HIDDEN: HOSPICE INPATIENT DEEP VEIN THROMBOSIS DETECTION STUDY

Version: 4.0

Date: 22.09.2016

Name of Sponsor: University of Hull

Sponsor Ref:

Funder: NIHR Research for Patient Benefit

Funder Ref: PB-PG-0614-34007

Authorised by:

Name: Role:

Signature: Date:

Name: Prof Miriam Johnson Role: CI

Signature:  Date: 22 Sept 2016

Sponsor

University of Hull will act as sponsor for trial. Delegated responsibilities will be assigned to the Universities and NHS trusts taking part in this study.

Funding

This study is funded by NIHR Research for Patient Benefit PB-PG-0614-34007.

Compliance

This study will adhere to the principles of good clinical practice as outlined in the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95). 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[1], the Data Protection Act 1998 [2], and other regulatory requirements as appropriate.

Chief Investigator
Prof Miriam Johnson
Professor of Palliative Medicine
Centre for Health & Population Sciences
Hull York Medical School
Hertford Building
The University of Hull
Hull, HU6 7RX

Co-Chief Investigator
Dr Clare White
Consultant in Palliative Medicine
Northern Ireland Hospice
Whiteabbey Hospital Grounds
Doagh Road
Newtownabbey, BT37 9RH

Co Investigators

Prof Max Watson
Consultant in Palliative Care
Northern Ireland Hospice
Whiteabbey Hospital Grounds
Doagh Road
Newtownabbey, BT37 9RH

Prof Simon Noble
Professor of Palliative Medicine
Marie Curie Palliative Care Research Centre
Cardiff University School of Medicine
1st Floor Neuadd Meirionnydd
Heath Park, Cardiff, CF14 4YS

Dr Annmarie Nelson
Scientific Director, Marie Curie Palliative Care Research Centre
Cardiff University School of Medicine
1st Floor Neuadd Meirionnydd
Heath Park, Cardiff, CF14 4YS

Dr Eoin Napier
Consultant Radiologist
Belfast Trust
Belfast City Hospital
Lisburn Rd
Belfast, BT9 7AB

Dr Victoria Allgar
Senior Lecturer in Medical Statistics
Hull York Medical School
Department of Health Sciences
The University of York
York. YO10 5DD

Coordinating Centre

Supportive care, Early Diagnosis, Advanced disease (SEDA) research group
University of Hull
Hull
HU6 7RX

Additional Recruiting Sites

Princess Alice Hospice
West End Lane,
Esher KT10 8NA

Marie Curie Hospice Belfast
1A Kensington Rd
Belfast BT5 6NF

Macmillan Unit
Antrim Area Hospital
Bush Road
Antrim
BT41 2

Other Research Partners

Belfast Health and Social Care Trust
Belfast City Hospital,
Lisburn Road,
Belfast BT9 7AB

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1 ABBREVIATIONS AND GLOSSARY

AKPS	Australia-modified Karnofsky Performance Scale
CAT	Cancer Associated Thrombosis
CI	Chief Investigator
DVT	Deep Vein Thrombosis
IPU	Inpatient Unit
LMWH	Low Molecular Weight Heparin
PE	Pulmonary Embolus
PIS	Participant Information Sheet
PS	Performance Status
SPCU	Specialist Palliative Care Unit
VTE	Venous Thromboembolism
VTEP	Venous Thromboembolism Prophylaxis

2 SUMMARY

2.1 LAY SUMMARY

Up to one in five cancer patients will develop blood clots in their veins known as deep vein thrombosis (DVT). A clot may break off from the DVT and travel to the lungs; known as a pulmonary embolism (PE). We do not know the true number of DVTS and PE as they may not cause symptoms. Neither do we know whether apparently “silent” DVTs, if untreated, go away by themselves, or go on to cause serious problems like swollen, painful legs (DVT), or chest pain, breathlessness, collapse or death (PE). There are national treatment recommendations to prevent DVT in cancer patients admitted to hospital. However, we do not know whether these should apply to patients with advanced cancer admitted to specialist palliative care units (SPCU) such as hospices, as treatment may not alter how long

patients have to live or improve symptoms and quality of life. We do not know if good effects outweigh side-effects of treatment (e.g. bleeding) in these patients.

The aim of the HIDDen study is to find out how many cancer patients admitted to hospice units have a DVT. An ultrasound scanner (a safe simple scan which uses sound waves like the scans used in pregnant women to see the baby in the womb), at the hospice bedside, will be used to scan patients' legs to test whether they have a DVT. Symptoms will be noted, and patients re-scanned a week later. Consecutive admissions to hospices in England (one site), Northern Ireland (three sites) and Wales (one site) will be recruited until at least 217 cancer patients not on treatment to prevent a blood clot have been scanned. This study will tell us how many cancer patients admitted to hospice units have DVTs and whether these cause problems. We will then understand better how we should treat people with *advanced* cancer.

3 BACKGROUND AND RATIONALE

Venous thromboembolism (VTE) is a common medical problem, which occurs in 1 in 1000 patients, affecting 6.5 million people annually worldwide. It causes a range of symptoms including painful leg swelling, breathlessness, cardiovascular collapse and death. The rate is higher in the cancer population, affecting 4 -43% of cancer patients during the course of their disease [3-7]. Factors that increase the thrombotic process in malignant disease in addition to the direct and induced release of tumour procoagulants have been reported extensively and include increasing age, metastatic burden and the use of chemotherapy. The true frequency of VTE is likely to be higher since asymptomatic and or incidental VTE are often found on routine imaging studies and at the time of post-mortem,[5, 6] and symptoms may mimic, and thus be attributed to, those caused by the cancer itself. As cancer patients now live longer with metastatic disease and palliative chemotherapy has become more available, the incidence of cancer-associated thrombosis (CAT) has increased. A 27% increase in overall CAT rates, with a 47% increase in those receiving chemotherapy specifically has been reported over an eight year period [8]. The prevention of VTE has

gained increasing attention within clinical research and health policy. International guidelines recommend cancer patients receive pharmacological thromboprophylaxis if admitted to hospital, unless contraindicated[9-11]. VTE prevention is also recognised as a Tier 1 priority for the NHS in England and Wales with financial incentives for appropriate risk assessment and thromboprophylaxis in England[11]. The National Institute for Health and Care Excellence (NICE) Guidelines for the prevention of venous thromboembolism in hospital in-patients based on systematic review, meta-analysis and health economic evaluation have specific guidelines for palliative care inpatients. However, the data informing these recommendations are extrapolated from general medical patient studies and NICE highlight the advanced cancer setting to be an area worthy of further research.

There has been considerable debate as to whether the data informing VTE prevention[5, 12-16] or diagnosis and management of VTE[17] in cancer inpatients can be applied to specialist palliative care units (SPCU) whether these are in hospital or hospice settings. In the past, patients admitted to hospices had a fairly short life expectancy and did not expect to be discharged. In this context the majority of these patients would not benefit from primary thromboprophylaxis. In more recent years the population of patients being admitted to what have become 'specialist palliative care units' has changed. Patients, often earlier in their disease trajectory, with a good performance status, and who may have months or even years to live may be admitted for a period of symptom control. There are limited data pertaining to the prevalence and incidence of VTE in hospice inpatients. One study using light reflection rheography to detect obstruction to lower limb venous flow of 258 inpatients suggested findings consistent with the presence of DVT in 135 (52%; 95% confidence interval 46-58)[18]. This study acknowledged several limitations; whilst a highly sensitive test, light reflection rheography is unable to identify the site or cause of obstruction to venous flow. However the study identified changes consistent with bilateral DVT, and thus potentially more extensive thrombosis, in 17%, and 9% had VTE confirmed on imaging.

DVT symptoms depend on the extent of thrombosis, the adequacy of collateral vessels, and the severity of associated vascular occlusion and inflammation[19]. The natural history of asymptomatic VTE in the SPCU is thus unclear and it is unknown whether the body's natural fibrinolytic system leads to resorption of asymptomatic thrombus or if there is propagation /embolisation resulting in symptoms. Qualitative research suggests hospice patients find primary thromboprophylaxis an acceptable intervention and would accept it, if offered[20]. Current practice varies across hospices with only a minority having a thromboprophylaxis policy or using primary prophylaxis in high-risk patients[13]. Qualitative data indicate that barriers to the use of thromboprophylaxis [14] in the hospice setting are based on several perceptions including:

• Belief that VTE is uncommon in the palliative care setting;

• Data supporting primary thromboprophylaxis is extrapolated from unrepresentative populations;

• The outcome measures used in thromboprophylaxis studies are of less relevance to patients with advanced cancer;

• The natural history of VTE in the advanced cancer patient is unclear.

Therefore the impact of VTE in palliative care patients requires clarification with respect to prevalence, incidence, symptom burden and impact on quality of life before clear guidance can be provided for clinician caring for cancer patients in this setting[16]. An outline of priorities for research that identifies these important issues has been suggested as follows:

• Identify the true prevalence and natural history of VTE in the palliative care setting;

• Develop appropriate outcome measures;

• Identify the clinical and symptom burden of VTE;

• Establish a consensus on what clinical/ symptomatic outcome difference would be required to change thromboprophylaxis practice;

• Establish the clinical and cost effectiveness of thromboprophylaxis.

An opportunity to establish the true prevalence of asymptomatic DVT and correlate radiological findings with the presence or development of patient relevant symptoms and outcomes would significantly impact on the clinical management of advanced cancer inpatients. Furthermore, it would inform the development of further palliative care VTE studies including the role of primary thromboprophylaxis, choice of drug and the overall impact of VTE prevention on quality of life and symptom burden.

There are several options for investigating the presence or absence of DVT. For a palliative care inpatient ideally this test should be quick, non-invasive, sensitive and specific. Compression ultrasonography with colour Doppler remains the best overall test for deep venous thrombosis in the context of this study. It is easy to perform, less expensive than most "high tech" studies, can be performed as a portable examination, and is highly reliable when the operator is adequately trained[21]. Furthermore, and of relevance to the SPCU setting, ultrasonography with the single criterion of vein compressibility has been confirmed to be a highly accurate, simple, objective, and reproducible non-invasive method for detecting proximal-vein thrombosis in patients with clinically suspected deep-venous thrombosis. Compared with venography, Doppler ultrasonography has a specificity of 99% (95% CI 97-100) for excluding a femoral DVT, a sensitivity of detecting a femoral DVT of 100% (95% CI 95-100) and an inter-rater reliability kappa of 1.[22]

VTE can be prevented in “at risk” populations

Venous thromboembolism (VTE) is common and cancer patients are seven times more likely to develop VTE than the general population, with some groups at very high risk. VTE prevention for hospitalised patients is an NHS Tier 1 health policy priority in England and Wales with financial incentives for VTE risk assessment and prevention in England. However, is debated whether it is appropriate to apply hospital VTE prevention guidelines to SPCU patients, with many inpatients not routinely being offered prevention.

VTE prevention in people with advanced cancer

Therefore, there is a current anomaly: the same patient with advanced cancer, if admitted to hospital, is likely to be offered VTE prevention in accordance to hospital guidelines, or, if admitted to an SPCU, is likely to not be offered prevention due to the lack of evidence relating to SPCU patients and the potential increased risk of thromboprophylaxis, although this potential increase in risk also applies to the hospitalised patient with advanced cancer.

SPCUs provide inpatient unit care for over 40,000 patients per year, 75% of whom have cancer [23]. In addition, during 2013, specialist palliative care teams provided advice and care for a further 206,180 patients per year in the community and 79,871 in hospital for whom clear advice as to who would receive net benefit from VTE prevention during periods of increased VTE risk would be helpful.

How the proposed study will address this gap

The need for a gold standard VTE prevalence study in SPCUs, with particular attention to site, symptom burden and natural history of VTE is long overdue. In order to guide palliative care clinicians in the use of VTE prevention, the clinically relevant prevalence of VTE in palliative care inpatients needs to be clarified. In this study, Doppler ultrasonography will be used to establish the number of proximal thromboses, the effect on the patient, as well as an understanding of the natural history of such thromboses; what proportion resorb, propagate, and embolise.

4 AIMS AND OBJECTIVES

4.1 Aims:

The primary aim of this study is to establish the prevalence of proximal lower limb deep vein thrombosis (DVT) and its associated symptoms in a population of consecutive patients with cancer admitted to specialist palliative care units (SPCUs).

The secondary aims are to establish the incidence of proximal lower limb DVT during SPCU admission in people with cancer and other conditions, the associated symptoms, the effect of thromboprophylaxis on the development of proximal lower limb DVTs, and the clinical utility of a commonly used clinical risk score for DVT (Well's score) in this population.

4.2 PRIMARY OBJECTIVES:

- To determine the prevalence of proximal lower limb DVT in cancer patients admitted to specialist palliative care units.

4.3 SECONDARY OBJECTIVES:

In patients with cancer and non-malignant conditions admitted to a SPCU to:

- assess longitudinally the weekly incidence of developing a proximal lower limb DVT during admission;
- determine the clinical signs and symptoms associated with proximal lower limb DVT including acute deterioration or sudden death that could be attributed clinically to pulmonary emboli;
- describe the clinical characteristics of patients with and without proximal lower limb DVT;
- compare the prevalence and weekly incidence of proximal lower limb DVT between those with a non-malignant condition and those with cancer;
- to investigate the relationship between anti-coagulants (including low molecular weight heparin thromboprophylaxis) on admission with the presence of DVT on admission, and development of DVT during admission
- determine the sensitivity and specificity of a clinical risk score for DVT (Well's score);

- determine if the presence of a proximal lower limb DVT impacts on length of stay in a SPCU or on overall survival.

5 STUDY OUTCOMES

5.1 PRIMARY OUTCOME

- Prevalence of proximal lower limb DVT in patients with cancer on admission to a SPCU.

5.2 SECONDARY OUTCOMES

- Incidence of developing a proximal lower limb DVT in patients with and without a diagnosis of cancer during admission to a SPCU
- Prevalence of clinical symptoms and signs attributable to VTE (proximal lower limb DVT and PE) on admission to a SPCU;
- Incidence of clinical symptoms and signs attributable to VTE (proximal lower limb DVT and PE) during admission to a SPCU;
- Incidence of acute deterioration or sudden death in patients with a known DVT that could be attributed to clinical pulmonary emboli;
- Clinical characteristics associated with the presence or absence of proximal lower limb DVT;
- Association between use of anticoagulation and presence or absence of DVT on admission and during admission to a SPCU
- Impact of proximal lower limb DVT on length of stay;

- Survival.

6 STUDY DESIGN

This is a prospective multicentre longitudinal observational prevalence study. Patients admitted to SPCUs will be scanned using a Doppler scanner for proximal lower limb DVT on admission and then weekly for the duration of their stay. Assessments will also be undertaken to assess any associated symptom burden.

7 STUDY PARTICIPANTS AND SETTING

All eligible patients admitted to participating Specialist Palliative Care Units (SPCUs) in the UK. Patients will be recruited from SPCUs. Participating SPCUs are:

• Princess Alice Hospice, England;

• Northern Ireland Hospice, Belfast;

• Marie Curie Hospice, Belfast;

• Macmillan Unit, Antrim;

• Marie Curie Hospice, Cardiff and the Vale, Penarth, Wales.

7.1 SITE ELIGIBILITY

SPCUs have been chosen

i) because they are already trained in the use of Doppler (Focused Abdominal Sonography in Palliative Care (FASP) course) (the English and Northern Ireland sites) and

ii) one specifically because they have not, to also assess the feasibility of training SPCU units who have not previously engaged with Doppler US training.

Two units are part of the Marie Curie Cancer Care organisation, which has a special interest in cancer-associated thrombosis.

7.2 SCREENING

All patients admitted to participating centres will be screened for eligibility by the admitting clinician. Centres involved in the study will have to sign up to this as a condition of participation. Research nurses will follow up to ensure that all admissions have been screened. A screening log will be kept to identify the proportion of patients admitted to each centre that meet study inclusion criteria.

7.3 PARTICIPANT SELECTION

Inclusion Criteria

- Admitted to a participating SPCU;
- 18 years or older;
- Able to give fully informed written consent or an available nominated consultee;
- No physical limitations to performing the ultrasound assessment.

Exclusion criteria:

- Patients on other clinical trials will be considered on a case by case basis;
- Patients who are considered by the clinical team likely to die within 5 days;
- Where, in the case of a patient without mental capacity, the nominated consultee is too distressed to be approached regarding the study in the opinion of the clinical team.
- Patients unable to understand English well enough to provide informed consent or comply with study assessments.

7.4 PARTICIPANT RECRUITMENT

All patients admitted to participating centres will be screened for eligibility by the admitting clinician. Centres involved in the study will be required to agree to this as a

condition of participation. Research nurses will follow up to ensure that all admissions have been screened. A screening log will be kept to identify the proportion of patients admitted to each centre that meet study inclusion criteria. This will apply to all admissions, and patients who are readmitted to the hospices will be screened for inclusion on each occasion, as each time a patient is admitted their disease and risk factors are likely to have changed from their previous admission.

Consecutive patients will be screened and eligible patients invited to participate by the admitting clinician. Interested patients will be given a participant information sheet and the opportunity to discuss the study with the research team. Consenting patients will have baseline assessments performed as soon as possible after admission, preferably on the same day, and no later than 48 hours, in order to determine an admission prevalence. The exception to this is in the event of a late Friday afternoon admission, the patient may be recruited as long as their Doppler can be performed on the Monday morning. Time from admission to Doppler will be noted. Patients who wish to leave it till the next day to decide can do so as long as the scan can be conducted within 48 hours. However, as the aim of the study is to find the prevalence of DVT on admission, and the study investigation is non-invasive, those who are happy to proceed to immediate consent will be able to do so. In the event that a patient has mental capacity and wishes to participate in the study, but is unable to sign consent (due to any cause), then verbal consent will be witnessed. The witness may be a family member or friend, or member of staff who is independent of the research team. A similar process is available for willing consultees who are unable to provide a written declaration.

Consultee agreement will be sought for patients without mental capacity on admission, but should the patient regain capacity, post-hoc consent to use their data will be required. Patients without capacity for consent will be included in this study as often patients admitted to a SPCU have a temporary reduction in their capacity due to a potentially reversible cause that also increases their VTE risk. Due to the impact of this potentially reversible pathology on VTE risk, and that the lack of capacity often signifies

a more ill group, data from patients with capacity to consent cannot be generalised to this group.

Participants are free to withdraw from the study at any time. Consultees may withdraw agreement at any time.

Data already collected up until withdrawal of consent will be used unless a participant who was included with consultee agreement regains mental capacity and does not consent (as discussed under ethical concerns). Participants who are withdrawing from the study Doppler examinations will be asked if they are willing to continue with other study assessments.

Although the regulations about the inclusion of patients who are unable to provide their own consent relates to England and Wales rather than Northern Ireland, current practice in Northern Ireland is to follow professional recommendations (e.g. GMC guidance;http://www.gmc-uk.org/guidance/ethical_guidance/5993.asp). Therefore the same process for recruiting participants without capacity will be the same for all sites.

8 STUDY PROCEDURES

8.1.1 DOPPLER SCAN PROCESS

Doppler ultrasound is the chosen method of detection, as compression ultrasonography with colour Doppler remains the best overall test for VTE in this context. This is due to its high sensitivity, specificity and potential availability in hospice units due to its portability, and in accordance with the rationale described above. It is easy to perform, less expensive than most "high tech" studies, can be performed at the bedside, and is highly reliable with trained operators[21].

Participants will be scanned by research nurses. The research nurses will be trained by Prof Max Watson (MW) and Dr Eoin Napier (EN) as part of the Focused Abdominal Sonography in

Palliative Care (FASP) course to perform compression ultrasonography. The FASP clinical training has been reviewed and approved for CPD credits by the Royal College of Physicians. It has been based on the FAST (Focused Abdominal Sonography in Trauma) approach which makes no attempt to train clinicians to be ultrasonographers but provides clinicians with access to ultrasound information to use in combination with their other clinical skills and knowledge to help them make better decisions. Short and specific training programmes such as these courses have been introduced in a variety of different clinical settings where clinician-conducted targeted ultrasound is used as an adjunct to information gathered from other clinical procedures. Examples where this is used in clinical practice include: detection of intra-abdominal and intraperitoneal fluid, urinary retention, DVTS and placement of long lines.

The nurses will complete the 2 day FASP course which includes a session on DVT assessment. In addition to this they will receive a further day's training in DVT examination conducted by MW and EN (Consultant radiologist), where they will have the opportunity to practice scanning on patients in the NI Hospice where the training will be undertaken. They will be trained to use the machines that will be used in the study, and how to record and send scan recordings to EN for quality assurance. The scan process in this study involves identifying the femoral vein from the long saphenous vein and femoral artery. Compressibility assessment of the common femoral vein will occur at 2cm increments throughout its length to the level of the popliteal fossa. If the vein is compressible throughout then a diagnosis will be made of 'no above knee DVT'. If the vein is not compressible at any point then the scan will be stopped and a diagnosis of DVT made. It is anticipated that the scan will take a maximum of 5-10 mins to do both legs and will be performed on admission (or within 48 hours) to the SPCU and then weekly thereafter.

Each scan will be recorded using the recording facility on the machine and a selection will be reviewed by a consultant radiologist, EN, for external validity. Any scan where a different result is found by the radiologist will be flagged up and the training of that nurse will be reviewed, as a very high agreement is expected. The first ten scans of each of the nurses will

be evaluated by EN to ensure diagnostic correlation (>23% of all scans double checked and "front-loaded"). Should there be any inaccuracy detected in the diagnosis from the scan, additional training will be provided by MW and scans from that nurse will be checked by EP until 5 consecutive scan results are agreed. Thereafter, EN will check a random 10% of the remaining scans, with the possibility that if there are significant concerns, then all scans from that nurse will be checked.

In addition, the participant scans may be performed by any of the study co-investigators if they, i) have no clinical responsibility at the unit, ii) have completed the same Doppler training as the research nurses including the two day FASP course, and iii) have in date GCP training. The machines will be bought from the budget for the research project, and will be standardised and have the ability to record the scans for external review for quality control purposes as discussed above. They will be portable so they can be transported between study centres if required.

It is recognized that there may be some measurement error, as with any investigation, and that this is likely to be more following a short training course such as this, at least initially, than following a longer one. However we feel that the following points allow that this error (which we will be able to estimate due to the checking process) is acceptable in the context of this primary research outcome.

1. The study asks the nurses to identify DVTs only in the area of the femur. The study will not attempt to assess thrombus present in the calf or the pelvis. This therefore is a much simpler test, and the nurse will diagnose one of 3 options: DVT present, no DVT present, or unable to evaluate.

2. We are looking for clinically significant numbers – that is, we are expecting a prevalence of between 15-25% and maybe more. This, and any correlations with clinical symptoms, will tell us whether this is a clinically relevant issue or not. Although we are doing all we can within our restrictions to be as precise as possible, by giving a further training session over and above the FASP course, and building a significant level of double checking, we believe this degree of imprecision is

acceptable with regard to the scientific outcome and the limitations of the study will be clearly presented.

3. Within the time and funding constraints of a study such as this, we feel we have the balance of training verses risk of imprecision as optimally as we can. Given that there has been no other study attempting to address this issue since Johnson and colleagues in 1999[18], we believe our proposed measure, even with its limitations will give us much needed important clinical information for the management of this neglected patient group.

8.1.2 CRITERIA FOR THE ATTENDING CLINICIAN TO ASSESS SCAN RESULT

It is not routine practice for patients, on admission or at any time during their admission, to undergo Doppler ultrasound, unless there is a clinical indication i.e. symptoms or signs of DVT. Unless patients have been specifically screened it would not be normal practice for clinicians or patients to know of the presence of an asymptomatic DVT. In addition, there is no evidence as to what happens to asymptomatic DVTs which are detected on a scan i.e. do they go on to cause clinical issues and therefore could potentially benefit from anticoagulant treatment, or do they resorb spontaneously without causing any clinical issues? As treatment for a DVT has potential side effects, it is ethically justifiable for this prevalence study to conceal the result so as not to influence clinical decision making. For this reason the results of the scan shall be kept confidential from the patient and clinician.

However the results of the scan may be revealed at the treating doctor's request if there is a clinical suspicion of VTE that would normally initiate a Doppler ultrasound request. If a patient is considered clinically by the treating team to have a DVT within 24 hours of the study Doppler scan, then the scan result will be given on request to the treating clinician to contribute to their clinical decision making. If the test result is not concordant with other clinical findings, then the patient can be referred by their usual clinician to their local radiology departmental if they feel this is required. Thus any result is only part of a clinical assessment and the potential limitations of the training will be fully acknowledged and

taken into account. It is important to stress that a negative scan does not exclude DVT if the symptoms suggestive of VTE have occurred more than a day after the scan was undertaken. In this circumstance, a repeat Doppler ultrasound could be performed as part of the usual clinical management of the patient under the direction of the clinical team.

8.1.3 TREATMENT DETAILS

This is a prospective multicentre longitudinal observational prevalence study intended to have as little impact on the patient's inpatient treatment as possible. With exception of the planned bedside Doppler Ultrasound, this study involves no additional clinical tests or interventions. No additional blood samples will be taken as part of this study. Where patients have had blood tests performed as part of routine practice, consent shall be sought to record these as part of the study.

The use of LMWH or other anticoagulants is at the discretion of the treating clinicians and will be recorded as part of this study. It will not affect participation in the study, as all patients will be included and followed up regardless of the use of anticoagulants or not.

8.2 STUDY ASSESSMENTS

8.2.1 BASELINE MEASURES

- Patient demographics: age, gender, ethnicity, comorbidities, smoking status (non, ex, current), and family history.
- Diagnosis and stage of disease, presence of pelvic disease;
- Treatment history (cancer patients - to include surgery, chemotherapy, radiotherapy, hormone therapy);
- Blood tests (if performed as part of clinical care): Biochemistry (to include albumin, urea, creatinine, eGFR,and CRP); full blood count; coagulation screen;

- Australian modified Karnofsky Performance Status (AKPS)[24]; this is a palliative care modified KPS which can detect change in status in 10% gradations and is thus likely to be more sensitive to change in this population who are all likely to be ECOG 3 or 4.
- VTE history, including treatment within the last month, or current prophylaxis;
- Concomitant medications (including those stopped within the previous 7 days);
- Bleeding and bleeding risk;
- Acceptability of Doppler scanning using a simple Likert scale following the initial scan.

8.2.2 WEEKLY ASSESSMENTS

Weekly assessment, including at baseline, of the following will be performed by the Research Nurses until participants are no longer fit for on-going assessments, have died, or have been discharged:

- Leg examination for presence of oedema, prominent veins, tenderness along the distribution of the deep venous system, calf swelling ≥3 cm compared to other calf (measured 10 cm below tibial tuberosity) by the research nurse;
- Symptoms of new onset/worsening leg oedema, leg or pleuritic chest pain, breathlessness;
- Presence of acute potentially reversible causes which increase the risk of DVT within the previous 12 weeks[25]
    - Recent major surgery
    - Acute medical illness
    - Recently bedbound due to acute medical illness
    - New diagnosis of spinal cord compression, expected to recover mobility
- Pathological fracture affecting mobility and expected to recover mobility
- A Wells score; (this is a clinical risk score used routinely in the hospital setting, but not the SPCU setting, NB. D-dimer test will not be done due to their oversensitivity in people with advanced cancer.)[26]

- Doppler ultrasound scan for proximal lower limb DVT;
- AKPS;
- Use of anticoagulation / thromboprophylaxis;
- Concomitant medication;
- Episodes of bleeding;
- Proven VTE by other methods.

The presence or new or worsening clinical symptoms and signs will be reported to the clinical team. The clinical team will make the decision regarding any further investigation or management.

8.2.3 FOLLOW UP

Patients will also be asked to consent for the research team to access their clinical records/contact their GP for study purposes e.g. date and cause of death.

8.3 STATISTICAL CONSIDERATIONS

8.3.1 SAMPLE SIZE

For our primary objective of prevalence of CAT in people admitted to hospice, assuming that the 17% of bilateral obstruction to lower limb venous return in hospice in-patients with cancer [18] represents more extensive thrombosis and thus those likely to have femoral DVT. In order to obtain an estimated prevalence of proximal lower limb DVT of cancer patients with 5% precision and 95% confidence level, a sample size of 217 cancer patients is needed. This is a reasonable assumption and is in keeping with previous estimates of CAT. It is projected from admission figures for the SPCUs involved that approximately 90% of admission will have cancer, leading to approximately 241 patients required to be recruited to ensure 217 cancer patients have been recruited.

For our secondary outcomes, which include assessment of hospice admissions with and without cancer, consecutive eligible patients will be recruited (*with or without cancer; with or without thromboprophylaxis*) until we have reached the required sample size of 217 cancer patients. Although we have no formal sample size calculation for the secondary outcomes, within the limits of the funding for this study, the research nurses will continue to recruit consecutive eligible patients, for the duration of the recruitment period, after the initial 217 cancer patients in order to get better information on the secondary outcomes to inform clinical practice and future research studies.

8.4 DATA ANALYSIS

The characteristics of the enrolled participants will be summarised using a descriptive analyses: categorical data will be presented as counts and percentages, and continuous data as the mean (standard deviation) or median (interquartile range) if data is skewed. The prevalence (within 48 hours after the patient's admission to SPCU) and the incidence (during the SPCU stay) of proximal lower limb DVT will be expressed as a percentage and the associated 95% confidence intervals (CI).

Univariate analyses (univariate logistic regression) will be performed to create odds ratios (ORs) for each patient and clinical characteristic, including and length of stay.

In light of the rarity of VTE events (approximately n = 40) and the number of predictors studied (n = 10), a multivariable regression model will be difficult because of concerns about the reliability of the model. However, an exploratory logistic regression analyses using backwards selection will be used to identify independent risk factors for proximal lower limb DVT on admission. The following risk factors will be included: patient characteristics, baseline venous thromboembolism risk factors, use of anticoagulants, AKPS, VTE history, concomitant medications, and bleeding and bleeding risk.

A further analysis will be used to identify risk factors for the incidence of proximal lower limb DVT during the admission. Logistic regression will be undertaken, which considers the proportion of new cases that develop in a given time period, i.e. the cumulative incidence. Risk factors may be present on admission, or may be acquired during the patient's stay in the unit as a result of changing condition, invasive procedures or treatments. The risk factors will include both factors at admission and those that may be acquired during the admission as discussed above.

As stated above, patients who are readmitted to the hospices will be screened for inclusion on each occasion, as each time a patient is admitted their disease and risk factors are likely to have changed from their previous admission. A sensitivity analysis will be undertaken to account for readmissions. This will be undertaken utilising a multilevel regression model for non-continuous outcomes, referred to as hierarchical generalized linear model. Multilevel data are distinguished from single-level data sets by the nesting of individual observations within individuals if the data consist of repeated measures. The covariates are specified as fixed effects, and the correlation of observations within patients over time is modelled by a covariance structure.

Sensitivity and specificity of the Well's score as a clinical score for the diagnosis of DVT will be calculated using ROC curve analysis.

The impact of proximal lower limb DVT on length of stay will also be analysed.

Survival analysis methods, proportional hazards regression, will be undertaken to look at the mortality rate and proximal lower limb DVT prevalence within 48 hours after the patient's admission to SPCU), and during the SPCU stay.

STATA will be used for statistical analysis.

8.4.1 STUDY EXIT:

- Patients who are too unwell to comply with the study requirements;
- Patients or consultees who withdraw consent for ongoing participation;

- Discharge from inpatient unit;
- Death.

8.4.2 WITHDRAWAL

Participants are free to withdraw from the study at any time without their care being affected and they do not have to give a reason. Proxies may withdraw consultee assent at any time without the care of the patient being affected and they do not have to give a reason. Data already collected up until withdrawal of consent will be used unless a participant who was included from consultee assent regains mental capacity and does not consent for the data to be used. Participants who are withdrawing from the study Doppler examinations will be asked if they would be willing to continue with other study assessments. The following information will be collected on the withdrawal form.

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

8.4.3 DEATH

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

- Date of death;
- Cause of death
- Significant associated factors such as: major bleed, clinically relevant non-major bleeding or VTE event.

9 DATA MANAGEMENT AND ARCHIVING

9.1 CONSENT FORMS

One to be given to the participant or next of kin, one for the patient notes, and one to be retained by the researcher and stored in a locked cabinet separated from other study data or linked documents.

9.2 ARCHIVING

Study documents will be retained for 5 years and then destroyed.

9.3 AT THE END OF THE STUDY

At the end of the study, the Doppler ultrasound machines will be retained and stored by Prof Max Watson and the research team for future ongoing research in this area.

10 REPORTING AND DISSEMINATION

We aim to publish the results of this study in peer-reviewed journals as well as present at national and international conferences.

If participant's wish, they (or their family) will be sent a lay summary of the study results.

11 ETHICAL AND REGULATORY CONSIDERATIONS

Criteria for the Attending Clinician to Assess Scan Result

It is not routine practice for patients, on admission or at any time during their admission, to undergo Doppler ultrasound, unless there is a clinical indication i.e. symptoms or signs of

DVT. It would not be normal practice for clinicians or patients to know of the presence of an asymptomatic DVT unless one had been discovered incidentally during imaging for another disease related matter. In addition, there is no evidence in people with advanced cancer as to whether asymptomatic DVTs which are detected on a scan cause clinical issues and therefore could potentially benefit from anticoagulant treatment, or resorb spontaneously without causing any clinical problem. As treatment for a DVT has potentially serious side effects such as bleeding (an event five times more likely in people with advanced cancer than those with early stage disease) which may be severe or even fatal, it is ethically justifiable for this prevalence study to conceal the result so as not to influence clinical decision making.

If scan results were routinely given to the attending clinician, the concern is that it might be very difficult for the clinician not to start the patient on anticoagulation. This would potentially putting the patient at risk of bleeding in a circumstance where there is no evidence to show that a patient would benefit from such treatment for an asymptomatic clot. For this reason the results of the scan shall be kept confidential from the patient and clinician. However the results of the scan may be revealed at the treating doctor's request if there is a clinical suspicion of VTE that would normally initiate a Doppler ultrasound request in usual clinical practice. Furthermore, if the research nurse detects clinical signs and symptoms of VTE which have not already been documented in the clinical record, he/she will draw this to the clinical team's attention, in case this has been overlooked.

It is important to stress that a negative scan does not exclude DVT if the symptoms suggestive of VTE have occurred more than a day after the scan was undertaken. In this circumstance, a repeat Doppler ultrasound could be performed as part of the usual clinical management of the patient under the direction of the clinical team.

This study is observational and thus has been designed with the aim that the study scans do not change usual management of VTE in this patient population which will continue as per accepted practice. However, we recognise that units which do not currently have on site Doppler scanning for DVT may develop a lower threshold for requesting to see the scan

results on clinical grounds, as being a recruiting site to a VTE study may raise clinical awareness of symptoms which may be due to VTE. This will not affect the primary outcome of DVT prevalence on admission.

Inclusion of patients without mental capacity

If only patients with capacity are included in this study, then there will still be no evidence to inform decision making with regard to providing thrombo-prophylaxis in people in whom a "best interests" decision must be made. Therefore we need to include patients without capacity in order to get applicable results for this group of patients. One of the most common causes of loss of capacity in SPCU patients is delirium, which, although can be treated, is a poor prognostic feature and therefore this patient group may have a different natural history in relation to VTE. In addition, often patients admitted to a SPCU have a temporary reduction in their capacity due to a potentially reversible cause (resulting in a delirium) that also increases their VTE risk e.g. infection, hypercalcaemia. Due to the impact of this potentially reversible pathology on VTE risk, data from patients with capacity to consent cannot be generalised to this group. Thus, unless it is considered that the patient is imminently dying, or that the relatives and friends who might have been a nominated consultee are considered by the clinical team to be too distressed to be approached about the study, patients will be eligible for inclusion, and their consultee will be approached for consent. Should the patient regain capacity, post-hoc consent to use their data will be required.

As Northern Ireland does not have specific guidance regarding inclusion of patients unable to provide their own consent, common practice is to comply with professional guidance (e.g. from the GMC). Thus patients without capacity will be recruited in the same way as for England and Wales.

Rapid Consent

Due to the nature of this trial it is impossible to allow for the usual 'cooling off' period before inclusion in the trial, as ideally patients need to be scanned on the day of admission, and often admissions are only planned on that day, so advance notice prior to admission cannot be given. Patients may withdraw consent at any time as described above, as may consultees. If a patient without capacity who was entered into the trial on the basis of consultee assent regains capacity and declines to participate – all data provided will be destroyed.

11.1 CONFIDENTIALITY AND DATA MANAGEMENT

The Chief Investigators and the research team of HIDDEN preserve the confidentiality of participants in accordance with the Data Protection Act 1998. All research data will be handled according to the principles of the Data Protection Act. Data will be stored on a password protected computer located in secure University buildings and appropriately backed up. Data transfer across participant organisations will be closely monitored and identifiable data e.g. consent forms will be sent by secure methods such as fax or hand delivered by members of the research team. All data will be retained for up to 5 years post study closure. The data and sample custodian for this study is the Chief investigator, Prof Miriam Johnson.

11.2 STUDY SPONSORSHIP

The University of Hull will act as sponsor for this study.

12 PROJECT MANAGEMENT

The project manager and two co-chief investigators will be responsible for the day to day management of the study. The project management group (PMG) will meet regularly (monthly in the first instance, then as needed) to ensure smooth running. The PMG will

consist of the investigators, project manager, statistician and two PPI members. A Project Steering Committee with an independent chair, PPI member and another independent clinician will be convened to meet 6 monthly.

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