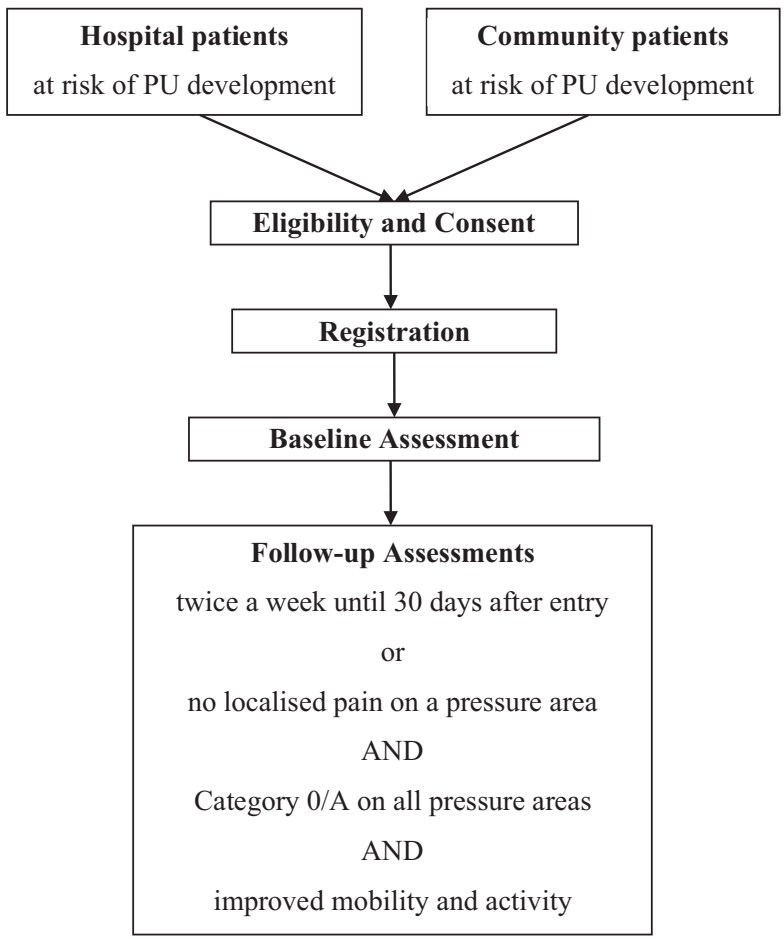
NB: This study protocol (version 4, dated 18 Jan 2010) is in a reduced format including only the study aims, methods and ethical considerations. Sections pertaining to study background have been removed as they are included as a chapter section. Information pertaining to serious adverse events, data monitoring, quality assurance, confidentiality, archiving, statement of indemnity, study organisational structure, and publication policy are available upon request

3 Flow diagram/trial summary



5 Aim and objectives

The main aim of this study is to explore the role of pain as an early predictor of Category 2 PU development (see Table 1).

Objectives are:

1. To assess whether the presence/absence of localised skin pain is a predictor of ≥ Category 2 pressure ulcer development.
2. To explore the relationship between skin classification category and reported pain and pain severity.
3. To identify variables which are independently predictive of ≥ Category 2 pressure ulcer development.

Table 1. NPUAP/EPUAP Pressure Ulcer Classification System[6]. For the purpose of the research the classification has been adapted to enable grading of normal skin and unstageable pressure ulcers.

Category	Description
Category 0 Healthy intact skin	No skin changes.
Category A Alterations to intact skin	Alterations to intact skin.
Category 1 Non-blanchable erythema of intact skin	Intact skin with non-blanchable erythema of a localised area usually over a bony prominence. Discolouration of the skin, warmth, oedema, hardness or pain may also be present. Darkly pigmented skin may not have visible blanching.
Category 2 Partial thickness skin loss or blister	Partial thickness loss of dermis presenting as a shallow open ulcer with a red pink wound bed, without slough. May also present as an intact or open/ruptured serum or sero-sanginous-filled blister.
Category 3 Full thickness skin loss	Full thickness tissue loss. Subcutaneous fat may be visible but bone, tendon or muscle are *not* exposed. Some slough may be present. *May* include undermining and tunnelling.
Category 4 Full thickness tissue loss	Full thickness tissue loss with exposed bone, tendon or muscle. Slough or eschar may be present. *Often* includes undermining or tunnelling.
Category U Unstageable	Full thickness skin loss in which actual depth of the ulcer is completely obscured by slough (yellow, tan, grey, green, or brown) and/or eschar (tan, brown, or black) in the wound bed.

6 Methods

6.1 Design

We plan to undertake a prospective cohort study with 30 days follow-up, in acute and community NHS Trusts involving 632 patients at high-risk of PU development.

6.2 Eligibility

6.2.1 Acute Hospital Patients Inclusion Criteria

1. acute vascular, orthopaedic, medical or care of the elderly admission
2. aged ≥ 18 years
3. have an expected total length of stay of 5 or more days
4. at high risk of PU development due to one or more of the following:
    a. bedfast/chairfast AND completely immobile/very limited mobility (see Appendix 2)
    b. localised skin pain on any pressure area skin site (see section 6.2.4)
    c. Category 1 PU on any pressure area skin site (see Table 1)
5. give their written, informed consent to participate
6. expected to be able to comply with follow-up schedule.

6.2.2 Community Patients Inclusion Criteria

1. evidence of acute illness through one or more of the following:
    a. recent hospital discharge to home/intermediate/community care/hospice/specialist palliative care
    b. existing community nursing patient with deterioration in overall condition or onset of acute illness
    c. new referral to community nursing due to acute illness, deterioration in existing condition, or care package breakdown.
2. aged ≥ 18 years
3. at high risk of PU development due to one or more of the following:
    a. bedfast/chairfast AND completely immobile/very limited mobility (see Appendix 2)
    b. localised skin pain on any pressure area skin site (see section 6.2.4)
    c. Category 1 PU on any pressure area skin site (see Table 1)
4. give their written, informed consent to participate

5. expected to be able to comply with follow-up schedule.

6.2.3 Exclusion Criteria (Acute Hospital & Community Patients)

1. Obstetrics, paediatrics, day case surgery, and psychiatric patients in both acute and community settings
2. Unable to provide written, informed consent
3. Unable to comply with follow-up assessment schedule
4. Deemed by the attending healthcare professional to be too unwell to be approached and/or complete the study assessment schedule
5. Unable to report the presence/absence of pain (e.g. unconscious)
6. Patients with two or more ≥ Category 2 PUs on any key pressure area skin sites (sacrum, buttocks, heels, hips; see Table 1).

6.2.4 Pain Questions

To determine if patients have localised skin pain on any pressure area skin site they will be asked the following two questions by a member of the research team. Patients will be eligible for inclusion under this criteria if they answer 'yes' to both questions.

1. At any time, do you get pain, soreness, or discomfort on a pressure area? *Prompt – back, bottom, hips, elbows, heels, or other as applicable to the patient?*
2. Do you think this is related to either: your pressure sore; laying in bed for a long time; sitting for a long time (*as appropriate*)?

6.3 Endpoints

The classification scale is adapted from the international classification scales[5] in order to meet practical data collection requirements for the purpose of research (Table 1). Specifically, Category 0 (no skin changes) is included to clearly distinguish skin assessment of normal skin from missing data and Category A (alterations to intact skin) is included as alterations to intact skin have been identified as independently predictive of Category 2 PU outcome[4,7].

The primary endpoint is defined as the development of a new Category ≥2 PU after registration and before study completion.

6.3.1 Follow-up

In the patient population recruited to the study we anticipate that hospital patients will be discharged to community settings and community patients may be admitted to hospital. Patients will continue follow-up across healthcare settings, with ethics and R&D approval sought in adjacent NHS Trusts to facilitate this. Patient follow-up will be discontinued when the patient fulfils one of the following criteria:

1. 30 days from registration OR
2. no longer at high risk because:
    a. no localised skin pain on any pressure area skin site (see section 6.2.4) AND
    b. Category 0/A on all pressure area skin sites AND
    c. improved mobility and activity (score of 3 or 4 on both the activity and mobility scores of the Braden Scale[8] Appendix 2) OR
3. death.

6.4 Recruitment and consent

Where eligibility is indicated by the attending clinical team, patients will be flagged to a member of the Trust Tissue Viability Team (TVT; Tissue Viability Nurse Consultant/Specialist/Research Nurse). The attending clinical team may or may not already include a member of the Trust TVT. A full verbal explanation of the study Patient Information Leaflet will be provided by the attending clinical staff or a member of the TVT for the patient to consider. This will include detailed information about the rationale, design, and personal implications of the study. Following information provision, patients will have as long as they need to consider participation and will be given the opportunity to discuss the study with their family and other healthcare professionals before they are asked whether they would be willing to take part in the study.

Assenting patients will then be invited to provide informed, written consent. A record of the consent process detailing the date of consent will be kept in the patient healthcare records. Assessment of eligibility and informed consent will usually be undertaken by a member of the TVT. The right of the patient to refuse consent without giving reasons will be respected. Further, the patient will remain free to withdraw from the study at any time without giving reasons and without prejudicing any further treatment.

Should the patient be capable of giving consent but physically unable to complete the written aspects of the consent form, witnessed consent should be obtained using the Witnessed Consent Form. An appropriate witness would be a family member or friend of the patient, or another member of the patient's healthcare team who is not directly involved in the research study.

The original consent form will be retained in the Investigator Site File, a copy of the consent will be given to the patient and a second copy filed in the patient healthcare notes.

7 Screening and registration

7.1 Screening

Participating research sites will be required to complete a log of all patients screened for eligibility. Anonymised information will be collected including:

- age
- gender
- ethnicity
- whether the patient is registered or not registered

Screened patients who are not registered either because they are ineligible or because they decline participation will also have the following information recorded:

- the reason not eligible for study participation OR
- the reason eligible but declined

This anonymised information will be returned on a monthly basis to the Clinical Trials Research Unit (CTRU).

7.2 Registration

Screened patients who are both eligible for study participation and provide written informed consent will be registered. Informed consent for entry into the study must be obtained prior to registration. Following confirmation of written informed consent and eligibility patients will be registered into the study by an authorised member of staff at the study research site.

Registration will be performed centrally using the CTRU automated 24-hour telephone registration system. Authorisation codes and PINs, provided by the CTRU, will be required to access the registration system.

The following information will be required at registration:

- Patient details, including initials, gender and date of birth
- Site code for research site
- Name of person making the registration
- Confirmation of eligibility
- Confirmation of written informed consent

Direct line for registration +44 (0)113 343 8278

8 Assessments and data collection

Assessments will be undertaken by members of the TVT as follows:

- Baseline assessment (after consent but prior to registration)
- Follow-up assessments twice weekly for 30 days or until study completion (see section 6.3.1).

8.1 Baseline Assessment

Authorised healthcare practitioners will record baseline information including:

8.2 Baseline demographics

- Patient's NHS ID
- Patient's Hospital/Trust number (if applicable)
- Name of NHS Trust
- NHS Facility/Service name (name of hospital/intermediate community nursing team)
- Type of admission/referral
- *Hospital patients only* - speciality (vascular/orthopaedic/medical-elderly)
- Date of admission to hospital/community referral
- Initials
- Date of birth
- Gender

- Ethnicity
- Confirmation General Practitioner (GP) letter sent
- Confirmation responsible healthcare professional letter sent (if applicable)

8.3 Personal data (to be retained in the site file and not returned to the CTRU)

- Patient name
- Patient location e.g. hospital/intermediate care/home
- *Community patients/hospital discharge patients only:*
- Patient address and telephone number
- GP name and address
- District Nurse name and address
- Other responsible healthcare professional (e.g. Specialist or Consultant Nurse) name and address
- *Hospital/hospitalised patients only:*
- Ward
- Responsible healthcare professional (e.g. Consultant Physician or Surgeon, a Specialist or Consultant Nurse) name and address

8.4 Risk factors and population characteristics

  - Skin assessment (sacrum, buttocks, heels, hips and other) using the skin classification scale (Table 1)
  - Braden Scale[8] subscales (Appendix 2)
  - Pain assessment (see section 8.2.1, Appendix 3)
- Diabetic status
- Other chronic wounds (type and location)
- Nutritional status
- Analgesic use
- Pressure ulcer prevention and treatment interventions

8.5 Follow-up assessments (twice-weekly up to 30 days)

- Skin assessment (sacrum, buttocks, heels, hips and other) using the skin classification scale (Table 1)
- Mobility/activity score using Braden Scale[8] (Appendix 2)

- Pain assessment (see section 8.2.1, Appendix 3)
- Analgesic use
- Pressure ulcer prevention and treatment interventions
- Serious Adverse Events (see section 11)
- Confirmation of continued eligibility (see section 6.3.1)

8.5.1 Pain Assessment

Patients will be asked the two screening questions for all pressure areas (see section 6.2.4) at baseline. Where patients answer yes to both screening questions at baseline these sites will be assessed using a numerical rating scale[9,10] for pain intensity (for most severe pain over the past week). In addition, duration of pain will be recorded.

Up to two Category 0-1 skin areas will be assessed using the Leeds Assessment Neuropathic Symptoms and Signs (LANSS) Pain Scale[11,12] (Appendix 3). The LANSS consists of a brief clinical assessment and is easy to score in a clinical setting. The questionnaire contains 5 symptom items and 2 clinical sensory testing items associated with neuropathic pain. The LANSS Scale is a clinically validated tool which allows assessment of neuropathic and inflammatory pain, and has been used in a wide variety of clinical settings[12]. The two sites assessed using the LANSS will include the most painful skin site located on the torso (i.e. sacrum, buttocks, ischial tuberosities, hips) and the most painful site located on a limb (i.e. heels, elbows). In addition, where a patient has a ≥ Category 2 PU at baseline, this will be assessed using the LANSS.

At follow-up patients will be asked the two screening questions for all pressure areas (see section 6.2.4) at each visit. Where pain at the skin site is reported intensity will be assessed using the numerical rating scale[9,10]. For the skin sites where the LANSS assessment was undertaken at baseline, this will be repeated at visits 4 and 8, until either study conclusion or when pain is no longer present at that skin site (i.e. one of the two screening questions is ‘no’).

All anonymised data will be returned to CTRU for data processing.

9 Statistical considerations

9.1 Sample size

Our aim in this study is to assess whether the presence of localised skin pain is predictive of whether or not a patient develops a new PU of Category 2 or above, after adjusting for the effects of other known risk factors which are: age, diabetes, nutritional status, presence of chronic wound on any skin site, presence of skin alterations, Category 1 ulcer on any site, and patient setting (hospital elective, hospital acute, community). As a patient's perception of pain is likely to be affected by the use of analgesics or other forms of pain relief, we will collect this data and include analgesic use as a covariate in the model.

For risk factor studies using logistic regression it is recommended that at least 10 patients with the event of interest are needed for reliable estimation of effects[13]. A model including 9 factors (pain, the seven pre-specified risk factors, and analgesic use) would therefore require a minimum of 90 patients to develop a new pressure ulcer of Category 2 or above. Previous research[7,14] suggests that approximately 15% of patients will develop a new PU of Category 2 or above within 30 days of entering the study. Based on this assumption and allowing for potential loss to follow up of 5% will require 632 patients to be recruited to this study.

Table 2 shows the largest difference in PU incidence that can be detected with a minimum of 80% power for patients with 10 or 20% pain at study entry with estimated PU event rates in the patients without pain of 10 and 15% and assumes that patients with pain at study entry are more likely to develop a new ulcer than those without pain at entry.

Table 2. Largest difference in PU incidence with 80% power.

Total	Baseline pain		PU incidence			PU incidence		
	With pain N (%)	Without pain N (%)	With pain	Without pain	Diff	With pain	Without pain	Diff
632	64 (10%)	568 (90%)	24.4%	10.0%	14.4%	30.9%	10.0%	15.9%
			OR 2.988 (1.594, 5.603)			OR 2.548 (1.432, 4.533)		
632	127 (20%)	505 (80%)	20.2%	15.0%	10.2%	26.5%	15.0%	11.5%
			OR 2.292 (1.363, 3.851)			OR 2.064 (1.300, 3.277)		

If we recruit 632 patients with 64 (10%) of them having pain on study entry this will allow us to detect a statistically significant difference ($p<0.05$) of 14.4% between those with and without pain using a chi-squared test (80% power, 5% significance) if 10% of patients without pain and 24.4% of those with pain develop a new PU within the 30-day follow up period, corresponding to an odds ratio (OR) of 2.988 with 95% CI (1.594, 5.603)

As this is an exploratory study and there is uncertainty around the assumption made to estimate sample size, the proportion of patients with pain at baseline and the incidence of PU development will be monitored by the statistical team throughout the study, and implications for sample size flagged to the Project Team.

10 Statistical analyses

10.1 General Considerations

Statistical analysis is the responsibility of the CTRU Statistician. The analysis plan outlined in this section will be reviewed and a final statistical analysis plan will be written before any data summaries or analyses are performed. The analysis plan will be written in accordance with current CTRU Standard Operating Procedures and will be finalised and agreed by the following people: the Trial Statistician and Supervising Statistician, the Chief Investigator, Senior Trial Manager, and Programme Manager. Any changes to the final analysis plan and reasons for change will be documented.

10.2 Primary Analysis

Logistic regression analysis will be used to assess the relationship between the presence or absence of localised pain at any skin site and the development of a PU of Category 2 or above, using univariate analysis, and also multivariable analysis accounting for the covariates (age, diabetes, skin alterations, Category 1 ulcer on any site, patient setting, and analgesic use). The odds ratios, 95% confidence intervals and p-values from all analyses will be presented. All primary analysis will be performed on a per-patient basis. An additional analysis will explore the relationship between pain at a specific skin site and the development of a new PU on the same site using multilevel logistic regression modelling to account for the clustering of skin sites within a patient.

10.3 Secondary Analysis

Additional analyses will also be undertaken to:

i) Explore the relationship between skin classification category and reported pain by summarising the presence/absence and severity of pain for each of the skin classification categories

ii) Identify variables which are independent predictors of Category 2 PU development. This will use logistic regression modelling as per the primary analysis but will use forwards and backwards selection modelling to identify the most suitable set of covariates for predicting PU development

iii) Assess the relationship between changes in pain over time and the time to PU development by treating pain as a time-dependent covariate in a Cox proportional hazards model both in a univariate analysis and after adjusting for the same covariates used in the primary analysis.

13.2 Ethical considerations

This study will include elderly and highly dependent patients considered as vulnerable. Ethical issues are largely related to the involvement of vulnerable adults/elderly patients with high levels of co-morbidity including acute and chronic illness. The ethical issues surrounding these potentially vulnerable patients have been addressed through the study design and the use of local staff including experienced clinical nurses, that is, members of the local TVT to assess patients.

The study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 52nd World Medical Association General Assembly, Edinburgh, Scotland, October 2000. Informed written consent will be obtained prior to registration into the study. The right of a patient to refuse participation without giving reasons will be respected. The patient will remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment. The study will be submitted to and approved by a main Research Ethics Committee (main REC) and the appropriate Site Specific Assessor for each participating centre prior to entering patients into the study. The CTRU will provide the main REC with a copy of the final protocol, patient information sheets, consent forms and all other relevant study documentation.

18 References

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Appendix 2: The Braden Scale

[NB: Data for the Braden scale was collected however the scale is omitted due to copyright. The Braden scale can be requested from URL: http://bradenscale.com/].

Appendix 3: The LANSS Pain Scale

Leeds Assessment of Neuropathic Symptoms and Signs[10] (with adaptations)[11]

[NB: The LANSS scale was collected however the scale is omitted due to copyright. The LANSS scale can be obtained from: Bennett M. The LANSS Pain Scale: The Leeds assessment of neuropathic symptoms and signs. Pain 2001; 92(1-2): 147-157].