitative data analysis for applied policy research. New York: Routledge; 1994.
23. Hussainy SY. Recruitment strategies for palliative cancer care patients and carers. International Journal of Pharmacy Practice. 2009;17(6):3.
24. Steinhauser KE, Clipp EC, Hays JC, Olsen M, Arnold R, Christakis NA, et al. Identifying, recruiting, and retaining seriously-ill patients and their caregivers in longitudinal research. Palliat Med. 2006 Dec;20(8):745-54. PubMed PMID: 17148529. Epub 2006/12/07. eng.
25. QDA Online. Learning Qualitative Data Analysis on the Web 2011.

APPENDIX 1: CTCAE (V4.03) – selected toxicities

Reference: Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010). U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES, National Institutes of Health, National Cancer Institute.

Adverse Event	1	2	3	4	5
Cardiac disorders					
Pericardial effusion	-	Asymptomatic effusion size small to moderate	Effusion with physiologic consequences	Life-threatening consequences; urgent intervention indicated	Death
Ventricular arrhythmia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Eye disorders					
Vitreous hemorrhage	Asymptomatic or mild symptoms; clinical or diagnostic observations only	Symptomatic; limiting instrumental ADL	Limiting self care ADL; vitrectomy indicated	Blindness (20/200 or worse) in the affected eye	-
Gastrointestinal disorders					
Anal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Cecal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Colonic hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Duodenal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Esophageal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Esophageal	-	Self-limited;	Transfusion, radiologic,	Life-threatening	Death

varices hemorrhage		intervention not indicated	endoscopic, or elective operative intervention indicated	consequences; urgent intervention indicated	
Esophagitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered eating/swallowing; oral supplements indicated	Severely altered eating/swallowing; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Esophageal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Gastric hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Gastritis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated	Severely altered eating or gastric function; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Gastrointestinal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Gastroesophageal reflux disease	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated	-	-
Hemorrhoidal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Ileal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Intra-abdominal hemorrhage	-	Medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicate	Death
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-
Jejunal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or	Transfusion, radiologic, endoscopic, or elective operative intervention	Life-threatening consequences; urgent	Death

		minor cauterization indicated	indicated	intervention indicated	
Lower gastrointestinal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Oral hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Pancreatic hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Rectal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Retroperitoneal hemorrhage	-	Self-limited; intervention indicated	Transfusion, medical, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Upper gastrointestinal haemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Vomiting	1 – 2 episodes (separated by 5 minutes) in 24 hrs	3 – 5 episodes (separated by 5 minutes) in 24 hrs	≥6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
General disorders and administration site conditions					
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest limiting self care ADL	-	-
Fever	38.0 – 39.0 degrees C (100.4 – 102.2 degrees F)	>39.0 – 40.0 degrees C (102.3 – 104.0 degrees F)	>40.0 degrees C (>104.0 degrees F) for ≤24 hrs	>40.0 degrees C (>104.0 degrees F for > 24 hrs	Death
Hepatobiliary disorders					
Hepatic hemorrhage	Mild; intervention not indicated	Symptomatic; medical intervention indicated	Transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Portal vein thrombosis	-	Intervention not indicated	Medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Injury, poisoning and procedural complications					

Dermatitis radiation	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate oedema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death
Intraoperative hemorrhage	-	-	Postoperative radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Postoperative hemorrhage	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; radiologic, endoscopic, or operative intervention indicated	Transfusion indicated of >=2 units (10 cc/kg for pediatrics) pRBCs beyond protocol specification; urgent radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Tracheal hemorrhage	Minimal bleeding identified on clinical or diagnostic exam; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Investigations					
Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage	-	-
Nervous system disorders					
Ischemia cerebrovascular	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	-	-	-
Intracranial hemorrhage	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Metabolism and nutrition disorders					
Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Renal and urinary disorders					
Renal hemorrhage	Mild symptoms; intervention not indicated	Analgesics and hematocrit monitoring indicated	Transfusion, radiation, or hospitalization indicated; elective radiologic, endoscopic or operative intervention indicated	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death

Reproductive system and breast disorders					
Ovarian hemorrhage	Minimal bleeding identified on imaging study or laproscopy; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Prostatic hemorrhage	Minimal bleeding identified on imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Spermatic cord hemorrhage	Minimal bleeding identified on imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Testicular disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic but not interfering with urination or sexual activities; intervention not indicated; limiting instrumental ADL	Severe symptoms; interfering with urination or sexual function; limiting self care ADL; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Uterine hemorrhage	Minimal bleeding identified on imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Vaginal hemorrhage	Minimal bleeding identified on clinical exam or imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Respiratory , thoracic and Mediastinal disorders					
Aspiration	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Altered eating habits; coughing or choking episodes after eating or swallowing; medical intervention indicated (e.g., suction or oxygen)	Dyspnoea and pneumonia symptoms (e.g., aspiration pneumonia); hospitalization indicated; unable to aliment orally	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Bronchopulmonary hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Laryngeal hemorrhage	Mild cough or trace hemoptysis; laryngoscopic findings	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or	Death

				intubation)	
Mediastinal hemorrhage	Radiologic evidence only; minimal symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening consequences; urgent intervention indicated	Death
Pharyngeal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Pleural hemorrhage	Asymptomatic; mild hemorrhage confirmed by thoracentesis	Symptomatic or associated with pneumothorax; chest tube drainage indicated	>1000 ml of blood evacuated; persistent bleeding (150-200 ml/hr for 2 - 4 hr); persistent transfusion indicated; elective operative intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Vascular disorders					
Superior vena cava syndrome	Asymptomatic; incidental finding of SVC thrombosis	Symptomatic; medical intervention indicated (e.g., anticoagulation, radiation or chemotherapy)	Severe symptoms; multimodality intervention indicated (e.g., anticoagulation, chemotherapy, radiation, stenting)	Life-threatening consequences; urgent multi-modality intervention indicated (e.g., lysis, thrombectomy, surgery)	Death
Thromboembolic event	Venous thrombosis (e.g., superficial thrombosis)	Venous thrombosis (e.g., uncomplicated deep vein thrombosis), medical intervention indicated	Thrombosis (e.g., uncomplicated pulmonary embolism [venous], non-embolic cardiac mural [arterial] thrombus), medical intervention indicated	Life-threatening (e.g., pulmonary embolism, cerebrovascular event, arterial insufficiency); hemodynamic or neurologic instability; urgent intervention indicated	Death

APPENDIX 2: EORTC QLQ-C30 Version 3.0

Quality of life questionnaire EORTC QLQ-C30
We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ___ ___ ___
Your birthdate (Day, Month, Year): __ __ / __ __ / __ __ __ __
Today's date (Day, Month, Year): __ __ / __ __ / __ __ __ __

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	**1**	**2**	**3**	**4**
2.	Do you have any trouble taking a long walk?	**1**	**2**	**3**	**4**
3.	Do you have any trouble taking a short walk outside of the house?	**1**	**2**	**3**	**4**
4.	Do you need to stay in bed or a chair during the day?	**1**	**2**	**3**	**4**
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	**1**	**2**	**3**	**4**

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	**1**	**2**	**3**	**4**
7.	Were you limited in pursuing your hobbies or other leisure time activities?	**1**	**2**	**3**	**4**
8.	Were you short of breath?	**1**	**2**	**3**	**4**
9.	Have you had pain?	**1**	**2**	**3**	**4**
10.	Did you need to rest?	**1**	**2**	**3**	**4**
11.	Have you had trouble sleeping?	**1**	**2**	**3**	**4**
12.	Have you felt weak?	**1**	**2**	**3**	**4**
13.	Have you lacked appetite?	**1**	**2**	**3**	**4**

Please go on to the next page

During the past week:	Not at All	A Little	a Bit	Quite Much	Very
14. Have you felt nauseated?	1		2	3	4
15. Have you vomited?	1		2	3	4
16. Have you been constipated?	1	2	3	4	
17. Have you had diarrhoea?	1	2	3	4	
18. Were you tired?	1	2	3	4	
19. Did pain interfere with your daily activities?	1		2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1		2	3	4
21. Did you feel tense?	1	2	3	4	
22. Did you worry?	1	2	3	4	
23. Did you feel irritable?	1	2	3	4	
24. Did you feel depressed?	1	2	3	4	
25. Have you had difficulty remembering things?	1		2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4	
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4	
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4	

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX 3: EQ-5D-5L. A standardised measure of health status developed by the EuroQol Group.

Reference: EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199-208.

Reference: Herdman M, Gudex C, Lloyd A, Janssen MF, Kind P, Parkin D, Bonsel G, Badia X. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Quality of Life Research (accepted for publication).

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ☐
I have slight problems in walking about ☐
I have moderate problems in walking about ☐
I have severe problems in walking about ☐
I am unable to walk about ☐

SELF-CARE

I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

PAIN / DISCOMFORT

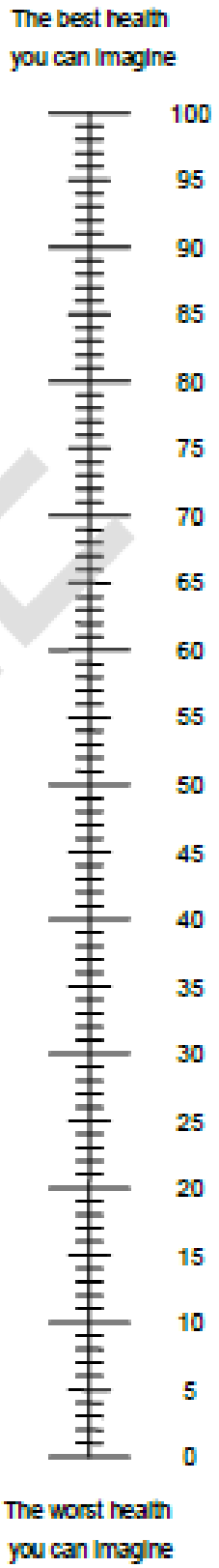
I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

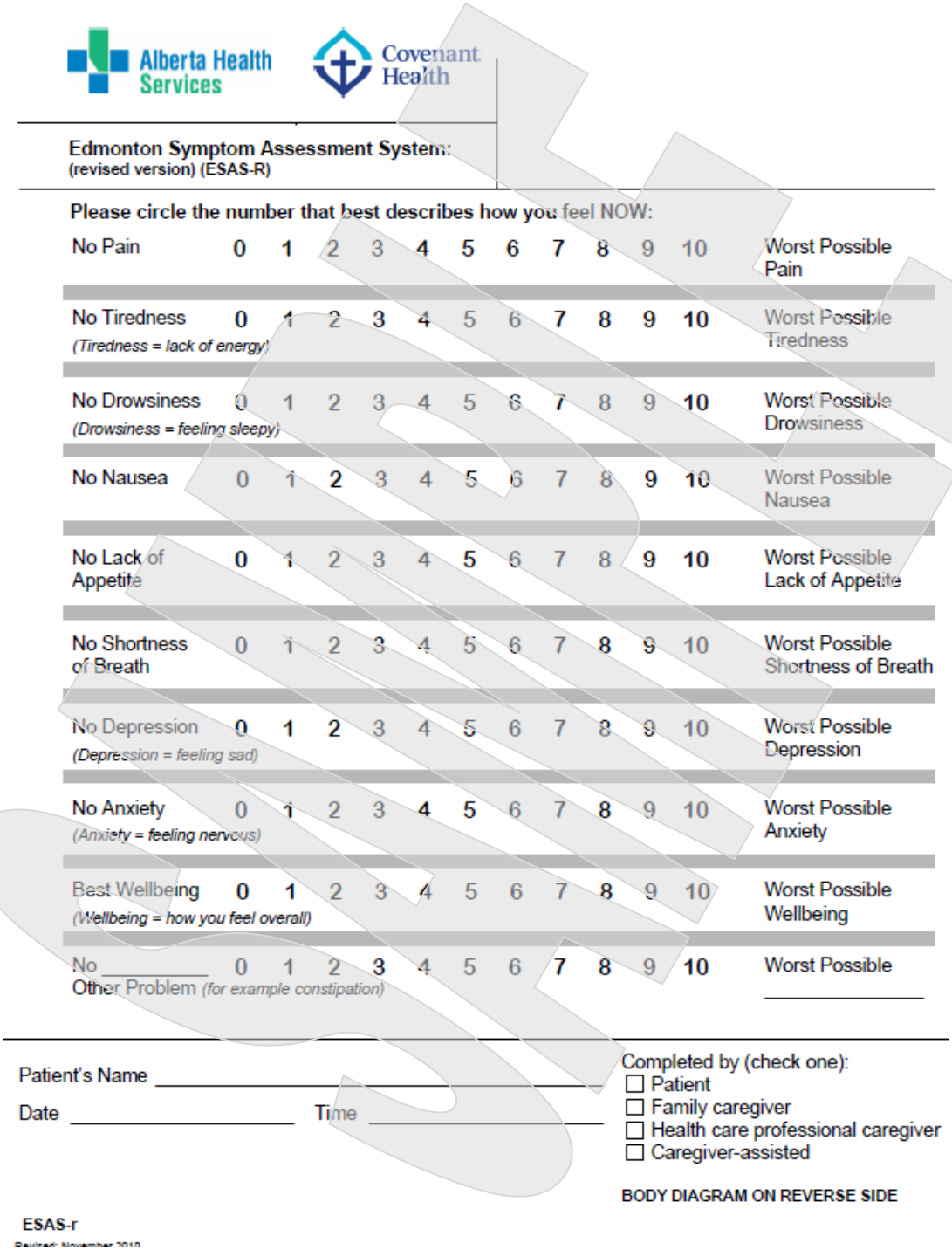
YOUR HEALTH TODAY = ☐



APPENDIX 4: Edmonton Symptom Assessment System: ESAS-r

Reference: Bruera E, Kuehn N, Miller MJ, Selmser P, Macmillan K. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. J Palliat Care 1991;7:6-9.

Reference: Watanabe S, Nekolaichuk C, Beaumont C, Mawani A. The Edmonton Symptom Assessment System: what do patients think? Support Care Cancer 2009; 17:675-683.



Alberta Health Services

Covenant Health

Edmonton Symptom Assessment System:
(revised version) (ESAS-R)

Please circle the number that best describes how you feel NOW:

No Pain	**0**	**1**	2	3	**4**	**5**	6	**7**	**8**	**9**	**10**	Worst Possible Pain
No Tiredness *(Tiredness = lack of energy)*	**0**	1	2	**3**	4	5	6	**7**	**8**	**9**	**10**	Worst Possible Tiredness
No Drowsiness *(Drowsiness = feeling sleepy)*	0	1	2	3	4	5	6	7	8	9	**10**	Worst Possible Drowsiness
No Nausea	0	1	**2**	3	4	5	6	7	8	**9**	**10**	Worst Possible Nausea
No Lack of Appetite	**0**	1	2	3	4	**5**	6	7	8	**9**	**10**	Worst Possible Lack of Appetite
No Shortness of Breath	0	1	2	3	4	5	6	7	**8**	9	10	Worst Possible Shortness of Breath
No Depression *(Depression = feeling sad)*	**0**	**1**	**2**	3	4	5	6	7	8	9	10	Worst Possible Depression
No Anxiety *(Anxiety = feeling nervous)*	0	1	2	3	**4**	**5**	6	7	**8**	9	10	Worst Possible Anxiety
Best Wellbeing *(Wellbeing = how you feel overall)*	**0**	**1**	2	3	4	5	6	7	**8**	9	10	Worst Possible Wellbeing
No _____ Other Problem *(for example constipation)*	0	1	2	**3**	4	5	6	**7**	**8**	9	**10**	Worst Possible _____

Patient's Name _____

Date _____ Time _____

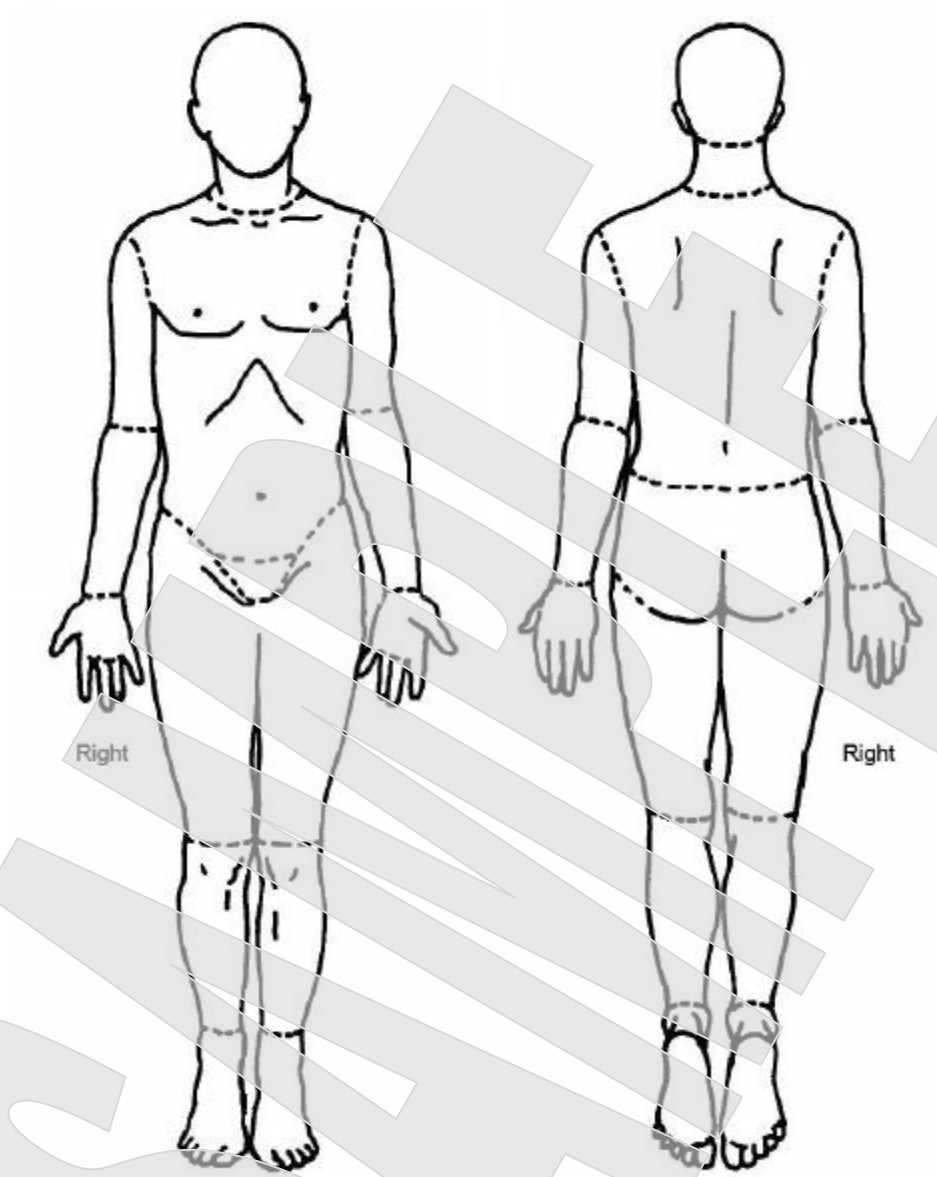
Completed by (check one):
☐ Patient
☐ Family caregiver
☐ Health care professional caregiver
☐ Caregiver-assisted

BODY DIAGRAM ON REVERSE SIDE

ESAS-r

Revised: November 2010

Please mark on these pictures where it is that you hurt:



WALES CANCER TRIALS UNIT

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