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HIDDEN2: Hospital Deep Vein Thrombosis Detection Study in Cancer Patients Receiving Palliative Care

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Abstract

Introduction

Medical patients, admitted acutely to hospital are at risk of venous thromboembolism (VTE). Clinical guidelines advise thromboprophylaxis prophylaxis for those at high risk of VTE. VTE is a common sequela of cancer, but guidelines take little consideration of cancer as an independent risk factor and their utility in palliative care patients is unclear. The Hospice Inpatient Deep Vein Thrombosis (DVT) Detection Study (HIDDen) reported a 28% prevalence of asymptomatic iliofemoral DVT in hospice patients of poor performance status and prognosis, calling into question the utility of thromboprophylaxis in the palliative care setting. However, the majority of cancer inpatients receiving palliative care are admitted to hospital through the acute medical setting, yet their risk factors for VTE may differ from those admitted to hospices.

Objective To better understand the prevalence and behaviours of VTE in cancer patients receiving palliative care who are admitted as an acute medical emergency.

Design Multicentre, observational cohort study.

Setting Secondary care acute hospitals in South Wales, UK.

Patients We plan to recruit 232 patients ≥18 years old with a diagnosis of incurable cancer, and/or receiving palliative or best supportive care who are admitted acutely to hospital. Patients will be followed up for a maximum of 6 months following registration.

Primary Outcome Presence of lower extremity DVT.

Secondary Outcomes Symptom burden attributed to DVT or Pulmonary Embolism (PE), patient performance status, patient demographics, and development of new VTE within 90 days of registration.

Analysis The study statistical analysis plan will document analysis, methodology and procedures.

Strengths and weaknesses of the study

- This study explores thromboprophylaxis in a vulnerable adult population which is often excluded from thromboprophylaxis research.
- It is a natural progression of the of the HIDDen study, using similar methodology and outcome measures.
- Strong patient public involvement has influenced the study design, set up and ongoing trial management.
- Results will have rapid impact on thromboprophylaxis policy within palliative care.
- The study does not record pulmonary emboli and so the results may under estimate the true prevalence of VTE in this population.

Keywords

Thromboprophylaxis, venous thromboembolism, palliative, deep vein thrombosis, prevalence,

Introduction

The prevention of Venous Thromboembolism (VTE), comprising of Deep Vein Thrombosis (DVT) and Pulmonary Embolus (PE), is a priority for NHS England and Wales which has been demonstrated to reduce avoidable harm and mortality in hospitalised patients[(1)]. It is recommended that all hospitalised patients and, by default, those receiving palliative care, are assessed for their risk of venous thrombosis and if appropriate offered Low Molecular Weight Heparin (LMWH) thromboprophylaxis Cancer patients are seven times more likely to develop VTE than non-cancer patients, with one in five developing VTE[(2)]. The clinical studies informing thromboprophylaxis guidelines are more than 20 years old and less than 15% of patients recruited to them had cancer [(3)].There has been considerable debate as to whether these data can be applied to palliative care

patients[4,5]. Furthermore, these studies excluded palliative care patients[5,6], who are at particular risk of thrombosis since the risk of VTE is greater as cancer becomes more advanced[4]. Specific patient exclusion criteria were poor performance status (PS), prognosis of less than 3 months survival, risk of bleeding, renal failure and abnormal liver function. However, this population is one of the most likely to develop VTE and potentially benefit from thromboprophylaxis[7, 8]. The Hospice Deep Vein Thrombosis Detection study (HIDDen) identified a 28% prevalence of DVT in palliative care patients[9]. There was minimal associated symptom burden and no survival difference between those with or without DVT. Patients had high care needs, with a median Australia-modified Karnofsky Performance Scale (AKPS) of 49 and a median survival of 44 days. An accompanying Lancet Haematology Editorial concluded that thromboprophylaxis was of limited utility in hospice patients of poor PS and prognosis[10].

Rationale

The HIDDen study has been considered practice changing for Specialist Palliative Care Units (SPCUs) and hospices, yet its application to the wider palliative care population remains unclear[11]. Over 80,000 palliative patients in the UK are admitted acutely to hospital per year, yet thromboprophylaxis may not only be unnecessary but also confer a significant risk of harm[12]. LMWH given as a daily injection carries a 2% and 12% risk of major and non-major haemorrhage respectively, and data from 1200 hospice inpatients suggests a 9.8% rate of clinically relevant bleeding[13, 14].

The HIDDEN2 study represents a natural progression of the original hospice-based HIDDen study as it is to be performed in a "healthier", better prognosis group of patients within the general palliative cancer patient population which is more representative of the majority of palliative care patients who are admitted to the acute setting. The HIDDen study demonstrated the feasibility of recruiting and performing lower limb imaging in hospice/SPCU-based palliative care cancer patients; it recruited ahead of schedule and gained significant 'buy-in' from patients and their respective families[15].

There is a clear need to establish and better understand the prevalence, symptom burden and natural history of VTE in advanced cancer patients admitted to hospital, to better inform clinical practice, avoid unnecessary harm and reduce unwarranted health service costs.

Primary Objective

The aims of this study are to better understand the prevalence and behaviours of VTE in cancer patients receiving palliative care who are admitted acutely to hospital. Specific objectives are to:

- Determine the prevalence of radiologically apparent DVT in palliative cancer patients within 48 hours of hospital admission
- Evaluate the symptom burden attributable to DVT

- Assess the impact of incidental DVT on symptom burden at 3 months
- Determine overall survival at 6 months
- Determine the incidence of new VTE within 90 days of hospital admission
- Evaluate the association of DVT incidence with patient demographics including performance status

Methods and Analysis

Study Design and Sample Size a multicentre, observational cohort study in South Wales, UK (Figure 1.). A target 232 patients will be recruited over 10 months and followed up for up to six months from study registration. This target will allow us to estimate the prevalence of DVT among advanced cancer patients admitted to acute hospitals with a 95% confidence interval of no more than plus or minus five percentage points based on 17% prevalence from the previous HIDDen study and expected dropout of 5%.

Eligibility criteria

Inclusion Criteria

Cancer patients ≥18 years of age who have no physical limitations that would exclude them from taking part in ultrasound assessments, are able to give fully informed written consent, and meet at least one of the following criteria: incurable cancer defined as metastatic or locally advance cancer with no curative treatment planned (palliative radiotherapy or systemic anti-cancer therapy (SACT) is acceptable if being administered for symptom control or palliative intent); under the care of community or hospital palliative care service; or on the GP community palliative care register.

Exclusion criteria

Patients who meet one or more of the following criteria are excluded: non-melanoma skin cancer; receiving SACT with curative intent; biologically controlled disease e.g. e.g. prostate-specific antigen normal prostate cancer; admission for anticipated end of life care; or patients who are considered by the clinical team as likely to survive less than 5 days.

Study Setting

Two hundred and thirty two patients will be recruited from three secondary care, acute hospitals in South Wales, UK. The study will be coordinated by the Centre for Trials Research (CTR), Cardiff University and sponsored by Aneurin Bevan University Health Board (ABUHB).

Registration

Patients who consent to take part by authorising the Informed Consent Form (ICF) will be registered on the day of consent by the recruiting site staff using a secure, remote, study-specific web-based database REDCap (Research Electronic Data Capture)[16, 17]. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources

All cancer patients 18 years of age or over admitted to participating sites will be screened consecutively prior to consent for eligibility and/or referred to the local study team by the admitting clinician or suitable delegate following the different presentation pathways at each participating site. Screening, eligibility and non-consent will be logged at site on a screening log. Eligible patients will be invited to participate in the study by the admitting clinician and/or suitable delegate as per local patient presentation pathway. Interested patients will be given the HIDDEN2 Participant Information Sheet (PIS) and Informed Consent Form (ICF) and the opportunity to discuss the study with the research team. Participants will be free to withdraw from the study at any time following registration without any impact on their routine hospital treatment or care.

Baseline assessments

Baseline assessment data will be collected on Day 1-4 following registration: demographics, medical history and treatment history, routine blood assessments, baseline AKPS status, VTE history and concomitant medication.

Observational Colour Duplex Ultrasonography (CDUS)

Study-specific baseline CDUS assessments will be performed preferably on the day of admission and within no more than 48 hours from study registration (day 1) in order to determine an admission VTE prevalence. However, exceptions will be allowed in the event of a late Friday afternoon admission. In such a case, the patient may be recruited only if their scan can be performed by the following Monday morning i.e. the scan may be delayed until Day 4. In this situation, the time-lapse between admission and the scan being conducted will be recorded. For patients who require longer than 4 days to consider participation, the scan can be delayed, however, it would still need to be conducted within 48 hours from study registration. Patients who are happy to proceed with immediate consent will be able to do so since the aim of the study is to find the prevalence of DVT on admission and the study investigation is non-invasive.

CDUS result blinding

In normal practice outside of study, neither clinician nor patient would be aware of the presence of an asymptomatic DVT on admission to hospital since it is unusual for patients to undergo CDUS on admission and throughout their stay; unless there is a clinical indication that CDUS is required either alone or in combination with compression ultrasonography to diagnose DVT. On the occasion CDUS is required as part of the patient's routine care the whole (upper and lower) leg would be scanned.

The research CDUS imaging differs from this local procedure as it will be limited to the femoral-popliteal segment only (upper thigh) to allow direct comparison to the original HIDDen study, and will not include investigation of the calf or superficial veins (lower leg). Thus, the research CDUS will not provide sufficient details for clinical diagnostic purposes. Additionally, the research CDUS would only be valid as an exclusory test for 24 hours post-scan, after which time a thrombus could have formed. As such, patients requiring a scan more than 24 hours after the research scan has been performed will require routine CDUS outside of study following local practice to ensure accuracy.

As HIDDEN2 is an observational study the study results must not impact on routine clinical management. Access to research CDUS scan data will be restricted to local site staff delegated on the site staff delegation log. Therefore the patient, and local clinical team responsible for routine treatment of the patient outside of study, will be blinded from the results of the research CDUS to avoid influencing clinical management of the patient and usual practice. Unblinding of study CDUS results to these staff will not be permitted.

Due to differences in approaches to routine ultrasonography management, reporting practices and staff individual participating sites will develop local study-specific procedures to mitigate and monitor for results 'unblinding events'.

Follow Up

The study will comprise of three data collection timepoints: day 1-4 of consent and registration, day 90 post-registration for follow-up VTE assessment, and day 182 (6 months) post-registration for survival. Of these timepoints, only the first visit will require patient interaction as considerable effort has been made to minimise patient visits. From the initial assessment, the team will identify whether DVT is present and collect demographic data in line with usual admission procedures.

On day 1-4, data will be captured from the patient to identify any leg or lung symptoms and to capture any illnesses within the past 90 days. All other required data will be obtained from the patient's Healthcare Record (HCR) and recorded within the baseline Case Report Form (CRF).

On day 90, data from radiological investigations undertaken since registration will be reviewed within the patient's HCR and any new VTE events documented within the day 90 CRF.

On day 182, any deaths that occurred during the study will be recorded on the associated CRF. Any deaths not recorded in real time during the study will be identified on day 182 when the patient's HCR will be reviewed to determine overall survival.

Primary Outcome

The HIDDEN2 study aims to investigate the presence of lower extremity DVT. To ensure consistency throughout the study, all scans will be performed by fully qualified and accredited vascular scientists and/or radiologists with experience of conducting ultrasounds. This will help ensure scan quality and obviate the requirement for the secondary review of scan reporting, which occurred in the original HIDDen study.

Secondary Outcomes.

Symptom burden attributable to DVT or PE. HIDDEN2 will investigate the presence of pain and/or swelling in each leg, and the presence of breathlessness and/or chest pain evaluated and recorded at baseline.

Patient performance status. HIDDEN2 will investigate the following demographics: cancer diagnosis, anti-cancer treatment within the past three months, current medications, history of any potentially reversible risk factor for DVT in the previous 12 weeks and routine blood assessments.

Development of new VTE within 90 days after admission. Any radiological investigations undertaken up to 90 days post-registration will be reviewed and any new VTE events documented. This 90-day cut-off is in keeping with the accepted definition of hospital acquired thrombosis and will be of relevance when interpreting the results against current government thromboprophylaxis policy. Any request for a routine computer tomography pulmonary angiogram (CTPA), ventilation/ perfusion scan or CDUS will be triggered by the presence of symptoms suggestive of VTE. The presence of symptoms according to the radiology request will be recorded. Any DVT or PE identified during a scan for any other indication (I.e. not primarily looking for VTE) will be recorded as "incidental" DVT or PE. This outcome measure is purely observational and will not affect patient care.

6-month survival. At six months post-registration, the Welsh Clinical Portal will be reviewed by the treating site staff to confirm if participants are still alive. Any patient deaths will be recorded along with cause and date of death on the associated CRF. This approach will ensure end of life patients and their families are not disturbed or inconvenienced.

Data management

The Sponsor will act as data controller. Cardiff University and individual participating sites will act as data processors. Data management procedures will be documented in a study Data Management Plan (DMP) in line with the Protection Impact Assessment section of the study risk assessment.

Study data will be collected and managed using REDCap electronic data capture tools hosted at Cardiff University [16, 17]. Paper CRFs will be used as backup should REDCap be inaccessible. Participating sites will log patient screening on a site-specific electronic screening log and send a redacted version via secure electronic transfer to the CTR for central monitoring purposes.

Patient and public involvement and engagement

The original HIDDen study had strong Patient and Public Involvement (PI) which was evaluated against the National Standards and PI has been instrumental in the subsequent development of HIDDEN2 (18). Following the publication of HIDDen, a stakeholder meeting was held to discuss the impact of all findings on patient care. This was attended by the study's PI lead, lay representatives from Hospice UK, Marie Curie, Macmillan, Thrombosis UK, with clinical representation from members of the British Society for Haematology, Multiprofessional Association for Supportive Cancer Care, International Society for Thrombosis and Haemostasis and the Association for Palliative Medicine. In conclusion, as a hospice-based study, the HIDDen study was considered practice changing, but it was not possible to extrapolate the findings to palliative care patients admitted to hospital, who may be at different stages of the cancer journey, particularly with respect to both, better PS and prognosis. Since the majority of palliative care patients are admitted to hospital and not hospices, this was considered a priority area for research. The following patient organisations and charities at the stakeholder meeting helped form the research question for HIDDEN2: Hospice UK, Marie Curie, Macmillan, Thrombosis UK and Anticoagulation UK.

There are two public PI partners on the HIDDEN2 Study Management Group (SMG), one of which supported the original HIDDen study and is also a HIDDEN2 Executive Committee (EC) member.

Public involvement will be monitored against National Standards throughout the HIDDEN2 study and fully documented in the main results publication, or a separate report.

Statistics and data analysis

All participants must have undergone a research CDUS to be included in the primary outcome analysis. We have not planned an interim analysis. The prevalence of DVT at hospital admission will be summarised with a 95% confidence interval. There is no formal sample size calculation for the

secondary outcomes. However, further analysis will summarise and compare the characteristics of all cancer patients with and without DVT. The symptoms of patients with and without DVT on admission will be tabulated at each time point. The association between the presence of DVT, symptoms, and survival up to six months will be assessed by fitting appropriate regression models and adjusting for patient characteristics. The regression coefficients and associated 95% confidence intervals and p-values from the analysis will be reported. The impact of any missing data on the conclusions drawn from our analyses will be considered. Plausible missing data mechanisms will be considered, allowing us to estimate the strength and direction of relationship between DVT and secondary outcomes. Full analysis details will be document in a Statistical Analysis Plan.

The study results will be published in a peer reviewed journal. All study publications will be made publicly available on the study website.

Data Sharing

Applications for access to the data, in a pseudonymised format, may be made to the corresponding author and will be reviewed in line with existing CTR SOPs and Sponsor processes. It is the intention of the research group to make data available for patient benefit, wherever possible.

Monitoring

The study risk assessment has categorised HIDDEN2 as low risk (comparable to the risk of standard medical care), thus low monitoring levels will be employed following a risk-adapted approach.

There is no formal Independent Data Monitoring Committee. A Project Management Group (PMG) will provide oversight on a regular weekly to monthly basis dependent on study stage. The PMG will report to the SMG, including two clinical dependent, one dependent PI, and one independent statistician Executive Committee (EC) members, on a quarterly basis. The CTR Cancer Trial Steering Committee will monitor the study once per annum.

Central monitoring will be conducted via routine data queries and quality control checks of ICFS and site participant screening logs, and will focus on accrual, consent, withdrawal, research CDUS results adherence and unblinding, and data integrity and protection.

No site monitoring is planned. However, ad hoc triggered site visits will be conducted if required to address site-related GCP or contractual non-compliance. Non-compliance identified centrally or at site will be reported to Research Ethics Committee (REC), the Sponsor and participating sites as applicable following CTR standard policies and procedures. The study is subject to inspection by REC/IRB as the regulatory body, and inspection and audit by Aneurin Bevan University Health Board (ABUHB) as Sponsor.

Acknowledgements

HIDDEN2 is sponsored by Aneurin Bevan University Health Board (ABUHB). ABUHB has delegated day-to-day management of the study to the Centre for Trials Research (CTR) at Cardiff University.

Contributors

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Ethics approval

The study has been approved by Wales Research Ethics Committee 4 (22/WA/0037; IRAS Number 306532) and adopted to the HCRW Portfolio (CPMS ID: 51887).

Provenance and peer review

HIDDEN2 has been peer reviewed by HCRW RfppB funding panel. The study EC includes an independent Statistician (Sarah Walker) and a dependent public involvement member.

References

1. Hunt BJ. Preventing hospital associated venous thromboembolism. BMJ. 2019;365:l4239.
2. Noble S, Pasi J. Epidemiology and pathophysiology of cancer-associated thrombosis. Br J Cancer. 2010;102 Suppl 1:S2-9.
3. NICE. Venous Thromboembolism in Over 16s: Reducing the Risk of Hospital-Acquired Deep Vein Thrombosis or Pulmonary Embolism. NICE guideline [NG89]. London, UK.; 2018.
4. 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.
5. Noble SI, Nelson A, Finlay IG. Factors influencing hospice thromboprophylaxis policy: a qualitative study. Palliat Med. 2008;22(7):808-13.
6. Noble SI, Finlay IG. Have palliative care teams' attitudes toward venous thromboembolism changed? A survey of thromboprophylaxis practice across British specialist palliative care units in the years 2000 and 2005. J Pain Symptom Manage. 2006;32(1):38-43.
7. Noble S, Johnson M. Finding the evidence for thromboprophylaxis in palliative care: first let us agree on the question. Palliat Med. 2010;24(4):359-61.
8. Johnson MJ, McMillan B, Fairhurst C, Gabe R, Ward J, Wiseman J, et al. Primary thromboprophylaxis in hospices: the association between risk of venous thromboembolism and development of symptoms. J Pain Symptom Manage. 2014;48(1):56-64.
9. White C, Noble SIR, Watson M, Swan F, Allgar VL, Napier E, et al. Prevalence, symptom burden, and natural history of deep vein thrombosis in people with advanced cancer in specialist palliative care units (HIDDen): a prospective longitudinal observational study. Lancet Haematol. 2019;6(2):e79-e88.
10. Sandset PM, Dahm AEA. Is venous thromboembolism a problem in patients with cancer in palliative care? Lancet Haematol. 2019;6(2):e61-e2.
11. Noble S. Venous thromboembolism in palliative care patients: what do we know? Thromb Res. 2020;191 Suppl 1:S128-S32.
12. NCPC. National Council for Palliative Care minimum dataset report 2012-13. 2013.
13. Samama MM, Cohen AT, Darmon JY, Desjardins L, Eldor A, Janbon C, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. N Engl J Med. 1999;341(11):793-800.
14. Tardy B, Picard S, Guirimand F, Chapelle C, Danel Delerue M, Celarier T, et al. Bleeding risk of terminally ill patients hospitalized in palliative care units: the RHESO study. J Thromb Haemost. 2017;15(3):420-8.

15. White C, Noble S, Watson M, Swan F, Nelson A, Johnson MJ. Optimised clinical study recruitment in palliative care: success strategies and lessons learned. BMJ Support Palliat Care. 2020;10(2):216-20.

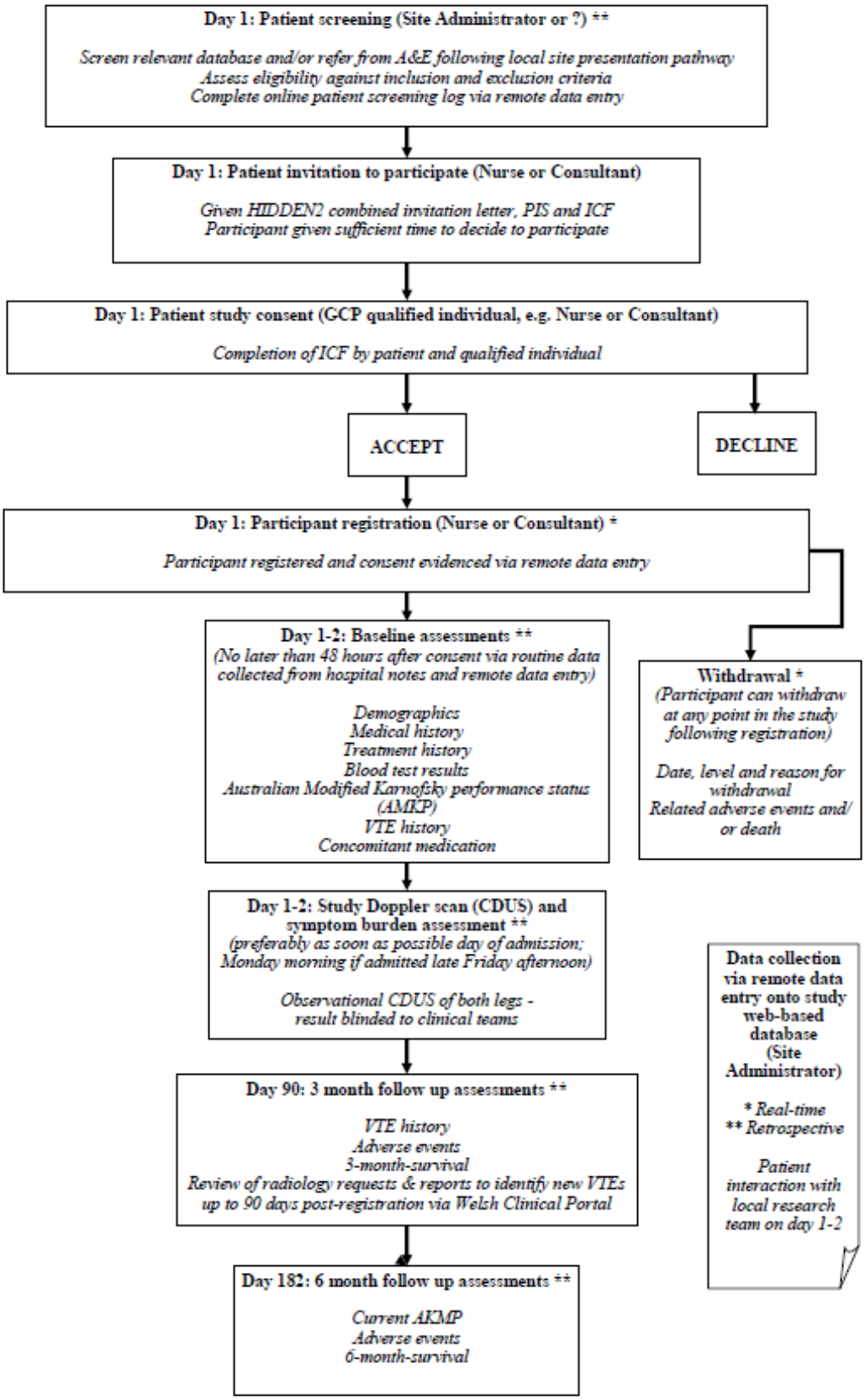
16 Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support, J Biomed Inform. 2009 Apr; 42(2):377-81.

17 Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, McLeod L, Delacqua G, Delacqua F, Kirby J, Duda SN, REDCap Consortium. The REDCap consortium: Building an international community of software partners, J Biomed Inform. 2019 May 9 [doi: 10.1016/j.jbi.2019.103208]

18 Seddon K, Elliot J, Johnson MJ White C, , Watson M, Nelson A, **Noble S.** Using the United Kingdom Standards for Public Involvement to evaluate the impact of public involvement in a Multinational Clinical Study. *Research Involvement and Engagement*. 2020 Apr 30; 7(1):22

Figures –

1. **Study schema**



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6.
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	8-9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N/A
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	N/A
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			N/A
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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HIDDEN2: Study Protocol for the Hospital Deep Vein Thrombosis Detection Study in Cancer Patients Receiving Palliative Care

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HIDDEN2: Study Protocol for the Hospital Deep Vein Thrombosis Detection Study in Cancer Patients Receiving Palliative Care

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Abstract

Introduction

Medical patients, admitted acutely to hospital are at risk of venous thromboembolism (VTE). Clinical guidelines advise thromboprophylaxis prophylaxis for those at high risk of VTE. VTE is a common sequela of cancer, but guidelines take little consideration of cancer as an independent risk factor and their utility in palliative care patients is unclear. The Hospice Inpatient Deep Vein Thrombosis (DVT) Detection Study (HIDDen) reported a 28% prevalence of asymptomatic iliofemoral DVT in hospice patients of poor performance status and prognosis, calling into question the utility of thromboprophylaxis in the palliative care setting. However, the majority of cancer inpatients receiving palliative care are admitted to hospital through the acute medical setting, yet their risk factors for VTE may differ from those admitted to hospices.

Objective To better understand the prevalence and behaviours of VTE in cancer patients receiving palliative care who are admitted as an acute medical emergency.

Design Multicentre, observational cohort study.

Setting Secondary care acute hospitals in South Wales, UK.

Patients We plan to recruit 232 patients ≥18 years old with a diagnosis of incurable cancer, and/or receiving palliative or best supportive care who are admitted acutely to hospital. Patients will be followed up for a maximum of 6 months following registration.

Primary Outcome Presence of lower extremity DVT.

Secondary Outcomes Symptom burden attributed to DVT or Pulmonary Embolism (PE), patient performance status, patient demographics, and development of new VTE within 90 days of registration.

Analysis The study statistical analysis plan will document analysis, methodology and procedures.

Ethics and dissemination Ethical approval from the Wales Research Ethics Committee, reference 22/WA/0037 (IRAS 306352) – the main trial results will be analysed as soon as practically possible and the publication shared with investigators and on Sponsor website; applications to access trial data will be subject to Sponsor review process.

Strengths and weaknesses of the study

- This study explores thromboprophylaxis in a vulnerable adult population which is often excluded from thromboprophylaxis research.
- It is a natural progression of the of the HIDDen study, using similar methodology and outcome measures.
- Strong patient public involvement has influenced the study design, set up and ongoing trial management.
- Results will have rapid impact on thromboprophylaxis policy within palliative care.
- The study does not record pulmonary emboli and so the results may under estimate the true prevalence of VTE in this population.

Keywords

Thromboprophylaxis, venous thromboembolism, palliative, deep vein thrombosis, prevalence,

Introduction

The prevention of Venous Thromboembolism (VTE), comprising of Deep Vein Thrombosis (DVT) and Pulmonary Embolus (PE), is a priority for NHS England and Wales which has been demonstrated to reduce avoidable harm and mortality in hospitalised patients(1). It is recommended that all hospitalised patients and, by default, those receiving palliative care, are assessed for their risk of venous thrombosis and if appropriate offered Low Molecular Weight Heparin (LMWH)

thromboprophylaxis Cancer patients are seven times more likely to develop VTE than non-cancer patients, with one in five developing VTE(2). The clinical studies informing thromboprophylaxis guidelines are more than 20 years old and less than 15% of patients recruited to them had cancer (3).There has been considerable debate as to whether these data can be applied to palliative care patients(4,5). Furthermore, these studies excluded palliative care patients(5,6), who are at particular risk of thrombosis since the risk of VTE is greater as cancer becomes more advanced(4). Specific patient exclusion criteria were poor performance status (PS), prognosis of less than 3 months survival, risk of bleeding, renal failure and abnormal liver function. However, this population is one of the most likely to develop VTE and potentially benefit from thromboprophylaxis(7,8). The Hospice Deep Vein Thrombosis Detection study (HIDDen) identified a 28% prevalence of DVT in palliative care patients(9). There was minimal associated symptom burden and no survival difference between those with or without DVT. Patients had high care needs, with a median Australia-modified Karnofsky Performance Scale (AKPS) of 49 and a median survival of 44 days. An accompanying Lancet Haematology Editorial concluded that thromboprophylaxis was of limited utility in hospice patients of poor PS and prognosis(10).

Rationale

The HIDDen study has been considered practice changing for Specialist Palliative Care Units (SPCUs) and hospices, yet its application to the wider palliative care population remains unclear(11). Over 80,000 palliative patients in the UK are admitted acutely to hospital per year, yet thromboprophylaxis may not only be unnecessary but also confer a significant risk of harm(12). LMWH given as a daily injection carries a 2% and 12% risk of major and non-major haemorrhage respectively, and data from 1200 hospice inpatients suggests a 9.8% rate of clinically relevant bleeding(13, 14).

The HIDDEN2 study represents a natural progression of the original hospice-based HIDDen study as it is to be performed in a “healthier”, better prognosis group of patients within the general palliative cancer patient population which is more representative of the majority of palliative care patients who are admitted to the acute setting. The HIDDen study demonstrated the feasibility of recruiting and performing lower limb imaging in hospice/SPCU-based palliative care cancer patients; it recruited ahead of schedule and gained significant ‘buy-in’ from patients and their respective families(15).

There is a clear need to establish and better understand the prevalence, symptom burden and natural history of VTE in advanced cancer patients admitted to hospital, to better inform clinical practice, avoid unnecessary harm and reduce unwarranted health service costs.

Primary Objective

The aims of this study are to better understand the prevalence and behaviours of VTE in cancer patients receiving palliative care who are admitted acutely to hospital. Specific objectives are to:

- Determine the prevalence of radiologically apparent DVT in palliative cancer patients within 48 hours of hospital admission
- Evaluate the symptom burden attributable to DVT
- Assess the impact of incidental DVT on symptom burden at 3 months
- Determine overall survival at 6 months
- Determine the incidence of new VTE within 90 days of hospital admission
- Evaluate the association of DVT incidence with patient demographics including performance status

Methods and Analysis

Study Design and Sample Size a multicentre, observational cohort study in South Wales, UK (Figure 1.). The trial opened to recruitment on 04 May 2022 and we plan to close recruitment on 30 Sep 2023. A target of 232 patients will be recruited and followed up for up to six months from study registration. This target will allow us to estimate the prevalence of DVT among advanced cancer patients admitted to acute hospitals with a 95% confidence interval of no more than plus or minus five percentage points based on 17% prevalence from the previous HIDDen study and expected dropout of 5%.

Eligibility criteria

Inclusion Criteria

Cancer patients ≥18 years of age who have no physical limitations that would exclude them from taking part in ultrasound assessments, are able to give fully informed written consent, and meet at least one of the following criteria: incurable cancer defined as metastatic or locally advance cancer with no curative treatment planned (palliative radiotherapy or systemic anti-cancer therapy (SACT) is acceptable if being administered for symptom control or palliative intent); under the care of community or hospital palliative care service; or on the GP community palliative care register.

Exclusion criteria

Patients who meet one or more of the following criteria are excluded: non-melanoma skin cancer; receiving SACT with curative intent; biologically controlled disease e.g. e.g. prostate-specific antigen normal prostate cancer; admission for anticipated end of life care; or patients who are considered by the clinical team as likely to survive less than 5 days.

Study Setting

Two hundred and thirty two patients will be recruited from three secondary care, acute hospitals in South Wales, UK. The study will be coordinated by the Centre for Trials Research (CTR), Cardiff University and sponsored by Aneurin Bevan University Health Board (ABUHB).

Registration

Patients who consent to take part by authorising the Informed Consent Form (ICF) will be registered on the day of consent by the recruiting site staff using a secure, remote, study-specific web-based database REDCap (Research Electronic Data Capture)(16, 17). REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources

All cancer patients 18 years of age or over admitted to participating sites will be screened consecutively prior to consent for eligibility and/or referred to the local study team by the admitting clinician or suitable delegate following the different presentation pathways at each participating site. Screening, eligibility and non-consent will be logged at site on a screening log. Eligible patients will be invited to participate in the study by the admitting clinician and/or suitable delegate as per local patient presentation pathway. Interested patients will be given the HIDDEN2 Participant Information Sheet (PIS) and Informed Consent Form (ICF) and the opportunity to discuss the study with the research team. Participants will be free to withdraw from the study at any time following registration without any impact on their routine hospital treatment or care.

Baseline assessments

Baseline assessment data will be collected on Day 1-4 following registration: demographics, medical history and treatment history, routine blood assessments, baseline AKPS status, VTE history and concomitant medication.

Observational Colour Duplex Ultrasonography (CDUS)

Study-specific baseline CDUS assessments will be performed preferably on the day of admission and within no more than 48 hours from study registration (day 1) in order to determine an admission VTE prevalence. However, exceptions will be allowed in the event of a late Friday afternoon admission. In such a case, the patient may be recruited only if their scan can be performed by the following Monday morning i.e. the scan may be delayed until Day 4. In this situation, the time-lapse between admission and the scan being conducted will be recorded. For patients who require longer than 4 days to consider participation, the scan can be delayed, however, it would still need to be conducted within

48 hours from study registration. Patients who are happy to proceed with immediate consent will be able to do so since the aim of the study is to find the prevalence of DVT on admission and the study investigation is non-invasive.

CDUS result blinding

In normal practice outside of study, neither clinician nor patient would be aware of the presence of an asymptomatic DVT on admission to hospital since it is unusual for patients to undergo CDUS on admission and throughout their stay; unless there is a clinical indication that CDUS is required either alone or in combination with compression ultrasonography to diagnose DVT. On the occasion CDUS is required as part of the patient's routine care the whole (upper and lower) leg would be scanned.

The research CDUS imaging differs from this local procedure as it will be limited to the femoral-popliteal segment only (upper thigh) to allow direct comparison to the original HIDDen study, and will not include investigation of the calf or superficial veins (lower leg). Thus, the research CDUS will not provide sufficient details for clinical diagnostic purposes. Additionally, the research CDUS would only be valid as an exclusory test for 24 hours post-scan, after which time a thrombus could have formed. As such, patients requiring a scan more than 24 hours after the research scan has been performed will require routine CDUS outside of study following local practice to ensure accuracy.

As HIDDEN2 is an observational study the study results must not impact on routine clinical management. Access to research CDUS scan data will be restricted to local site staff delegated on the site staff delegation log. Therefore the patient, and local clinical team responsible for routine treatment of the patient outside of study, will be blinded from the results of the research CDUS to avoid influencing clinical management of the patient and usual practice. Unblinding of study CDUS results to these staff will not be permitted.

Due to differences in approaches to routine ultrasonography management, reporting practices and staff individual participating sites will develop local study-specific procedures to mitigate and monitor for results 'unblinding events'.

Follow Up

The study will comprise of three data collection timepoints: day 1-4 of consent and registration, day 90 post-registration for follow-up VTE assessment, and day 182 (6 months) post-registration for survival. Of these timepoints, only the first visit will require patient interaction as considerable effort has been made to minimise patient visits. From the initial assessment, the team will identify whether DVT is present and collect demographic data in line with usual admission procedures.

On day 1-4, data will be captured from the patient to identify any leg or lung symptoms and to capture any illnesses within the past 90 days. All other required data will be obtained from the patient's Healthcare Record (HCR) and recorded within the baseline Case Report Form (CRF).

On day 90, data from radiological investigations undertaken since registration will be reviewed within the patient's HCR and any new VTE events documented within the day 90 CRF.

On day 182, any deaths that occurred during the study will be recorded on the associated CRF. Any deaths not recorded in real time during the study will be identified on day 182 when the patient's HCR will be reviewed to determine overall survival.

Primary Outcome

The HIDDEN2 study aims to investigate the presence of lower extremity DVT. To ensure consistency throughout the study, all scans will be performed by fully qualified and accredited vascular scientists and/or radiologists with experience of conducting ultrasounds. This will help ensure scan quality and obviate the requirement for the secondary review of scan reporting, which occurred in the original HIDDen study.

Secondary Outcomes.

Symptom burden attributable to DVT or PE. HIDDEN2 will investigate the presence of pain and/or swelling in each leg, and the presence of breathlessness and/or chest pain evaluated and recorded at baseline.

Patient performance status. HIDDEN2 will investigate the following demographics: cancer diagnosis, anti-cancer treatment within the past three months, current medications, history of any potentially reversible risk factor for DVT in the previous 12 weeks and routine blood assessments.

Development of new VTE within 90 days after admission. Any radiological investigations undertaken up to 90 days post-registration will be reviewed and any new VTE events documented. This 90-day cut-off is in keeping with the accepted definition of hospital acquired thrombosis and will be of relevance when interpreting the results against current government thromboprophylaxis policy. Any request for a routine computer tomography pulmonary angiogram (CTPA), ventilation/ perfusion scan or CDUS will be triggered by the presence of symptoms suggestive of VTE. The presence of symptoms according to the radiology request will be recorded. Any DVT or PE identified during a scan for any

other indication (I.e. not primarily looking for VTE) will be recorded as "incidental" DVT or PE. This outcome measure is purely observational and will not affect patient care.

6-month survival. At six months post-registration, the Welsh Clinical Portal will be reviewed by the treating site staff to confirm if participants are still alive. Any patient deaths will be recorded along with cause and date of death on the associated CRF. This approach will ensure end of life patients and their families are not disturbed or inconvenienced.

Data management

The Sponsor will act as data controller. Cardiff University and individual participating sites will act as data processors. Data management procedures will be documented in a study Data Management Plan (DMP) in line with the Protection Impact Assessment section of the study risk assessment.

Study data will be collected and managed using REDCap electronic data capture tools hosted at Cardiff University (16, 17). Paper CRFs will be used as backup should REDCap be inaccessible. Participating sites will log patient screening on a site-specific electronic screening log and send a redacted version via secure electronic transfer to the CTR for central monitoring purposes.

Patient and public involvement and engagement

The original HIDDen study had strong Patient and Public Involvement (PI) which was evaluated against the National Standards(18) and PI has been instrumental in the subsequent development of HIDDEN2 (18). Following the publication of HIDDen, a stakeholder meeting was held to discuss the impact of all findings on patient care. This was attended by the study's PI lead, lay representatives from Hospice UK, Marie Curie, Macmillan, Thrombosis UK, with clinical representation from members of the British Society for Haematology, Multiprofessional Association for Supportive Cancer Care, International Society for Thrombosis and Haemostasis and the Association for Palliative Medicine. In conclusion, as a hospice-based study, the HIDDen study was considered practice changing, but it was not possible to extrapolate the findings to palliative care patients admitted to hospital, who may be at different stages of the cancer journey, particularly with respect to both, better PS and prognosis. Since the majority of palliative care patients are admitted to hospital and not hospices, this was considered a priority area for research. The following patient organisations and charities at the stakeholder meeting helped form the research question for HIDDEN2: Hospice UK, Marie Curie, Macmillan, Thrombosis UK and Anticoagulation UK.

There are two public PI partners on the HIDDEN2 Study Management Group (SMG), one of which supported the original HIDDen study and is also a HIDDEN2 Executive Committee (EC) member.

Public involvement will be monitored against National Standards throughout the HIDDEN2 study and fully documented in the main results publication, or a separate report.

Statistics and data analysis

All participants must have undergone a research CDUS to be included in the primary outcome analysis. We have not planned an interim analysis. The prevalence of DVT at hospital admission will be summarised with a 95% confidence interval. There was no formal sample size calculation for the secondary outcomes. However, further analysis will summarise and compare the characteristics (age, sex, type of cancer diagnosis, treatment, history of DVT, symptoms of DVT or PE, AKPS, and baseline blood profiles) of all cancer patients with and without DVT. Univariable logistic regression models will be performed to create odds ratios (ORs) and 95% CIs for the occurrence of the DVTs. The following risk factors will be included in each model: age, sex, baseline DVT and venous thromboembolism risk factors, use of anticoagulants, AKPS score, venous thromboembolism history, bleeding history, and bleeding risk. Based on the previous HIDDEN trial, a multivariate logistic regression model will include age, AKPS score, history of DVT/VTE, and the presence of leg oedema. Any additional variables with a p value of less than 0.1 from the univariable analysis will be added to the multivariable model. The final adjusted model will include all the above-named variables, plus those that have a p-value <0.05 in the initial multivariable model. Adjusted ORs with 95% CIs will be presented.

The number of patients with new VTE events occurring within 90 days of admission, and the number of patient deaths within 6 months will be reported. Kaplan Meier curves will be constructed to compare survival according to whether patients had proximal lower limb deep vein thrombosis within 48 hours after the patient's admission to hospital. A log-rank test will be used to compare survival in by DVT status. Participants who have not died by the end of survival data collection will be censored at the date last known to be alive.

Further exploratory analysis will also be undertaken to evaluate development of symptoms attributable to DVT and pulmonary embolism (PE), bleeding associated with and without thromboprophylaxis and the effect of COVID-19 in our study.

The impact of any missing data on the conclusions drawn from our analyses will be considered. Plausible missing data mechanisms will be considered, allowing us to estimate the strength and direction of relationship between DVT and secondary outcomes. Full analysis details will be document in a Statistical Analysis Plan.

The study results will be published in a peer reviewed journal. All study publications will be made publicly available on the study website.

Data Sharing

Applications for access to the data, in a pseudonymised format, may be made to the corresponding author and will be reviewed in line with existing CTR SOPs and Sponsor processes. It is the intention of the research group to make data available for patient benefit, wherever possible.

Monitoring

The study risk assessment has categorised HIDDEN2 as low risk (comparable to the risk of standard medical care), thus low monitoring levels will be employed following a risk-adapted approach.

There is no formal Independent Data Monitoring Committee. A Project Management Group (PMG) will provide oversight on a regular weekly to monthly basis dependent on study stage. The PMG will report to the SMG, including two clinical dependent, one dependent PI, and one independent statistician Executive Committee (EC) members, on a quarterly basis. The CTR Cancer Trial Steering Committee will monitor the study once per annum.

Central monitoring will be conducted via routine data queries and quality control checks of ICFS and site participant screening logs, and will focus on accrual, consent, withdrawal, research CDUS results adherence and unblinding, and data integrity and protection.

No site monitoring is planned. However, ad hoc triggered site visits will be conducted if required to address site-related GCP or contractual non-compliance. Non-compliance identified centrally or at site will be reported to Research Ethics Committee (REC), the Sponsor and participating sites as applicable following CTR standard policies and procedures. The study is subject to inspection by REC/IRB as the regulatory body, and inspection and audit by Aneurin Bevan University Health Board (ABUHB) as Sponsor.

Acknowledgements

HIDDEN2 is sponsored by Aneurin Bevan University Health Board (ABUHB). ABUHB has delegated day-to-day management of the study to the Centre for Trials Research (CTR) at Cardiff University.

Contributors

Provision of study materials or patients: Noble.S., Pease.N., Alikhan.R., Bryant.K., Groves.T., Wallace.R.

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Data analysis and interpretation: Casbard.A., Noble.S., Raisanen.L., Kitson.T.

Patient representation: Seddon.K., Smith.D.

Manuscript writing: Kitson.T., Noble.S., Casbard.A., Thomas.I., Upton.L.

Final approval of manuscript: All authors.

Accountable for all aspects of the work: All authors

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Ethics approval

The study has been approved by Wales Research Ethics Committee 4 (22/WA/0037; IRAS Number 306532) and adopted to the HCRW Portfolio (CPMS ID: 51887).

Provenance and peer review

HIDDEN2 has been peer reviewed by HCRW RfppB funding panel. The study EC includes an independent Statistician (Sarah Walker) and a dependent public involvement member.

Competing Interests

No competing interest.

Figure Legend

1. Study schema

References

1. Hunt BJ. Preventing hospital associated venous thromboembolism. BMJ. 2019;365:l4239.
2. Noble S, Pasi J. Epidemiology and pathophysiology of cancer-associated thrombosis. Br J Cancer. 2010;102 Suppl 1:S2-9.
3. NICE. Venous Thromboembolism in Over 16s: Reducing the Risk of Hospital-Acquired Deep Vein Thrombosis or Pulmonary Embolism. NICE guideline [NG89]. London, UK.; 2018.
4. 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.
5. Noble SI, Nelson A, Finlay IG. Factors influencing hospice thromboprophylaxis policy: a qualitative study. Palliat Med. 2008;22(7):808-13.
6. Noble SI, Finlay IG. Have palliative care teams' attitudes toward venous thromboembolism changed? A survey of thromboprophylaxis practice across British specialist palliative care units in the years 2000 and 2005. J Pain Symptom Manage. 2006;32(1):38-43.
7. Noble S, Johnson M. Finding the evidence for thromboprophylaxis in palliative care: first let us agree on the question. Palliat Med. 2010;24(4):359-61.
8. Johnson MJ, McMillan B, Fairhurst C, Gabe R, Ward J, Wiseman J, et al. Primary thromboprophylaxis in hospices: the association between risk of venous thromboembolism and development of symptoms. J Pain Symptom Manage. 2014;48(1):56-64.
9. White C, Noble SIR, Watson M, Swan F, Allgar VL, Napier E, et al. Prevalence, symptom burden, and natural history of deep vein thrombosis in people with advanced cancer in specialist palliative care units (HIDDen): a prospective longitudinal observational study. Lancet Haematol. 2019;6(2):e79-e88.
10. Sandset PM, Dahm AEA. Is venous thromboembolism a problem in patients with cancer in palliative care? Lancet Haematol. 2019;6(2):e61-e2.
11. Noble S. Venous thromboembolism in palliative care patients: what do we know? Thromb Res. 2020;191 Suppl 1:S128-S32.
12. NCPC. National Council for Palliative Care minimum dataset report 2012-13. 2013.
13. Samama MM, Cohen AT, Darmon JY, Desjardins L, Eldor A, Janbon C, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. N Engl J Med. 1999;341(11):793-800.
14. Tardy B, Picard S, Guirimand F, Chapelle C, Danel Delerue M, Celarier T, et al. Bleeding risk of terminally ill patients hospitalized in palliative care units: the RHESO study. J Thromb Haemost. 2017;15(3):420-8.

15. White C, Noble S, Watson M, Swan F, Nelson A, Johnson MJ. Optimised clinical study recruitment in palliative care: success strategies and lessons learned. BMJ Support Palliat Care. 2020;10(2):216-20.

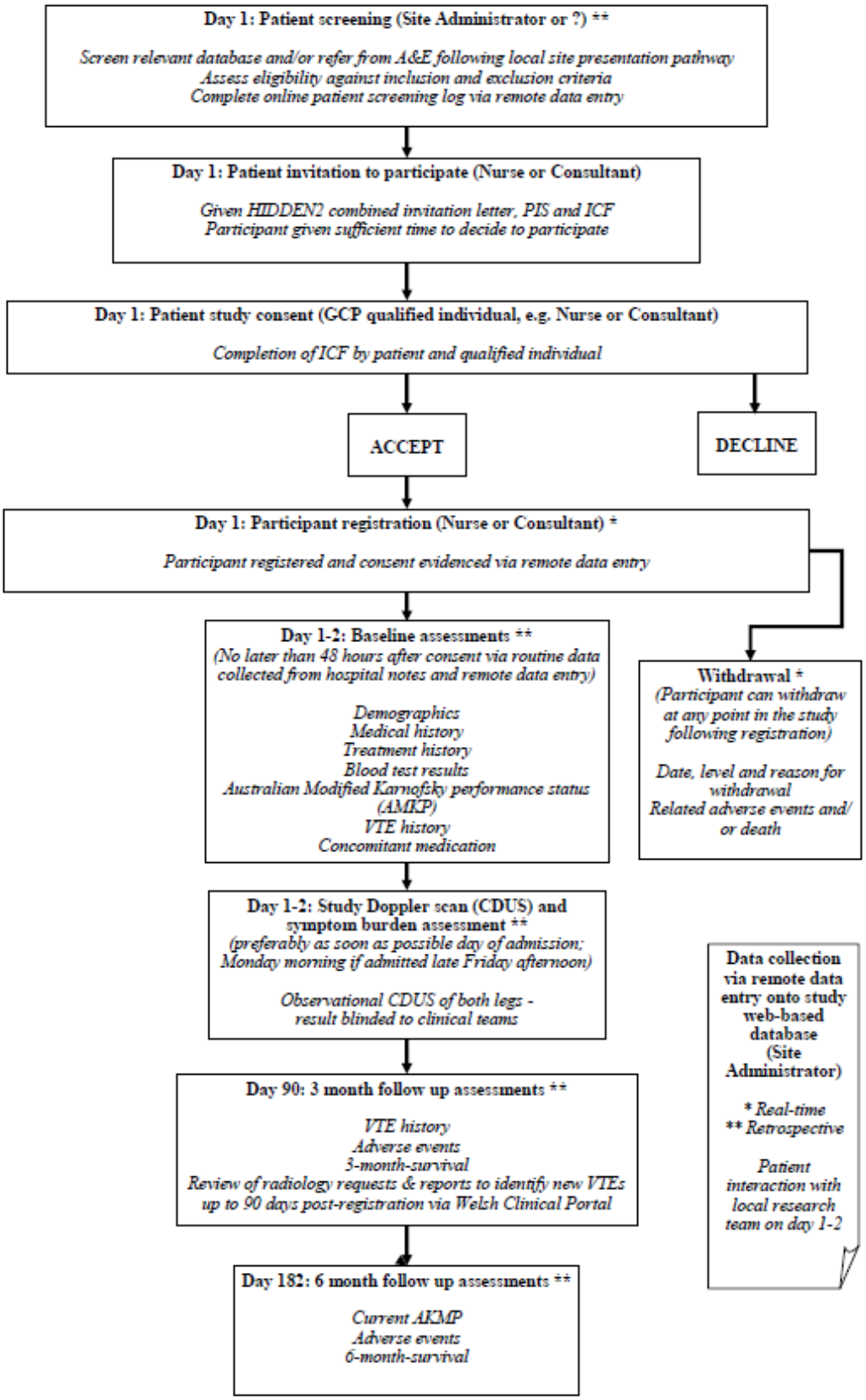
16 Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support, J Biomed Inform. 2009 Apr; 42(2):377-81.

17 Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, McLeod L, Delacqua G, Delacqua F, Kirby J, Duda SN, REDCap Consortium. The REDCap consortium: Building an international community of software partners, J Biomed Inform. 2019 May 9 [doi: 10.1016/j.jbi.2019.103208]

18 Seddon K, Elliot J, Johnson MJ White C, , Watson M, Nelson A, **Noble S.** Using the United Kingdom Standards for Public Involvement to evaluate the impact of public involvement in a Multinational Clinical Study. *Research Involvement and Engagement*. 2020 Apr 30; 7(1):22

Figures –

1. **Study schema**



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6.
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	8-9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N/A
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	N/A
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			N/A
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10.

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.