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

Protocol

Version 1.0

05.01.2022

Sponsor:	**ANEURIN BEVAN LOCAL HEALTH BOARD (ABUHB):** Aneurin Bevan Local Health Board Headquarters, St. Cadoc's Hospital, Lodge Road, Caerleon, Newport, NP18 3XQ
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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the relevant study regulations, GCP guidelines, and CTR's SOPs.
I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Director of Cancer, Centre for Trials Research **Name: Prof Richard Adams**	Professor Richard Adams **Signature**	06.01.2022 **Date**
Chief Investigator: **Name: Prof Simon Noble**	Professor Simon Noble **Signature**	06.01.2022 **Date**

General Information This protocol describes the HIDDEN2 study and provides information about the procedures for entering participants into the study. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other participants. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the study. Problems relating to the study should be referred, in the first instance, to CTR at HIDDEN2@cardiff.ac.uk

Contact details – Chief Investigator & Co-Investigators

CHIEF INVESTIGATOR

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Study Co-ordination:

The HIDDEN2 study is being coordinated by the Centre for Trials Research (CTR), Cardiff University, a Clinical Research Collaboration (UKCRC) registered clinical trials unit.

For **all queries,** please contact the HIDDEN2 team through the main study email address. Any clinical queries will be directed through the Study Manager to either the Chief Investigator or a Co-Investigator

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Clinical queries:

Clinical queries
HIDDEN2@cardiff.ac.uk
All clinical queries will be directed to the most appropriate clinical person.

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Glossary of abbreviations

ABUHB	Aneurin Bevan University Health Board (Sponsor)
AE	Adverse Event
CDUS	Colour duplex ultrasonography
AKPS	Australia Modified Karnofsky Performance Status
CF	Consent Form
CFV	Common femoral vein
CI	Chief Investigator
CRF	Case Report Form
CTPA	Computer Tomography Pulmonary Angiogram
CTR	Centre for Trials Research
CTU	Clinical Trials Unit
CU	Cardiff University
DVT	Deep vein thrombosis
EC	Executive Committee
GCP	Good Clinical Practice
GP	General Practitioner
HAT	Hospital acquired thrombosis
HB	Health Board
HCRW	Health Care Research Wales
HIDDen	Previous Study: The Hospice Deep Vein Thrombosis Detection study
HIDDEN2	This Study: Hospital Deep Vein Thrombosis Detection Study in Cancer Patients Receiving Palliative Care
HRA	Health Research Authority
IC	Informed consent
ICH	International Conference on Harmonization
IRAS	Integrated Research Application System
IRB	Institutional Review Board
ISF	Investigator Site File
LMWH	Low molecular weight heparin
NHS	National Health Service
OS	Overall survival
PE	Pulmonary embolus
PFS	Progression-free survival
PI	Principal Investigator
PIS	Participant Information Sheet
POPV	Popliteal vein
PSA	Prostate Specific Antigen
QA	Quality Assurance
QC	Quality control
R&D	Research and Development
REC	Research Ethics Committee
SACT	Systemic Anti-Cancer Therapies
SMF	Study Master File
SMG	Study Management Group
SPCU	Specialist Palliative Care Unit
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
SVF	Superficial femoral vein
VTE	Venous Thromboembolism

1 Amendment History

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment No.	Protocol version no.	Date issued	Summary of changes made since previous version
N/A	0.1 – 1.0 (drafts)	N/A	Pre-submission drafts

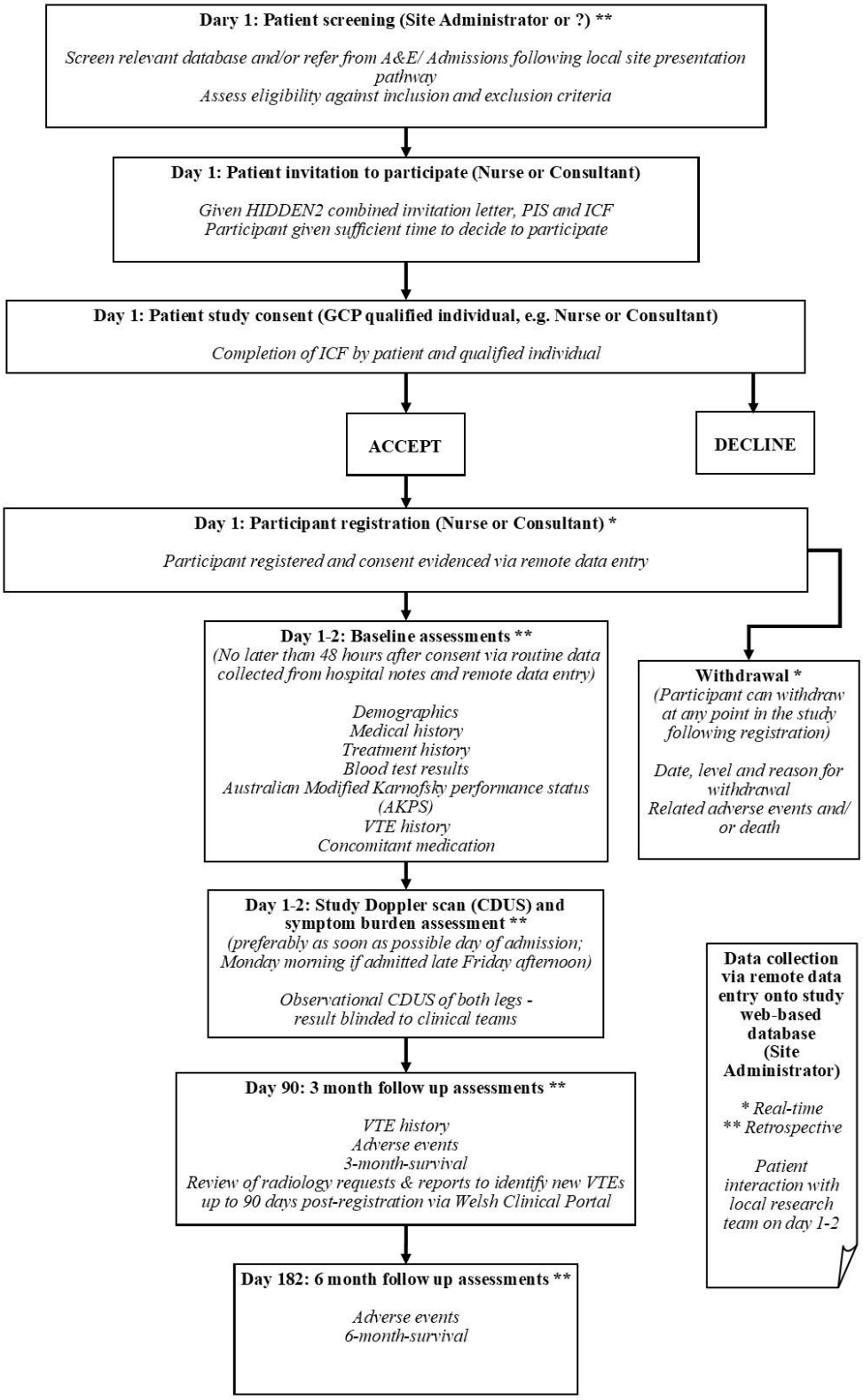
2 Synopsis

Short title	**Hospital Deep Vein Thrombosis Detection Study in Cancer Patients Receiving Palliative Care**
Acronym	**HIDDEN2**
Sponsor	Aneurin Bevan University Health Board (ABUHB)
Sponsor ref:	AB/228
Funder	Health Care Research Wales
Funder ref.	RfPPB-2-1747(P)
CTR Portfolio Number	1178
IRAS number:	306352
REC ref:	TBA
HCRW Portfolio:	TBA
Clinicaltrials.gov ref:	TBA
Study design	Multicentre observational non-CTIMP cohort study
Study participants	Cancer patients with a diagnosis of incurable cancer, receiving palliative care/best supportive care who are admitted acutely (as an emergency) to hospital
Planned sample size	232
Planned number of sites	4
Inclusion criteria	1. Cancer patient of 18 years of age and over 2. Able to give fully informed written consent 3. Meets one or more of the following criteria: - Incurable cancer defined as metastatic or locally advanced cancer with no -curative treatment planned* - Under the care of community or hospital palliative care services. - On the GP community palliative care register 4. No physical limitations to performing the ultrasound assessment. ** Palliative radiotherapy or SACT is acceptable if being administered for symptom control or palliative intent.*
Exclusion criteria	1. Non melanoma skin cancer 2. Receiving anticancer treatments with curative intent 3. Biologically controlled disease e.g. PSA normal prostate cancer 4. Admission for anticipated end of life care 5. Patients who are considered by the clinical team likely to die within 5 days
Follow-up duration	6 months
Planned study period	15 months
Primary objective	To identify how many cancer patients receiving palliative care have radiological evidence of DVT when admitted acutely to hospital.
Secondary objectives	To identify - What symptoms these patients have. - The impact of incidental DVT over time on symptom burden, clinical management and 6-month survival. - The incidence of new VTE within 90 days of hospital admission.

	- The relationship between DVT incidence and patient demographics including performance status.
Primary outcomes	Presence of lower extremity DVT.
Secondary outcomes	- Symptom burden attributable to DVT or PE - Patient performance status - Patient demographics - Development of new VTE within 90 days at admission: - 6-month survival

3 Study summary & schema

3.1 Study schema



3.2 Study lay summary

Patients with cancer are at a high risk of developing potentially dangerous blood clots (venous thromboembolism or VTE) due to the release of molecules which make the blood stickier. The risk of developing VTE is further increased by surgery, sudden medical illness and anticancer treatments such as chemotherapy, hormone therapy and immunotherapy. Most VTEs start as blood clots in the legs known as Deep Vein Thromboses (DVT) which may have no symptoms but classically present as swollen legs. Untreated, these DVTs can break off and lodge in the lungs forming Pulmonary Emboli (PEs), causing a breadth of symptoms including cough, shortness of breath, chest pain, collapse and sometimes death.

Emergency hospital admission increases the risk of VTE by 20% regardless of whether a patient has cancer or not. Consequently, VTE prevention amongst hospitalised patients is a priority for NHS England and Wales and has been shown to reduce avoidable harm and death.

The studies upon which clinical guidelines for preventing VTE (thromboprophylaxis) are based, are over 20 years old and included less than 15% cancer patients. Also, studies excluded patients who were likely to have a poor outcome or poor performance status (PS). It is therefore unclear whether we should apply these guidelines to patients with advanced cancer who are receiving palliative care.

The Hospice Deep Vein Thrombosis Detection study (HIDDen) looked at how many hospice patients were affected by VTE and how useful thromboprophylaxis would be for these patients. Leaving out 35% of patients who were admitted for end-of-life care, 28% of the remaining patients demonstrated large volume DVT. These caused few symptoms and there was no survival difference between those with or without DVT. Patients had high care needs and an average survival of 44 days. A Lancet Haematology Editorial concluded that thromboprophylaxis was of limited utility in hospice patients of poor PS and prognosis. These data have already changed the way we treat these patients.

The UK hospice/Specialist Palliative Care Unit (SPCU) population represents a fraction of palliative care inpatients - the majority (up to 80,000 per year) are admitted to hospital. Other data suggests the acutely admitted palliative patient is of better PS and prognosis and the data from HIDDen may not be applicable in the hospital setting.

As a natural progression of HIDDen, we believe it is important that the study is repeated in the hospital setting, in a larger earlier-stage of their cancer journey, better prognosis population. We propose a study in advanced cancer patients to find out:

- How common DVT is in these patients when they come into hospital?

- What symptoms attributable to DVT do these patients have?
- The 90-day incidence of hospital acquired thrombosis.
- If there is an association between DVT and survival?

HIDDen2 is a multicentre observational non-CTIMP cohort study. We plan to recruit 232 patients from four acute hospitals across South East Wales over 10 months, so that we may answer these important questions. By not undertaking this research we risk continuing to treat some of our most vulnerable poorly cancer patients according to guidelines derived from out-of-date studies from an unrepresentative population.

4 Background

Our target population are patients with a diagnosis of incurable cancer, receiving palliative care/ best supportive care who are admitted acutely (as an emergency) to hospital.

The prevention of venous thromboembolism (VTE) comprising of DVT and pulmonary embolus (PE) is a policy for NHS England and Wales and has been demonstrated to reduce avoidable harm and mortality in hospitalised patients[(1)]. 60% of VTEs occur within 90 days of hospital admission and the prevention of hospital acquired thrombosis (HAT) is a priority for the Welsh Government[(1)]. It is currently recommended that all hospitalised patients, including those receiving palliative care, will receive low molecular weight heparin (LMWH) thromboprophylaxis.

Cancer patients are at particular high risk of VTE; they are seven times more likely to develop VTE which occurs in up to 20% of cancer patients[(2)]. The clinical trials informing NICE guidance for VTE prevention are over 20 years old and less than 15% recruited had cancer[(3)]. Furthermore, studies excluded cancer patients receiving palliative care, who are at particular risk of thrombosis since the risk of VTE is greater as cancer becomes more advanced. [(4)]. There has been considerable debate as to whether these data can be applied to specialist palliative care units (SPCU) whether these are in hospital or hospice settings since these studies excluded patients from this population[(5)]. Specific exclusion criteria included those of poor PS, those with limited prognosis (less than 3 months), a risk of bleeding, renal failure, and liver failure. However, this population is one of the most likely to develop VTE and who might benefit from thromboprophylaxis[(6,7)].

The recently published Hospice Deep Vein Thrombosis Detection study (HIDDen) identified a 28% prevalence of femoral DVT[(8)]. There was minimal associated symptom burden and no survival difference between those with or without DVT. Patients had high care needs (AMKP 49) and mean survival of 44 days. An accompanying Lancet Haematology Editorial concluded that thromboprophylaxis was of limited utility in hospice patients of poor PS and prognosis[(9)].

4.1 Rationale for current study

The HIDDen study has changed clinical practice in SPCUs and hospices, with guidelines no longer recommending thromboprophylaxis in selected hospice patients [1,7]. However, most cancer patients receiving palliative care are admitted to acute hospitals and not hospices and the use of thromboprophylaxis will be determined by the place they are admitted i.e. whether they are admitted acutely or to a hospice/ SPCU. Over 80,000 palliative patients are admitted acutely per year and thromboprophylaxis may not only be unnecessary, but also confer a significant risk of harm [10]. LMWH given as a daily injection usually carries a 2% risk of major and 12% non-major haemorrhage and data from 1200 hospice inpatients suggests a 9.8% rate of clinically relevant bleeding [3,11].

This study represents a natural progression of the original HIDDen study, in a larger earlier-stage but palliative population, having previously demonstrated feasibility to recruit hospice/SPCU-based palliative care cancer patients ahead of schedule and gained significant "buy-in" from patients and their families [12].

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.

5 Study objectives/endpoints and outcome measures

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:

- Prevalence of radiologically apparent DVT in palliative cancer patients within 48 hours of hospital admission.
- Evaluation of symptom burden attributable to DVT.
- Impact of incidental DVT on symptom burden and survival at 3 and 6 months
- Incidence of new VTE within 90 days of hospital admission
- Correlation of DVT incidence with patient demographics including performance status.

5.1 Primary objectives

To identify how many cancer patients receiving palliative care have radiological evidence of DVT when admitted acutely to hospital.

5.2 Secondary objectives

To identify

- What symptoms attributable to DVT do these patients have.
- The impact of incidental DVT on symptom burden, clinical management and survival over 3 and 6 months.
- The incidence of new VTE within 90 days of hospital admission.
- The relationship between DVT incidence and patient demographics including performance status.

5.3 Primary outcomes measure(s)

Presence of lower extremity DVT.

In the original HIDDen study, patients underwent 3 point compression ultrasonography of the upper legs. This was performed by trained clinical trial nurses, with every scan being reviewed by an independent consultant radiologist. However, quality assurance processes suggested the initial scans were of insufficient quality. Consequently the first 3 months of scans were not included in the final analysis.

To ensure consistent quality throughout this study, all scans shall be performed by fully qualified and accredited vascular scientists or ultrasonographers. This will ensure scan quality and obviate the need for secondary review of scan reporting. In order to allow comparison with the original HIDDen study, scan shall once again be limited to the upper leg (iliofemoral, femoropopliteal and popliteal). Calf veins and superficial veins shall not be imaged or reported.

The scanning procedure is likely to take between 20-30 minutes. Formal feedback from the HIDDen study reported the procedure to be an acceptable intervention of minor if any inconvenience to the patient.

The diagnosis of DVT will require the identification of one or more filling defects by either colour duplex ultrasonography (CDUS), compression ultrasonography or a combination of both.

Scans will report the following characteristics as per the CRF:

- Presence of DVT: yes/ no
- Site of DVT: iliofemoral/ fempopliteal/ popliteal
- Age of thrombus: acute/ resolving/old

5.4 Secondary outcomes measure(s)

Symptom burden attributable to DVT or PE

The presence of pain and /or swelling in each leg (for DVT) and the presence of breathlessness and or chest pain (for PE) will be evaluated and recorded on the baseline CRF.

Any radiology request to investigate the presence of DVT or PE during the 6-month study period, shall be recorded as a symptom attributable to VTE. Where the indication for the investigation is unclear, an independent adjudication committee shall be convened.

Patient performance status

The Australia Modified Karnofsky Performance Status (AKPS) shall be recorded at enrolment. This is a global assessment of performance status which has previously been shown to be an independent predictor of prognosis and VTE risk.

Patient demographics

The following demographics shall be obtained from the notes and will have no impact on the care of the participant.

- Cancer diagnosis,
- Anticancer treatments within the past three months,
- Current medicines (including ongoing anti-cancer treatments)
- History of any potentially reversible risk factor for DVT in previous 12 weeks
- Routine bloods if recorded as part of hospital admission
    - Full blood count
    - Renal biochemistry
    - Liver function tests
    - Bone profile
    - Clotting profile

Development of new VTE within 90 days at admission:

Radiology investigations undertaken up to 90 days post enrolment shall be reviewed on the Welsh clinical portal and new VTE events will be documented.

A 90-day cut off is in keeping with the accepted definition of hospital acquired thrombosis (“any VTE occurring within 90 days of hospital admission”) 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 shall be recorded.

Any DVT or PE identified during a scan for any other indication (I.e. not primarily looking for VTE) shall be recorded as "incidental" DVT or PE.

This outcome measure is purely observational and does not affect patient care.

6-month survival

During the six months after enrolment participant death shall be recorded on the Death CRF including date and cause of death. The Welsh Clinical Portal shall be reviewed by the treating site staff to confirm if participants are still alive to support Death CRF completion. This approach will ensure patients and their families are not disturbed or inconvenienced.

6 Study design and setting

This is a multiple centre observational cohort study, to be undertaken in Southeast Wales.

HIDDEN2 aims to recruit 232 patients over 10 months.

Participating sites are as follows:

- Royal Gwent Hospital, Newport
- Grange University Hospital, Cwmbran
- Velindre University Cancer Centre, Cardiff
- University Hospital Wales Cardiff

All adults with cancer admitted as an emergency to the participating hospital shall be screened for eligibility by the admitting team. Patients meeting the inclusion criteria shall be approached by the research nurse or delegated research medic and given written and verbal information regarding the study. They will be given opportunity to consider participation and to discuss it with their families. Those who agree to participate in the study shall be consented by a suitable member of the research team and participation registered centrally at the CTR.

The study will comprise of three data collections at the following time points: Day 1 of registration, Day 90 and Day 182 (6 months). Only the first visit will require interaction with the participant.

Every effort has been made to minimise patient visits. For this reason, only the first visit (during which time they are a hospital inpatient) will require the patient's involvement; from this we will ascertain the presence or not of DVT, as well as collect demographic data as part of usual admission clerking.

Day 1-4: CDUS and symptom burden assessment

CDUS shall be undertaken as detailed in Sections 5.3 and 11 of this protocol.

Participants will be asked about any leg or lung symptoms on the day of consent as well as highlighting any illnesses within the last 90 days.

All other clinical data and demographics shall be obtained from patient's notes/ electronic records and recorded on the Baseline CRF.

Day 90: Review of radiology requests and reports

Radiology investigations undertaken up to 90 days post enrolment shall be reviewed on the Welsh clinical portal and new VTE events will be documented.

These will be recoded on the Day 90 CRF.

Day 182 (6 months): survival

This shall be recorded as per section 5.4 and 11 of this protocol.

N.B. Day 90 and 182 assessment data may be collated by site retrospectively.

Ethical Considerations: Blinding of CDUS result to clinical team

It is not normal practice for patients to undergo CDUS on admission or at any time during their hospital stay unless there is a clinical indication, i.e. symptoms or signs of DVT. Likewise, it is not normal for clinicians or patients to know of the presence of an asymptomatic DVT on admission to hospital.

This is an observational study and clinical teams shall be blinded from the result of the research CDUS, to avoid influencing clinical management and allow usual practice to continue.

There are two practical ethical issues which deserve consideration:

- *Should patients found positive for DVT be anticoagulated?*

  The rationale for anticoagulation is to prevent the propagation and embolization of further thrombus. This is based on data observed in non-cancer patients with symptomatic DVT. However the natural history of *asymptomatic* DVT is unknown and data from the HIDDen study identified

28% prevalence of asymptomatic DVT. None of these progressed to symptomatic DVT or pulmonary embolus. Furthermore there was no survival difference between patients with or without screening detected DVT. It is also important to recognise that anticoagulation for cancer associated DVT or PE carries a significant bleeding risk. The landmark CLOT study identified a major bleeding rate of 6% with case series in the advanced cancer population suggesting bleeding rates as high as 11.8%. Therefore there appears to be clear equipoise between the theoretical risks of not anticoagulating asymptomatic DVT against published bleeding data associated with anticoagulating advanced cancer patients.

- *If clinicians suspect a DVT, could the research CDUS be unblinded?*

It is unlikely, but possible, that the treating clinician may wish to investigate for a DVT during the patient's hospital admission. At first glance, it would seem reasonable to unblind the CDUS, to save requesting another investigation. However, this will not be permitted for the following reasons. Firstly, the research scan is limited to the upper leg (thigh) and does not image the calf or superficial veins. Whilst this meets the needs of the HIDDEN2 study (and allows comparison with the original HIDDen study) it would be of insufficient detail to meet the clinical needs of the physician since a "negative" research scan could miss any calf DVT or superficial vein thrombosis encroaching the saphenofemoral junction (routine scan is of whole leg; upper and lower). Secondly, a negative scan is only a helpful exclusory test for the first 24 hours post scan, after which thrombus could have formed. Therefore any patients requiring a scan more than 24 hours after the research scan would still require a fresh scan for accuracy, and a small proportion of participants may have a research and routine scan. Potential participants will be fully informed of this approach in the HIDDEN2 PIS.

6.1 Risk assessment

An Observational Study Risk Assessment has been completed to identify the potential hazards associated with the study and to assess the likelihood of those hazards occurring and resulting in harm. This risk assessment considers.

- The known and potential risks and benefits to human subjects
- How high the risk is compared to normal standard clinical practice
- How the risk will be minimised/managed

This study has been categorised as low risk, where the level of risk is comparable to the risk of standard medical care. A copy of the study risk assessment may be requested from the Study Manager.

The study risk assessment is used to determine the intensity and focus of monitoring activity (see section 22.1).

7 Site and Investigator selection

This study will be carried out at four hospital participating sites within Southeast Wales. Each site will be required to complete a registration form to confirm that they have adequate resources and experience to conduct the study.

Before any site can begin recruitment a Principal Investigator at each site must be identified. The following documents must be in place and copies sent to the HIDDEN2 Study email account (see contact details on page 4):

- Written communication (letter or email) confirming capability and capacity from the site's R&D Department, following sharing of the local information pack
- Favourable opinion of host care organisation/PI from REC
- A signed model agreement including roles and responsibilities
- Current, signed Curriculum Vitae and GCP training certificate of the Principal Investigator (PI)
- Completed Site Staff Delegation Log
- Full contact details for all host care organisation personnel involved, indicating preferred contacts for R&D, administration, and data queries
- A copy of the most recent approved version of the Participant Information Sheet (PIS) and Informed Consent Form (ICF) on host care organisation headed paper
- A copy of the most recent approved GP letter on host care organisation headed paper
- Returned copy of the Self-Evident Correction Log signed by the PI.

Upon receipt of all the above documents, the Study Manager will send written confirmation to the PI/lead Research Nurse detailing that the centre is now ready to recruit participants into the study. This letter/email must be filed in each site's Study Investigator Site File (ISF). Along with the written confirmation, the site should receive a study pack holding all the documents required to recruit into the study.

Occasionally during the study, amendments may be made to the study documentation listed above. The CTR will issue the site with the latest version of the documents as soon as they become available.

It is the responsibility of the CTR to ensure that they obtain confirmation of capability and capacity from local R&D organisations to implement the new documents.

Site initiation will be by a face-to-face site visit by the study CI and Trial Manager or by teleconference if attendance of key personnel is considered unfeasible or unnecessary.

A per-participant monetary contribution to locally incurred research costs may be redeemed by sites from the Sponsor via the CTR at the end of the recruitment and follow up phase, following the pre-requisites and procedure specified in the site-specific agreement. Sites will also be eligible to claim NHS support costs for the study followed routine procedures.

8 Participant selection

Participants are eligible for the study if they meet all the following inclusion criteria and none of the exclusion criteria apply. All queries about participant eligibility should be directed to the Study Manager before registration.

8.1 Inclusion criteria

1. Cancer patient of 18 years of age and over
2. Able to give fully informed written consent
3. Meets one or more of the following criteria:
    - Incurable cancer defined as metastatic or locally advanced cancer with no curative treatment planned*
    - Under the care of community or hospital palliative care services.
    - On the GP community palliative care register
4. No physical limitations to performing the ultrasound assessment.

** Palliative radiotherapy or SACT is acceptable if being administered for symptom control or palliative intent.*

8.2 Exclusion criteria

1. Non melanoma skin cancer
2. Receiving anticancer treatments with curative intent
3. Biologically controlled disease e.g. PSA normal prostate cancer
4. Admission for anticipated end of life care
5. Patients who are considered by the clinical team likely to die within 5 days

9 Recruitment, Screening, and registration

9.1 Participant identification

All adult cancer patients 18 years of age or over admitted to participating sites will be screened 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. Sites involved in the study will have to sign up to this as a condition of participation. The research nurse or suitable delegate will follow up to ensure that all admissions have been screened. A study screening log will be kept by the site identifying the proportion of patients admitted to each site that are eligible.

Consecutive patients will be screened, and eligible patients invited to participate by the admitting clinician and/or suitable delegate as per local patient presentation pathway. Interested patients will be given a PIS/ICF and the opportunity to discuss the study with the research team.

Participants are free to withdraw from the study at any time following registration.

9.2 Screening logs

An electronic screening log will be collected and managed using REDCap electronic data capture tools hosted at Cardiff University [14,15]. Sites will use the log to record all ineligible and eligible but not consented/not approached patients so that any biases from differential recruitment will be detected. A paper log will be used as emergency back up under the scenario that the database is inaccessible, e.g. server down.

9.3 Recruitment rates

A total of 232 participants will be recruited at an expected rate of 5 per month/site over a period of approximately 10 months. The PMG and SMG will review, and report to the Funder and Sponsor, recruitment rates on a regular basis. Subject to funder and Sponsor approval, lower than anticipated recruitment rates (e.g. due to the impact of COVID-19) may be addressed by one of more of the following mitigations if appropriate: extending the recruitment phase, delaying the study and funding end date, opening additional participating sites.

9.4 Informed consent

The patient's written informed consent must be obtained using the HIDDEN2 ICF, which follows the PIS. As participants will be recruited in the emergency hospital admission setting, patients should be given sufficient time after the initial invitation to participate before being asked to sign the ICF.

Informed consent must be obtained prior to the patient undergoing procedures that are specifically for the purposes of the study. Consent may be taken by the site PI or suitably trained (GCP or equivalent consent sub-component) and delegated research associate, e.g. nurse. Participants must provide a wet ink signature.

Only when written informed consent has been obtained from the patient and they have been registered into the study can they be considered a study participant.

One copy of the signed ICF should be given to the participant, the original copy kept in the local ISF, and a further copy with the participant's hospital notes. A fourth copy should be sent via secure electronic transfer (Fastfile or suitable local site equivalent) to the CTR to enable compliance quality control checks to be undertaken.

The right of the participant to refuse to participate in the study without giving reasons must be respected at all times. Similarly, the participant must remain free to withdraw at any time from the study without giving reasons and without prejudicing their routine hospital treatment.

9.5 Registration

Consented patients will be registered to the study by the recruiting site staff using remote data entry via the HIDDen2 study web-based database. Registration will be in real-time on the day of consent. Full details of the registration process and a weblink to the database will be documented in the study registration SOP and provided in the local ISF during site set up. A paper Registration CRF and procedure will be provided for use under the scenario that the database is inaccessible, e.g. when the supporting server is not available.

10 Withdrawal & lost to follow-up

10.1 Withdrawal

Participants have the right to withdraw consent for participation in any aspect of the study at any time following their consent to take part. The participant's routine hospital care will not be affected at any time by withdrawing from the study.

If a participant initially consents but subsequently withdraws from the study, clear distinction must be made as to the level of withdrawal and what specific aspect(s) of the study the participant is withdrawing from, following the date of withdrawal. These aspects could be one or more of the following:

Withdrawal from baseline assessment

Withdrawal from study CDUS scan

Withdrawal from 3 or 6 month follow up data collection

Withdrawal from future research

The withdrawal of participant consent shall not affect the study activities already carried out and any data collected prior to participant withdrawal will be retained based on the informed consent given on the HIDDEN2 ICF before withdrawal.

In all instances participants who consent and subsequently withdraw should be asked to complete an optional withdrawal form provided in the ISF. If the participant declines to complete the withdrawal form, the form should be completed on the participant's behalf by the local PI based on information provided by the participant. This withdrawal form and accompanying Withdrawal CRF should be emailed to HIDDEN2@cardiff.ac.uk. Queries relating to potential withdrawal of a participant should be forwarded to HIDDEN2@cardiff.ac.uk.

10.2 Lost to follow up

We anticipate the number of patients lost to follow up will be minimal since follow up will only require access to patient electronic records, which will cover patient data, even if they relocate within Wales.

In the event of a participant moving out of Wales, the most recent GP will be contacted by the site for up to date contact details.

The Welsh Clinical Portal shall be reviewed by the treating site staff to confirm if participants are still alive, to support Death CRF completion.

11 Assessments

Participants are anticipated to remain on study for up to 6 months form the date of consent.

Assessment data will be collected at three separate time points from the date of consent: screening/registration/baseline (day 1-2), 3 months (90 days) follow up and 6 months (182 days) follow up.

Only two follow ups are planned, neither requiring interaction with the participants and data for both will be collected retrospectively.

Study-specific assessments will only be carried out at baseline and adhoc (e.g. withdrawal). All other study assessment data will be sourced directly from routinely collected hospital data held in participant's hospital notes and/or appropriate clinical databases.

Site staff will be trained in data collection procedures and assessments through attendance at an online or face-to-face site initiation meeting.

Table 1. Schedule of study patient-facing procedures and assessments[1]. Italicised procedures and assessments are study-specific, the remainder are preformed routinely in this patient cohort.

Procedure/assessment	**Visit**				
	1 (baseline[2])		**2 Day 90 (3 month)**	**3 Day 182 (6 months)**	**Adhoc as required**
	Day 1	**Day 1-4**			
Screening including eligibility assessment	X				
Informed consent (if eligible)	X				
Registration (after consent)	X				
Demographics	X				
Medical history	X				
Treatment history	X				
Blood tests	X				
AKPS status	X			x	
VTE history	X				
Identification of new VTEs via review of radiology requests and reports			X		
Concomitant medication	X				
Observational CDUS both legs[2]		X			
Adverse events[4]			X	X	
Survival/mortality			X	X	
DVT Symptom assessment through discussion with participant	X				
Withdrawal (if applicable)					X

[1] Amended from the HRA CTIMP protocol template (2016).

[2] Baseline assessments will be 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 if their Doppler can be performed on the Monday morning, i.e. under this scenario Doppler may be delayed until Day 4. Time from admission to Doppler will be noted. Patients who wish to leave it till the next day to decide can do so if 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.

[3] Observational CDUS of upper leg only to be conducted as follows. The scan image will not be recorded.

[4] Adverse events to routine non-study patient treatment will be collected as part of the research data set. However, AEs to the observational CDUS will not be collected as the HIDDEN2 study as the regulatory oversight bodies do not mandate formal pharmacovigilance monitoring or reporting for such an observational study.

13 Statistical considerations

13.1 Sample size

We will recruit 232 patients from 4 acute hospitals across South East Wales over 10 months. This number of participants 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 5 percentage points based on 17% prevalence from the previous HIDDen study and expected dropout of 5%.

13.2 Missing, unused & spurious data

Detail will be recorded in the study Statistical Analysis Plan (SAP).

13.3 Procedures for reporting deviation(s) from the original SAP

These will be submitted to REC as substantial amendments where applicable and recorded in subsequent versions of the Protocol and SAP.

13.4 Inclusion in analysis

All participants must have undergone a CDUS to be included in the primary outcome analysis

14 Analysis

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

14.1 Main analysis

The prevalence of DVT at hospital admission will be summarised with associate 95% confidence interval. We have no formal sample size calculation for the secondary outcomes within the limits of the funding for this study. However, further analysis will summarise and compare the characteristics of all cancer patients with and without DVT. The symptoms of patients with DVT will be tabulated at each time point. The association between the presence of DVT, symptoms, and survival ***up to*** six months will be also assessed by fitting ***appropriate*** regression models, adjusting for patient characteristics. The regression coefficients and associated 95% confidence intervals and p-values from the analysis will be reported. We will consider the impact of missing data on the conclusions drawn ***from*** our analyses. Plausible missing data mechanisms will be considered, allowing us to estimate the

strength and direction of relationship between DVT and secondary outcomes. We have not planned an interim analysis.

14.1.1 Sub-group & interim analysis

No interim analyses are planned.

15 Data Management

Data management procedures will be documented in the study Data Management Plan (DMP).

Table 2. Source data associated with each type of study data.

Study data	**Source data**								
	eCRFs	Paper Informed consent form	Participant medical notes	Admissions database	Electronic hospital database	Radiology requests and report	CDUS	Discussion with participant	Withdrawal form
Screening including eligibility assessment				X					
Informed consent (if eligible)		X							
Registration (after consent)	X								
Baseline demographics			X						
Baseline medical history			X						
Baseline treatment history			X						
Baseline blood tests			X						
Baseline AKPS status			X						
Follow up AKPS			X						
Baseline VTE history			X						
Identification of new VTEs						X			
Baseline concomitant medication			X						
Observational CDUS both legs							X		
Adverse events			X						
Survival/mortality			X						
Symptom assessment								X	
Withdrawal (if applicable)									X

The local CI and local PI will authorise the self-evident correction log. Source data verification will be conducted as described in the study Data Management Plan.

15.1 Data collection

15.2 Completion of CRFs

15.2.1 Paper CRFs

With the exception of a paper withdrawal form (see Section 10.1), paper CRFs will not be used for this study. Participating sites will be provided with screenshots of electronic CRFs, suitable for printing to support data collection where the trial database is not immediately accessible.

15.2.2 Electronic CRFs

Study data will be collected and managed using REDCap electronic data capture tools hosted by Cardiff University[13,14]. REDCap (Research Electronic Data Capture) 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. REDCap will be accessed by CTR and local site staff using a unique username and password, and will comply with UK GDPR 2018 regulations. A weblink to the HIDDEN2 REDCap database will be provided in the local ISF during site set up.

A user name and password will be supplied to all study team members responsible for data entry upon completion of study-specific training prior to opening individual sites to participant recruitment.

Web-based data collection forms should be completed as follows either in real-time, retrospectively or adhoc as described in the database end user instructions provided in the Site Investigator File during study set up and include:

- Screening
- Registration
- Baseline assessment
- 3 month follow up
- 6 month follow up
- Withdrawal
- Death

15.2.3 Data Queries

The CTR Data Manager will review data entered remotely by sites on to the study database on a regular basis. If missing or questionable data are identified, the Data Manager will raise a data query on the study-specific data clarification form. The data clarification form will be emailed to the site staff delegated to respond to data queries on the site staff delegation log. The site shall be requested to respond to the data query on the data clarification form as soon as feasible.

All answered data queries and corrections should be signed and dated by a delegated member of staff at the relevant participating site. The completed data clarification form should be returned to the CTR by email to HIDDEN2@cardiff.ac.uk and a copy retained at the site along with the participants' CRFs.

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

Sites must submit all CRF data within 1 month of the date of last participant last visit at site to allow sufficient time for data queries and analysis.

16 Translational research or sub study

No translational work is planned

17 Protocol/GCP non-compliance

The PI should report any non-compliance to the study protocol and/or the conditions and principles of GCP to the CTR via email to HIDDEN2@cardiff.ac.uk as soon as they become aware of it. Upon receipt, the CTR will review the notification and provide follow up instructions to the site, including provision of an appropriate non-compliance proforma where applicable. The CTR will log non-compliances on the study non-compliance log and follow up and report to the Sponsor and regulatory bodies as applicable following standard CTR non-compliance SOPs.

18 End of Study definition

The end of the study is defined as the date of final data capture to meet the study endpoints.

The Sponsor must notify the main REC of the end of a clinical study within 90 days of its completion or within 15 days if the study is terminated early.

19 Archiving

The SMF and SSF containing essential documents will be archived at an approved external storage facility for a minimum of 5 years. The CTR will archive the SMF and SSFs on behalf of the Sponsor. The local site PI is responsible for archival of the local ISF at site on approval from Sponsor. Essential documents pertaining to the study shall not be destroyed without permission from the Sponsor.

20 Regulatory Considerations

20.1 Ethical and governance approval

This study protocol has been submitted through the Integrated Research Application System (IRAS) to Health Care Research Wales (HCRW) and has approval from a Research Ethics Committee (REC) that is legally "recognised" by the United Kingdom Ethics Committee Authority for review and approval.

Confirmation of capability and capacity to support the study will be obtained from each host care organisation who will consider local governance requirements and site feasibility. The Research Governance approval of the host care organisation must be obtained before recruitment of participants within that host care organisation.

20.2 Data Protection

The sole joint controller and owner for this study is Aneurin Bevan UHB (Sponsor). The data processors for this study are Cardiff University and the four participating sites and their overarching HBs.

The CTR will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained. Data will be stored in a secure manner and will be registered in accordance with the UK GDPR 2018 and DPA 2018 and subsequent amendments.

Participants will only be identified by the CTR on communications and data forms by their unique study registration number assigned at registration and year of birth. Sites should not send any additional personal identifiable data fields to the CTR.

Study data will be stored in a secure password protected database on a secure server at Cardiff University. Only those individuals required to review the data for trial and/or regulatory inspection purposes will be permitted access. Data will not be transferred .

The PIS will provide participants with full details of what data fields will be collected, the purpose for their collection, and how they will be stored and managed. The study Risk Assessment will include a data protection impact assessment which will also document this information.

20.3 Indemnity

Non-negligent harm: This study is an academic, investigator-led and designed study sponsored by Aneurin Bevan UHB and coordinated by the CTR. The CI, local PIs and CTR do not hold insurance against claims for compensation for injury caused by participation in a clinical study and therefore cannot offer any non-negligent harm indemnity.

Negligent harm: In accordance with Technical Note 12 Indemnity for Clinical Research for research Sponsored by a Welsh body, Welsh Risk Pool Services provides indemnity cover against successful negligence claims arising from the management and conduct of the study. Where NHS employees are responsible for the design of a study, indemnity cover will also be provided for negligent harm arising from the study design. Aneurin Bevan UHB does not accept liability for any breach in the other NHS Organisations duty of care, or any negligence on the part of employees of these NHS Organisations.

All participants will be recruited at NHS sites and therefore the NHS indemnity scheme/NHS professional indemnity will apply with respect to claims arising from harm to participants at site management organisations.

20.4 Study sponsorship

The study is being sponsored by ABUHB. ABUHB shall be responsible for ensuring that the study is performed in accordance with the following:

- Conditions and principles of GCP
- Declaration of Helsinki (1996)
- UK Policy Framework for Health and Social Care Research
- UK GDPR
- Other regulatory requirements as appropriate

The Sponsor has/will be delegating certain responsibilities to the CTR at Cardiff University, the CI, local PIs, host sites and other stakeholder organisations as appropriate in accordance with relevant agreements informed by regulation and study type.

20.5 Funding

This study is funded by the Welsh Government via the HCRW Research for Patient and Public Benefit (RfPPB) Scheme and shall be registered on the HCRW research portfolio.

21 Study management

21.1 SMG (Study Management Group)

The SMG will comprise the CI, Co-Investigators, CTR study staff, and at least 1 of each of the following representatives: lay research partner, radiography advisor, nursing advisor, and Sponsor. The SMG will meet quarterly (and more frequently when required, e.g. during study set up) either face-to-face or via remote online methods as specified in the combined SMG/EC Charter. SMG members will be required to sign up to the remit and conditions as set out in the SMG Charter.

21.2 EC (Executive Committee) and CTR TSC

As HIDDEN2 is an observational study the SMG will report to an Executive Committee responsible for the combined oversight of study steering and data monitoring. The EC will be a sub-group of the SMG and will meet at least twice a year either face-to-face or via remote online methods as specified in the combined SMG/EC Charter. EC members will be required to sign up to the remit and conditions set out in the EC Charter. For completeness the SMG will also report to the CTR TSC on an annual basis under the remit of the CTR TSC charter.

21.3 Project Management Group (PMG)

The Project Management Group (PMG) will be responsible for day-to-day management of the study and will comprise the CI, CTR study staff (e.g. Trial Manager, Data Manager), and additional members of the SMG as required on an adhoc basis. The PG will meet weekly and report to the SMG.

22 Quality Control and Assurance

22.1 Monitoring

The study risk assessment has been used to determine the intensity and focus of central and on-site monitoring activities. Low monitoring levels will be employed and are fully documented in the study monitoring plan.

Monitoring site visits are not planned. However, triggered monitoring visits will be conducted if required to follow up site-related non-compliance. Investigators should agree to allow study related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. Participant consent for this will be obtained via the ICF.

Findings generated from triggered on-site and central monitoring will be shared with the Sponsor, CI, PI & local R&D.

The CTR will monitor consent and withdrawal compliance via quality control checks of ICFs, withdrawal forms and withdrawal CRFs against staff delegation logs and the study clinical database both upon initial receipt at the CTR, and via final reconciliation during study closure.

22.2 Audits & inspections

The study is subject to inspection by REC/IRB as the regulatory body. The study may also be subject to inspection and audit by Aneurin Bevan HB under their remit as Sponsor.

23 Publication policy

All study publications and presentations will be documented and managed as set out in the study publication plan, and authorised by the SMG, Sponsor and Funder. The Protocol will published as a peer reviewed Protocol paper. The Study results will also be published in a peer reviewed journal. PPI input through the course of the study will be documented in a PPI report. The protocol, results and PPI input may also be presented at conference(s) in oral or written format. All study publications will be made publicly available via the CTR study website at https://www.cardiff.ac.uk/centre-for-trials-research/research/studies-and-trials/view/hidden.

24 Milestones

1. Funding start date 01/10/2021
2. Open first site to recruitment 31/01/2022
3. Recruit first participant 01/02/2022
4. Recruit last participant 30/11/2023
5. End of 3 month follow up 28/02/2023
6. End of 6 month follow up 31/05/2023
7. End of data collection/analysis 31/05/2023
8. Final report to funder, Sponsor and REC 31/05/2023
9. Funding end date 31/05/2023

25 References

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26 Study documents

1. HIDDEN2 Risk Assessment
2. HIDDEN2 PIS/ICF
3. HIDDEN2 Recruitment SOP
4. HIDDEN2 Screening Log
5. HIDDEN 2 Enrolment and Consent Log
6. HIDDEN2 Self Evident Correction Log
7. HIDDEN2 Study Database
8. HIDDEN2 Data Management Plan
9. HIDDEN2 Monitoring Plan
10. HIDDEN2 Statistical Analysis Plan
11. HIDDEN2 Publication Plan
12. HIDDEN2 SMG/EC Charter
13. CTR TSC Charter
14. HIDDEN2 Sponsor-Cardiff University Agreement
15. HIDDEN2 Model Site Agreement

27 Appendices

1. Australia Modified Karnofsky Performance Status (AKPS)

Appendix 1. Australia Modified Karnofsky Performance Status (AKPS)[15]

The Australia-modified Karnofsky Performance Scale (AKPS)

The Australia-modified Karnofsky Performance Scale (AKPS) is a measure of the patient's overall performance status or ability to perform their activities of daily living. It is a single score between 10 and 100 assigned by a clinician based on observations of a patient's ability to perform common tasks relating to activity, work and self-care. A score of 100 signifies normal physical abilities with no evidence of disease. Decreasing numbers indicate a reduced performance status.

How to assess AKPS

1 Use the AKPS definitions to determine the initial rating on admission or commencement of an episode of care.
2 Assess routinely. A minimum of daily in an inpatient setting, at each visit in a community setting or each consult.
3 Assess whenever there is a phase change and at episode end when the patient is discharged.
4 Assessment may be conducted face to face or over the phone.
5 Record the rating as assessed (scores in increments of 10). In between scores such as 45, 55 or scores such as 50-60 are invalid.

AKPS ASSESSMENT CRITERIA	SCORE
Normal; no complaints; no evidence of disease	100
Able to carry on normal activity; minor sign of symptoms of disease	90
Normal activity with effort; some signs or symptoms of disease	80
Cares for self; unable to carry on normal activity or to do active work	70
Able to care for most needs; but requires occasional assistance	60
Considerable assistance and frequent medical care required	50
In bed more than 50% of the time	40
Almost completely bedfast	30
Totally bedfast and requiring extensive nursing care by professionals and/or family	20
Comatose or barely rousable	10
Dead	0

Examples of questions

"Have there been any changes today with the patient's ability to attend to activities of daily living?"
"Is the patient requiring more physical care today?"
"How much time is the patient actually spending in bed?"