Pressure **RE**lieving **S**upport **SU**rfaces: a **R**andomised **E**valuation 2

(PRESSURE 2)

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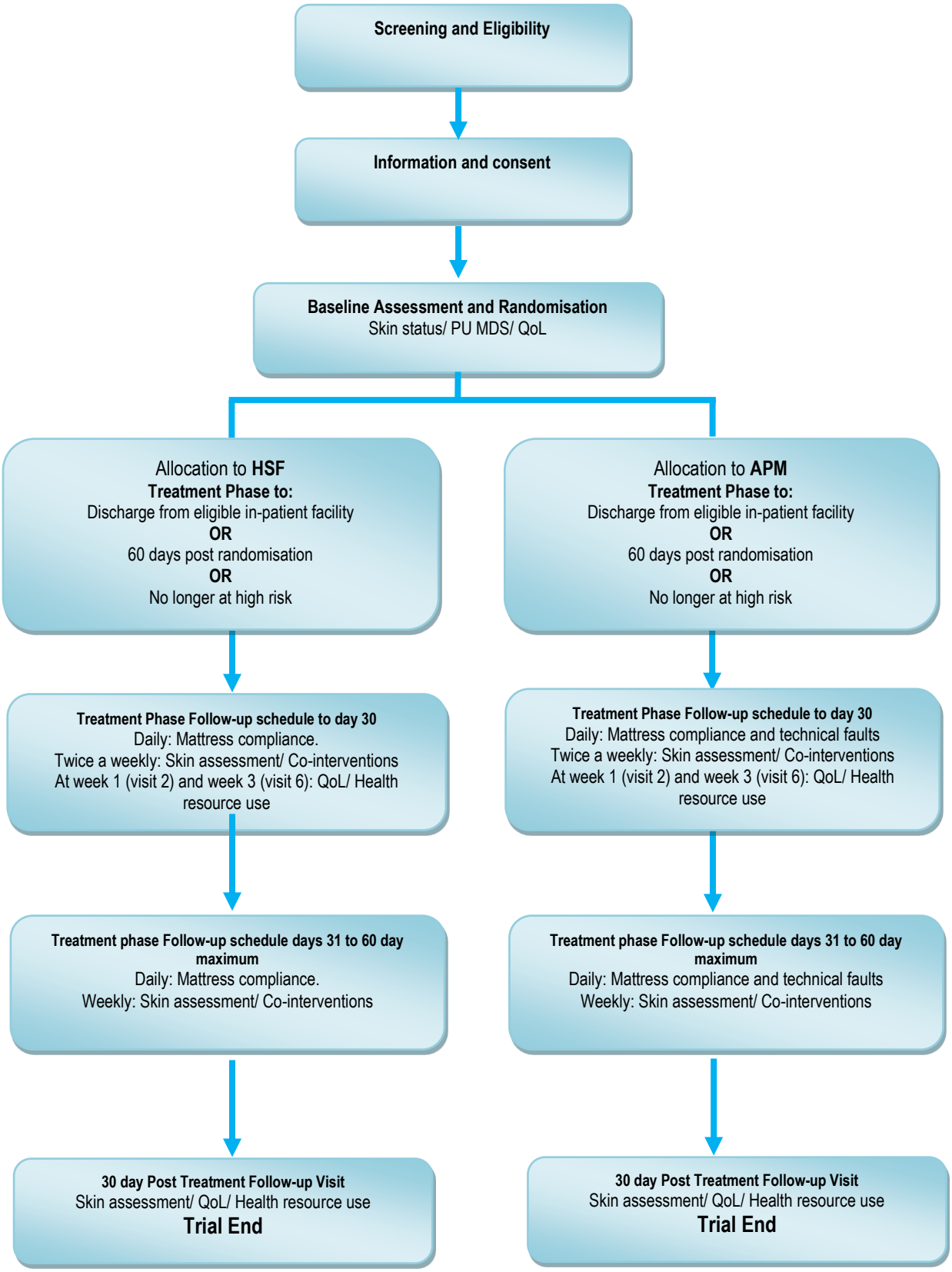

4. GLOSSARY OF TERMS AND DEFINITIONS

APM	Alternating Pressure Mattress
AE	Adverse Event
CRF	Case Report Form
CI	Chief Investigator
CRN	Clinical Research Nurse
CQUIN	Commissioning for Quality and Innovation
CTRU	Clinical Trials Research Unit
DMEC	Data Monitoring and Ethics Committee
EPUAP	European Pressure Ulcer Advisory Panel
EQ5D	EuroQol 5D; A standardised instrument for use as a measure of health outcome.
GCP	Good Clinical Practice
GP	General Practitioner
HCPC	Health and Care Professions Council
HRQoL	Health Related Quality of Life
HSF	High Specification Foam
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ISF	Investigator Site File
ITT	Intention To Treat
ICU	Intensive Care Unit
MDS	Minimum Data Set
MCS	Mental Component Summary
NRES	National Research Ethics Service
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NMC	Nursing and Midwifery Council
NPUAP	National Pressure Ulcer Advisory Panel
PCS	Physical Component Summary
PU	Pressure Ulcer
PUQOL	Pressure Ulcer Quality of Life
PI	Principal Investigator
PIL/ICD	Patient Information Leaflet/Informed Consent Document
PURSUN	Pressure Ulcer Research Service User Network
QIL	Quality of Life Index
QALY	Quality Adjusted Life Year
REC	Research Ethics Committee
RCT	Randomised Controlled Trial
RHCP	Registered Healthcare Professional
RU SAE	Related Unexpected Serious Adverse Event
SF12	A health survey to measure functional health status.
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
TVT	Tissue Viability Team

5. BACKGROUND

Pressure **U**lcers (PUs) represent a major burden to patients, carers and the healthcare system [1, 2], affecting approximately 1 in 10 hospital and 1 in 20 community patients [3]. They impact greatly on physical, social and psychological domains resulting from one or more of the following - distressing symptoms including pain, exudate and odour, increased care burden, prolonged rehabilitation, requirement for bed-rest, hospitalisation and, where people with chronic long-term conditions work, causing prolonged work-related sickness absence [1].

PUs are described as 'an area of localised damage to the skin and underlying tissue caused by sustained mechanical load' and they range in severity from non-blanchable erythema (Category 1), superficial skin loss (Category 2) to severe ulcers involving fat, muscle and bone (Category 3, 4 or unstagable)[4].

The primary cause of a PU is mechanical load in the form of pressure or pressure and shear, applied to soft tissues, generally over a bony prominence (NPUAP/EPUAP 2009). It is universally recognised that both intensity and duration of pressure are of prime relevance in the development of a PU. PUs develop when the soft tissues are no longer able to tolerate the sustained mechanical loads that develop between bony prominences and a support surface e.g. the sacrum and a mattress [4]. They are a cross-specialty problem, a complication of serious acute or chronic illness in patient populations characterised by high levels of co-morbidity and mortality [5].

A PU risk factor systematic review identified the risk factor domains emerging most frequently as independent predictors of PU development including mobility/activity, perfusion (including diabetes) and skin/PU status. Moisture, age, haematological measures, nutrition and general health status are also important, but did not emerge as frequently. Body temperature and immunity require further confirmatory research. There is limited evidence that race and gender are important to PU development (Coleman et al in press).

For the past 2 decades PUs have been identified in successive Department of Health (DoH) policies as a key quality indicator [6,7], with associated guidelines for prevention[8,9] and treatment [10]. Reflecting concern about quality, impact and cost, more recently the DoH have set out the ambitious aim of eliminating all avoidable PUs in NHS provided care [11], developed a Commissioning for Quality and Innovation (CQUIN) payment framework to facilitate this [12], identified PUs as a high impact action for Nursing and Midwifery [13] and are incorporated into the National Operating Framework [14]. In 2004 UK costs were estimated to be £1.4-2.1 billion annually, equivalent to 4% of total NHS expenditure [2], due to increased length of hospital stay, hospital admission, community nursing, treatments (reconstruction surgery/ mattresses/ dressings/ technical therapies) and complications (serious infection). Litigation is also a burden to NHS resources and is predicted to increase due to both general societal trends, and changes in the law which has led to investigation of severe PUs by government agencies to detect institutional and professional neglect of vulnerable adults [15].

Interventions for PU Prevention

The mainstay of PU prevention practice is the provision of pressure redistribution support surfaces (mattresses, cushions) and patient repositioning, to minimise both the intensity and duration of pressure exposure of vulnerable skin sites, not adapted to loading [4, 9,16].

Pressure-relieving mattresses either distribute the patient's weight over a larger contact area providing 'constant low pressure' or they mechanically vary the pressure beneath the patient,

so reducing the duration of the applied pressure (alternating pressure mattresses) [16]. There are a range of 'constant low pressure' mattresses which are classified as 'low tech' (for example foam, gel, water) and 'high tech' (electrically powered air and bead beds). All the alternating pressure mattresses are electrically powered and classified as 'high tech' [16].

In this study we are proposing to compare the two main mattress types utilised within the NHS including *high specification foam* (HSF) mattresses which are classified as a 'low tech constant low pressure device' and *alternating pressure mattresses* (APMs) which are 'high tech' support surfaces [16].

Mattress intervention effectiveness

Overall in this field the quality of trials is poor (small underpowered studies without allocation concealment, intention to treat analysis or *a priori* sample size estimates) [16, 17]. NICE guidelines and systematic review evidence highlight that resource availability is not based upon robust health economic evaluation and there is no systematic way of considering patients priorities for interventions [9, 16].

The 3rd update to the Cochrane systematic review of support surfaces for PU prevention [16] was published in 2011. The review identified ten randomised controlled trials (RCTs) comparing the effectiveness of APMs with a range of constant low pressure devices (including HSF, gel, silicone, water, static air). Most trials showed no evidence of a difference between treatment groups, although some were too small and underpowered to detect clinically important differences. The quality and heterogeneity of the trials also precluded pooling.

Of the 10 RCTs, only 1 study compared a HSF (visco-elastic) and alternating pressure mattresses [18] as part of a 2 by 2 factorial design incorporating two methods of risk assessment and two mattress interventions (APM overlay plus air cushion vs. Foam with 4 hourly turning plus air cushion). The study was single centre and recruited patients from surgery, internal medicine and elderly care. Patients aged 18 or over, with an expected length of stay of more than three days were recruited and randomised to be 'risk assessed' using either the Braden Scale or observation of a Grade 1 skin area. Those identified as at risk then had a second level randomisation, with allocation to an APM or HSF with four hourly turning. A total of 447 patients had the second level randomisation and the incidence of PUs (Grade 2 or above) was 15.3% (34/222) in the APM arm and 15.6% (35/225) in the HSF plus turning arm. Outcome data was recorded by ward staff. There were more heel ulcers reported in the HSF arm, but more severe ulcers developed in the APM arm. An adjusted analysis incorporating risk assessment was not reported. Results are confounded by the inclusion in the foam arm of a 4 hourly turning schedule and the potential for contamination between methods of risk assessment were not explored (including impact upon outcome assessment – i.e. staff in the Grade 1 risk assessment arm were already alert to pressure damage), and a major limitation is that outcome data was recorded by ward staff.

The review concluded that the relative merits of APMs and constant low pressure devices are unclear. The review recommended the evaluation of APMs compared to constant low pressure devices (such as HSF) due to their widespread use [16]. Similarly, NICE guidelines recommended 'Comparisons are needed, in groups at elevated risk, of alternating pressure devices with: lower tech alternatives (for example, different types of high-specification foam mattresses and other constant low-pressure devices)' [9].

A similar recommendation was made in the first systematic review in this field [19] which identified the need for independent, well-designed, multi-centre RCTs to compare the clinical and cost effectiveness of:

1. Alternating pressure mattresses with less costly alternating pressure overlays, and

2. Alternating pressure devices with 'low tech' constant low pressure alternatives (such as different types of HSF).

An HTA commissioning brief in 1998 included both 1 and 2 above, but there was at that time a reluctance by clinicians to randomise high risk patients to HSF, so the trial funded by the HTA, PRESSURE 1 [20], dealt with only the first of the two research priorities and compared overlay and replacement APMs.

However, since then many UK hospitals have replaced traditional hospital mattresses with HSF as standard for some or all clinical specialities. In addition, NICE guidance [9] and the widespread use of profiling electric beds have increased clinical confidence in the use of HSF for high risk patients. Furthermore, qualitative and quantitative evidence suggests that patients do not like APMs [20, 21, 22], and results of the PRESSURE 1 trial [20, 23] showed a lack of difference in clinical outcomes between expensive APM replacement mattresses and cheaper APM overlay mattresses. These developments in the knowledge base and clinical experiences have challenged previously held views of effectiveness based upon non randomised evaluations, which inferred the superiority of alternating pressure devices.

The patient perspective

There is evidence from qualitative studies exploring the lived experience of patients with PUs [21,22] and secondary endpoint data in PRESSURE 1 [20, 23] that patients do not like APMs. Alternating pressure mattresses comprise large air filled pockets which inflate and deflate in cycles. The alternating sensation is disliked by some patients and can cause feelings of nausea and impact upon sleep. In addition, upon patient movement, the air filled pockets are compressed and patients find it difficult to mobilise in bed and also report feeling unstable at the mattress edge, either when they are getting in and out of bed or feeling like they will be 'rolled out of bed', creating an unsafe feeling [20,21,22]. Other issues include noise from the pump, technical failure and attendant alarms. This was further supported by members of the PU Research Service User Network (PURSUN) [24], who were involved in the development of this proposal and are represented on the trial team (KW). They feel strongly that APMs can be uncomfortable and debilitating, restrict movement and independence, exacerbate existing balance/mobility problems and leave patients in need of extra care.

NHS Practice

NICE guidance states that 'Decisions about which pressure-relieving device to use should be based upon cost considerations and an overall assessment of the individual. Holistic assessment should include all of the following: identified levels of risk, skin assessment, comfort, general health state, lifestyle and abilities, critical care needs and acceptability of the proposed pressure-relieving equipment to the patient and/or carer.'[9]. It is not clear what 'cost considerations' means, but in practice decisions are generally made on unit costs and not cost effectiveness, this being challenged following publication of PRESSURE 1 where it was demonstrated that despite no clinical difference between mattresses, there was a 64% probability that the expensive APM replacement (unit cost ~£4,000) was more cost effective than the cheaper APM overlay (unit cost ~£1000)[20].

Traditional hospital foam mattresses (with a marbled cover) have been superseded by HSF mattresses with both a 'high performance' foam core and a cover designed to minimise

hammocking. There is good evidence of the benefit of HSF compared to traditional hospital mattresses in reducing the incidence of PUs in high risk patient populations [16] and HSF is in widespread use in the NHS, with many hospitals providing all patients with HSF as 'standard'. Following NICE guidance [9] HSF is the recommended 'minimum' standard care for those assessed as 'vulnerable to PUs'. Unit costs vary from £180-600.

Despite the lack of evidence of benefit, APMs are also in widespread use in the UK for 'at risk' patients. Unit costs vary from £1000-5000. In our recent multi-centre prevalence involving 9 hospitals across 3 NHS Trusts and ~3000 patients, approximately 20% of mattresses in the adult care setting were APMs (unpublished data PURPOSE pain prevalence RP-PG-0407-10056: 2008). NICE guidance states 'although there is no evidence that high-tech pressure relieving mattresses and overlays are more effective than high specification (low-tech) foam mattresses and overlays, professional consensus recommends that consideration should be given to the use of alternating pressure or other high-tech pressure relieving systems: as a first-line preventative strategy for people at 'elevated risk' as identified by holistic assessment; when the individual's previous history of PU prevention and/or clinical condition indicates that he or she is best cared for on a high-tech device; when a low-tech device has failed.'[9].

A limitation with the NICE guidance is the lack of operational definition of the terms 'vulnerable to PUs' and 'elevated risk' and in practice these terms have not been adopted. In addition the guidance requires local interpretation at both hospital policy and individual patient level and we know that there is clinical uncertainty relating to mattress provision for high risk patients. Indeed this has been evidenced in our recently completed 634 patient multi-centre NIHR PURPOSE pain cohort study (RP-PG-0407-10056: 2008) where mattress allocation by ward staff to our corresponding key target population (mobility impaired and/or Category 1 PU) was 48% HSF: 52% APM (unpublished data), reflecting a lack of standardised practice.

Summary
In light of the priority being given to PU prevention by the NHS, the high cost and lack of evidence relating to the effectiveness of mattresses in common use in the NHS, adhoc practice in mattress allocation and the disadvantages and difficulties reported by patients in the use of APMs we are proposing to undertake a randomised controlled trial to compare HSF and APMs in a high risk in-patient population.

6. AIMS AND OBJECTIVES

The aim of this study is to determine the clinical and cost effectiveness of high specification foam (HSF) and alternating pressure mattresses (APM) when both are used in conjunction with an electric profiling bed frame in secondary and community in-patients facilities with evidence of acute illness, for the prevention of Category 2 (and above) pressure ulcers.

6.1 Primary Objective

The primary objective is to compare the time to developing a new category 2 or above pressure ulcer, in patients using HSF to those using APM by 30 days post end of treatment phase.

6.2 Secondary objectives

1. To compare the time to developing a new category 3 or above pressure ulcer, between patients using HSF and those using APM
2. To compare the time to developing a new category 1 or above pressure ulcer, between patients using HSF and those using APM
3. To compare the time to healing of pre-existing Category 2 pressure ulcers between patients using HSF and those using APM
4. To determine the impact of HSF and APM on health related quality of life
5. To determine the incremental cost-effectiveness of APM compared to HSF from the perspective of the health and social care sectors.
6. To compare incidence of mattress change between patients using HSF and those using APM
7. To compare safety between patients using HSF and those using APM

6.3 Secondary validation objectives

1. To assess the responsiveness of the PU-QOL-Prevention (PU-QOL-P) instrument
2. To determine extent of under and over-reporting of Category 2 and above PUs

7. DESIGN

The trial is a multicentre, open, randomised, double triangular sequential, parallel group trial, with two planned interim analyses.

A maximum of 2954 consenting high risk patients from secondary and community in-patients with evidence of acute illness will be randomised on a 1:1 basis to receive either HSF or APM in conjunction with an electric profiling bed. Since this is a group sequential trial with two interim analyses the patient numbers are a maximum and may be lower depending on the results of the interim analysis. The group sequential design provides an efficient design through the possibility of early stopping for demonstrating either futility of the trial or inferiority of either mattress.

Treatment phase follow-up assessments will be undertaken up to a maximum of 60 days post randomisation. These will be undertaken by a trained registered healthcare professional/clinical research nurse twice weekly from randomisation up to 30 days, then once weekly up to 60 days. The treatment phase is defined as the period from randomisation to discharge from an eligible in-patient facility or 60 days, or when the patient is considered no longer at high risk, whichever is soonest. A final skin assessment will be undertaken 30 days from the end of the treatment phase.

The main trial will be supplemented with a QoL sub-study for responsiveness validation of the PU-QoL-P instrument.

The trained registered healthcare professional/clinical research nurse will conduct the assessment of skin sites. As it is not possible to blind participants or the Tissue Viability Team (TVT), a validation sub study, using photography with blinded central review and expert clinical assessment of the skin sites, will be carried out to assess any bias in the reporting (over or under -reporting) of category 2 or above pressure ulcers.

The local Tissue Viability Team (TVT) may include the local Principal Investigator, Tissue Viability Nurse Specialist/Consultant and Clinical Research Nurse/registered healthcare professional. It is a requirement for healthcare professionals working in these roles to be registered with the Nursing & Midwifery Council (NMC), Healthcare Professional Council (HCPC) or other relevant body.

7.1 Blinding Validation sub-study

Ideally we would have a blinded assessment of the primary trial outcome – the development of a Category 2, or above, pressure ulcer. However, in this mattress trial it is not possible to blind participants, the clinical team or the clinical research nurse/registered healthcare professional (as it is obvious if a patient is on either an APM or an HSF mattress – due to the presence of a pump, sound of pump and appearance of bed and sheeting). This poses a risk to internal validity if clinical research nurses/registered healthcare professionals are influenced in some way by the mattress, with biased under or over reporting of the primary endpoint (Category 2 or above PUs). That is, it is possible that the trial primary outcome could be mis-reported by clinicians, if there are explicit or covert preferences for one mattress over the other. For example this might lead to the reporting of an area of skin damage as being secondary to incontinence, or being classed as not severe enough to be a Category 2 PU, if a nurse/registered healthcare professional feels that they are on the 'best' mattress and that any damage is 'not likely' to be a pressure ulcer. If a trial has a potentially biased primary outcome measure then the findings of the trial might not be reliable, hence we need to assess whether there is any potential bias, and estimate the potential amount of over-reporting or under-reporting of skin damage as a Category 2 or above pressure ulcer.

A validation sub study, using photography with blinded central review, will therefore be carried out to assess any under-reporting or over-reporting of category 2 or above pressure ulcers and establish whether future trials can utilise central review of photography for blinded primary outcome assessment. Photography will be undertaken only where patient consent/consultee agreement or nearest relative/Guardian/welfare attorney (Scotland) is provided.

Potential bias will be assessed in two ways;
1. Over-reporting of Category 2 or above PUs - A trained clinical research nurse/registered healthcare professional will photograph all Category ≥2 pressure ulcers at first observation (baseline or follow-up).
2. Under-reporting of Category 2 PUs – Here the local Principal Investigator (or delegate) will undertake a full skin assessment and photography of the two pressure areas (one torso and one limb/other) in a random sample of 10% of patients at their centre (blind to the Clinical Research Nurse/registered healthcare professional assessment). The CTRU will notify the principal investigator or delegate by email when a participant skin assessment is due.

PRESSURE 2 will be the first PU prevention trial, to our knowledge, to use photographic information to contribute to the primary outcome. We need to understand the acceptability of photography for prevention trials, where missing data can threaten the power and internal validity of the trial. In leg ulcer healing trials there are a small number of high quality trials, where the outcome has been validated through photography [25, 26]. It is not currently understood whether patients will allow photography of pressure ulcers and intact skin over bony prominences such as the sacrum, buttocks and hips, during trial follow up. If we find that a significant minority of patients do not find photography of body sites acceptable, then this will impact its utility for central blinded review and the primary outcome measure in future trials. Therefore we will also assess the practical aspects of using photography such

as acceptability to patients, potential impact upon trial recruitment, compliance with photographs, reasons for non-compliance.

We will report:

a) The number and proportion of patients who refused to have their pressure ulcers photographed by the clinical research nurse/registered healthcare professional, with reason, if provided.
b) The number and proportion of patients who refused to have their at risk skin sites or pressure ulcers photographed by the local Principal Investigator or delegate.
c) The assessment of the inter-rater reliability between expert clinical assessment and central photographic review
d) Assessment of the impact of the use of central photographic review upon trial conclusion.

8. ELIGIBILITY

Acute secondary and community NHS Trust in-patient admissions will be screened for eligibility by the clinical research nurse/registered healthcare professional in consultation with ward staff. Patients will be eligible at any point during their in-patient stay (and irrespective of Trust provider) if they fulfil the following **inclusion** criteria:

1. Evidence of acute illness through:
    a. acute admission to secondary care hospital, community hospital or NHS funded intermediate care/rehabilitation facility.
    b. secondary care, community hospital or NHS funded intermediate care/rehabilitation facility in-patient with onset of acute illness secondary to elective admission.
    c. Recent secondary care hospital discharge to community hospital or NHS funded intermediate care/ rehabilitation facility.
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 (Braden Activity score 1 or 2 and Mobility score 1 or 2) [27]
    b. Category 1 PU on any pressure area skin site.
    c. Localised skin pain on a healthy, altered or category 1 pressure area skin site.
5. Consent to participate (written, informed consent/witnessed verbal consent/consultee agreement or nearest relative/Guardian/welfare attorney (Scotland)).
6. Expected to comply with the follow up schedule
7. The patient is on an electric profiling bed frame

Patients will be **excluded** if they fulfil any of the following exclusion criteria:

1. Have previously participated in the PRESSURE 2 trial
2. Have a current or previous Category ≥3 PU
3. Have planned admission to ICU where standard care is alternating pressure mattress provision.
4. Unable to receive the intervention (for example, sleep at night in a chair or unable to be transferred to randomised mattress)
5. Patient weight is lower or higher than weight limits for HSF and alternating pressure mattresses (<45Kg/>180Kg)
6. It is ethically inappropriate to approach the patient

Eligibility waivers to the inclusion/exclusion criteria are not permitted

9. RECRUITMENT PROCESS

9.1 Recruitment Setting

The recruitment setting will be secondary care hospital, community hospital or NHS funded intermediate care/rehabilitation facilities. Research centres will be required to have obtained local ethical and management approvals and undertake a site initiation meeting with the Clinical Trials Research Unit (CTRU) prior to the start of recruitment into the study.

The sequential trial design will allow early termination if the research question is answered. The maximum number of patients required will be 2954 recruited over a 3 year period; however, interim analyses will be conducted once recruitment reaches approximately 1508 and 2236 patients (corresponding to 300 and 445 events) and an assessment made on whether the trial should continue.

9.2 Eligibility Screening

Patients admitted to secondary care hospital, community hospital or NHS funded intermediate care/rehabilitation facilities will be screened for potential participation in the PRESSURE 2 trial and assessed for eligibility.

9.2.1 Non Randomisation

Participating research sites will be required to complete a log of all patients screened for eligibility who are not randomised either because they are ineligible or because they decline participation. The following anonymised information will be collected on the screening log:

- age
- gender
- ethnicity
- current mattress type
- date screened

and

- the reason not eligible for trial participation

or

- declining participation despite being eligible

or

- other reason for non-randomisation

9.3 Informed consent and eligibility

The Principal Investigator (PI) retains overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki 1996. Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the study and are out-with standard routine care at the participating site. The right of a participant to refuse participation without giving reasons must be respected. The participant must remain free to

withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment and be provided with a contact point where he/she may obtain further information about the trial. Where a participant is required to re-consent or new information is required to be provided to a participant it is the responsibility of the PI to ensure this is done in a timely manner and according to any timelines requested by the CTRU.

The PI takes responsibility for ensuring that all vulnerable subjects are protected and participate voluntarily in an environment free from coercion or undue influence.

Where eligibility is indicated by the attending clinical team, patients will be flagged to a member of the Trust TVT. A full verbal explanation of the study Patient Information Leaflet will be provided by 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 be formally assessed for eligibility and invited to provide informed consent, which must be obtained prior to randomisation.

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.

Under circumstances where patients lack capacity and are unable to provide written or witnessed informed consent then consultee agreement or nearest relative/Guardian/welfare attorney (Scotland) will be obtained on behalf of the patient (see section 9.3.2 below).

9.3.1 Photography

As the study design includes a novel methodology of photographing skin sites this will be specified on the consent form. If the patient, consultee or nearest relative/Guardian/welfare attorney (Scotland) wishes to take part in the study but does not want photographs then consent will be taken with an opt-out clause.

9.3.2 Consultee Agreement or nearest relative/Guardian/welfare attorney (Scotland)

A large proportion of patients suffering from PUs or at risk of PUs have receptive or comprehension or language difficulties. They may also have general cognitive impairment affecting their understanding and/or dementia. Cognition impacts upon compliance with repositioning and self-care. The use of the electric profiling functionality is an integral component of the intervention package (profiling bed plus mattress) and it is important that the trial population is representative of the normal NHS patient population. To ensure that the study population is representative of the clinical population assessed in the course of usual care, recruitment procedures will facilitate consultee or nearest relative/Guardian/welfare attorney (Scotland) agreement.

The assessment of capacity will relate specifically to decisions pertaining to this particular research project. Each patient will be assumed to have capacity unless it is established that they lack capacity. Ward based nurses identifying patients for study participation will be

asked to consider aspects of capacity before any approach to patients is made and during the information giving stage prior to consent. The TVT member will assess the patient's ability to understand what decisions they need to make and why; the consequences of the decision to participate; their ability to understand, use and retain the information related to the decision to participate and be able to communicate their decisions effectively (as specified in the Mental Capacity Act 2005) If there is any concern about capacity the ward nurse/TVT member will consult further with other members of the attending clinical team and/or relative/carer/friend (as appropriate) and a decision will be made with the relative/carer/friend as to whether the patient is able to provide written consent. Where the patient is thought not to have capacity to consent, a relative, carer or friend who is interested in the patient's welfare will act as a personal consultee or nearest relative/Guardian/welfare attorney (Scotland).

The relative/carer/friend will be involved in the information and decision making process with the patient and will advise the TVT member on their presumed wishes and feelings and consultee or nearest relative/Guardian/welfare attorney (Scotland) assent will be obtained on behalf of the patient. The relative, carer or friend will be advised to set aside their own views and provide advice on the participation of the patient in the research, taking into consideration the patient's wishes and interests. Research participants will not be required to do anything which is contrary to any advance decisions or statements that have been made by them in relation to their treatment or any other matter. Advance decisions made by the patient about their preferences and wishes will always take precedence.

If despite taking all reasonable steps a personal consultee cannot be identified and contacted then a nominated consultee or nearest relative/Guardian/welfare attorney (Scotland) would be approached. This person would have no connection with the research project. They would be nominated by the TVT member; they would most likely be the participant's lead clinician. The consultee or nearest relative/Guardian/welfare attorney (Scotland) would be provided with the information leaflet describing the research study and the role of the consultee/nearest relative/Guardian/welfare attorney and it would be emphasised that they are being asked to act on behalf of the participant, rather than any personal views or feelings.

Where a patient has been enrolled into the study after consultee or nearest relative/Guardian/welfare attorney (Scotland) agreement and they subsequently regain capacity, a member of the research team will discuss the study with the patient; provide a full verbal explanation of the trial and a Patient Information Leaflet explaining the trial and their participation in the trial. This will include detailed information about the consultee or nearest relative/Guardian/welfare attorney (Scotland) agreement, rationale, design, and personal implications of the study. Following information provision, patients will have as long as they need to consider ongoing 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 continue participation in the study. As per section 9.3 above the patient will remain free to withdraw from the study at any time without giving reasons and without prejudicing his/her further treatment and be provided with a contact point where he/she may obtain further information about the trial. Assenting patients will be invited to provide informed consent/witnessed verbal consent for ongoing participation. Those who do not wish to continue in the trial will be withdrawn.

9.4 Randomisation

Screened patients who are both eligible for study participation and provide written informed consent/witnessed verbal consent/consultee or nearest relative/Guardian/welfare attorney

(Scotland) agreement will be randomised. Following confirmation of informed consent, eligibility and completion of baseline assessments (including questionnaires), patients will be randomised by an authorised member of the research team at the site using the CTRU automated secure 24-hour telephone randomisation service. Authorisation codes and PINs, provided by the CTRU, will be required to access the randomisation system.
The following information will be required at randomisation:

- Participant details, including initials, gender and date of birth
- Site code for research site
- Name of person making the randomisation
- Confirmation of eligibility
- Confirmation of informed consent.
- NHS number
- Confirmation of completion of baseline skin assessments.
- Details relating to the patient characteristics (see below).

Patients will be randomised in a 1:1 allocation ratio, to receive either HSF or APM and will be allocated a trial number. A computer-generated minimisation programme that incorporates a random element will be used to ensure intervention groups are well balanced for the following participant characteristics, details of which will be required for randomisation.

- Centre
- PU status (no pressure ulcer, Category 1, Category 2)
- Secondary care hospital, community hospital / intermediate care or rehabilitation facility.
- Consent (written, witnessed verbal, consultee or nearest relative/Guardian/welfare attorney (Scotland) agreement).

The randomisation system will include an automated internal check using NHS number to confirm that the patient has not been recruited to the trial previously. This is a risk in this study since the recruitment period is for 3 years and involves adjacent acute and community NHS Trusts.

Patients who have provided written or witnessed verbal consent will also complete the EQ5D, PUQoL-UI and the SF12 questionnaires. Where a patient has been enrolled into the study after consultee agreement or nearest relative/Guardian/welfare attorney (Scotland), they will have the EQ5D and PUQoL-UI completed as per the Proxy questionnaire pack. (The proxy pack is administered by the Clinical Research Nurse/Registered Healthcare Professional on behalf of the patient).

Direct line for randomisation +44 (0)113 343 7956

10. TREATMENT DETAILS

10.1 Treatment Details

Patients will be randomised to either HSF or APM (overlay or replacement) products used by the participating centre. All patients will have an electric profiling bed frame as an adjunct to

the trial mattress. The treatment phase is from randomisation to discharge from an eligible in-patient facility OR 60 days from randomisation OR no longer at high risk, whichever is soonest. No longer at high risk is defined as no Category 1 or above PU on any skin site AND no localised skin pain on any pressure area skin site AND improved mobility and activity (Braden Activity score 3 or 4 AND Mobility score 3 or 4) [27].

Mattress specifications: as this is a pragmatic trial, operational specifications for both HSF and APM will be developed and defined in the PRESSURE 2 Mattress Specification Guideline, rather than standardisation of mattresses for all trial patients, since this would reduce the generalisability of the trial findings which would be product specific. This is further supported by the recent Cochrane systematic review of support surfaces for PU prevention [16] which identified five RCTs comparing different types of HSF and concluded that there is no obvious 'best' HSF alternative. Similarly, the review identified four RCTs comparing different types of APM, including the large PRESSURE 1 trial [20, 23] (assessed as having low risk of bias) which compared alternating pressure overlay and replacement mattresses on 1971 patients, found no evidence of a clinical difference between the mattresses.

All mattresses will comply with the Medical Devices Regulations SI2002/618. The PRESSURE 2 Mattress Specification Guideline for HSF will include foam density (foam fatigue and foam hardness) and mattress cover characteristics (removable, minimum two way stretch, vapour permeable, covered zips) as defined in BS 3379 [28]. PRESSURE 2 Mattress Specification Guideline for APMs will include minimum and maximum values for cell height, cycle time and cycle frequency [20, 23]. Trial compliant mattresses will be identified at each centre. The PRESSURE 2 Mattress specification guideline has been developed detailing eligible mattresses. After randomisation an eligible mattress will be sourced and allocated by the clinical research nurse/registered healthcare professional. Mattress allocation is expected within 24 hrs of randomisation.

The PRESSURE 2 Mattress Specification Guideline will also provide details of excluded mattresses including: Low air loss mattresses; combination mattresses e.g. static foam and alternating cells, static foam and gel, alternating and low air loss; and other continuous static low pressure mattresses including fibregel, fluid and air filled mattresses.

10.2 Cessation of treatment

In line with usual clinical care, cessation or alteration of regimens at any time will be at the discretion of attending clinical team or the participants themselves. All participants withdrawn from the intervention will continue follow-up assessments unless unwilling to do so and case report forms will continue to be completed.

11. ASSESSMENTS/ SAMPLES/ DATA COLLECTION

All baseline and outcome assessments will be undertaken by a trained clinical research nurse/registered healthcare professional. Treatment phase follow-up assessments will be undertaken twice weekly from randomisation to day 30 and once weekly from days 31 to 60. A follow-up assessment will be undertaken 30 days from the end of the treatment phase.

Trained clinical research nurses/registered healthcare professionals will record the demographic information and undertake assessments as follows:

Baseline
Baseline demographic information: NHS number, date of birth, gender, date of admission, type of admission, category of medical condition (e.g. medical, surgical), ethnicity, confirmation General Practitioner (GP) letter sent and confirmation Consultant letter sent.

Clinical assessment: pre-randomisation mattress, skin assessment, Category ≥ 2 photography (where present), pain assessment, risk factors (mobility status, sensory perception, diabetes, conditions affecting macro and micro circulatory function, nutrition, skin moisture, friction and shear), height and weight (self-report or notes where available), PU prevention interventions (for example, turning, specialist cushions), and duration and size of ulcer for patients with a pre-existing Category 2 PU.

Patient questionnaires: SF-12, Pressure Ulcer Quality of Life – Utility Index (PUQoL-UI) and EQ-5D, or proxy questionnaire pack where necessary.

Personal data: (to be retained in the site file and not returned to the CTRU): name, hospital number, ward location, patient address and telephone number, GP name and address, responsible hospital consultant name.

Randomisation: Mattress allocation, date and time of mattress provision

Follow-up
Treatment phase follow-up (daily): Mattress compliance and technical faults

Treatment phase follow-up (2 times weekly to day 30, then once weekly to day 60) Skin assessment (including pain and photography of Category ≥ 2 ulcers where present) and PU prevention interventions or confirm end of treatment phase (discharge, 60 days or no longer at risk).

Treatment phase follow-up Week 1 (visit 2) and Week 3 (visit 6): Healthcare resource utilisation, questionnaires (SF-12, PUQoL-UI and EQ-5D) or proxy questionnaire pack where necessary.

Post-treatment phase follow-up (30 days from end of Treatment phase): Skin assessment (including photography if required), healthcare resource utilisation, questionnaires (SF-12, PUQoL-UI and EQ-5D) or proxy questionnaire pack where necessary.

11.1 Skin Assessments

Skin will be assessed by trained clinical research nurses/registered healthcare professionals using the international PU classification (NPUAP/ EPUAP 2010), with additional skin status descriptors in order to meet practical data collection requirements for the purpose of research. ‘0’ will be recorded to indicate that skin has been assessed and is normal. Incontinence associated dermatitis (IAD) will be noted where this is observed and ‘A’ will be recorded where there is an alteration to intact skin, for example discolouration, dry skin. These are included as alterations to intact skin have been identified as independently predictive of Category 2 PU outcome [23, 29, 30]. PUs when present will be classified and recorded using the NPUAP/EPUAP classification as follows: Category 1 non-blanchable erythema; Category 2 superficial skin loss/blister; Category 3/4 cavity wounds involving fat, muscle and bone or Unstageable where wound debridement is required to enable classification [4].

At baseline and each visit, all major anatomical skin areas at risk of PU development (sacrum, right and left buttocks, hips, heels and elbows), will be assessed by the clinical research nurse/registered healthcare professional and confirmed as '0' (i.e. normal skin), IAD (incontinence associated dermatitis), A (alteration to intact skin) or the presence of a PU (Category 1-U).

11.2 Photography

Minimising risk of over-reporting: Clinical Research Nurses/registered healthcare professionals will photograph each Category 2 pressure ulcer at first observation (baseline or follow-up) providing both clinical and photographic evidence of pressure ulcer status. These photographs will be sent to the CTRU for blinded central endpoint review.

Minimising risk of under-reporting: To assess the potential for under-reporting pressure ulcers, we need photographs of both ulcers and non-ulcerated skin for assessment against an independent clinical expert assessment. The CTRU will randomly identify 10% of the patients for expert clinical assessment of all skin areas and photography of two skin areas by the local Principal Investigator or delegate (i.e. not involved in the primary patient assessments and CRF completion and blind to the Clinical Research Nurse/registered healthcare professional assessments). The local Principal Investigator or delegate will photograph two skin areas including one torso and one limb skin site. If the patient has one Category 2 or above pressure ulcer, this will be photographed. If there is more than one Category 2 or above pressure ulcer, the photographs will include one skin site with a pressure ulcer and one skin site without.

A standard study camera will be supplied to each site together with a work instruction detailing the use of a standardised photographic method including the use of calibration strips for colour measurement. For the purposes of consistency and interpretation of photographic data, it is imperative that only the study camera supplied is used to take photographs. In addition, the work instruction will provide clear instructions on the anonymisation, secure transfer and deletion of the photographs (that is, there will be no local storage of photographs on the camera or NHS computer). Central blinded review of the photographs will be undertaken by expert clinical nurse specialists.

All photography will be subject to patient consent/consultee or nearest relative/Guardian/ welfare attorney (Scotland) agreement at recruitment and also verbal agreement at the time of the baseline assessment/follow-up visit.

11.3 Risk factors

Risk factors will be recorded using the framework provided by the PU Minimum Data Set (PU-MDS) which is part of the NIHR PURPOSE Programme (RP-PG-0407-10056: 2008) and based upon a systematic review of the risk factor literature and was developed using consensus methods. The PU-MDS includes descriptors for the key risk factors including: mobility status, sensory perception, diabetes, conditions affecting macro and micro circulatory function, nutrition and skin moisture.

11.4 Pain

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

assessed as having localised skin pain on a pressure area 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; lying in bed for a long time; sitting for a long time (*as appropriate*)?

11.5 Quality of life (QoL)

QoL will be assessed using the SF-12, PUQoL-UI and EQ-5D instruments.

11.6 Health care resource utilisation

Health care resource utilisation will be abstracted from healthcare records (in-patient and out-patient) and a short researcher administered questionnaire (use of community health and social care).

11.7 Trial Completion

Trial completion is defined as the end of follow-up (i.e. 30 days post treatment phase), withdrawal or death. The treatment phase is defined as the time from randomisation to discharge from an eligible in-patient facility OR 60 days from randomisation OR no longer at high risk, whichever is soonest. No longer at high risk is defined as no Category 1 or above PU on any skin site AND no localised skin pain on any pressure area skin site AND improved mobility and activity (Braden Activity score 3 or 4 AND Mobility score 3 or 4) [27].

For clarification, those patients with capacity at study entry who have provided written informed consent or witnessed verbal consent who subsequently loose capacity will be withdrawn from the trial.

11.8 Essential Documents

Participating sites will be expected to maintain a file of essential trial documentation (Investigator Site File), which will be provided by the CTRU, and keep copies of all completed CRFs for the trial.

11.9 Protocol Deviations

The CTRU undertake to adopt all reasonable measures to record data in accordance with the protocol. Under practical working conditions, however, some minor variations may occur due to circumstances beyond the control the CTRU. All such deviations will be documented on the study records, together with the reason for their occurrence; where appropriate, deviations will be detailed in the published report.

11.10 Definition of End of Trial

The end of the trial is defined as the date of the last participant's last data item.

12. SERIOUS ADVERSE EVENTS PROCEDURES

12.1. General Definitions

An adverse event (AE) is any untoward medical occurrence in a patient or clinical study subject which does not necessarily have a causal relationship with this device/procedure and can include:

- any unintentional, unfavourable clinical sign or symptom
- any new illness or disease or the deterioration of existing disease or illness
- any clinically relevant deterioration in any laboratory assessments or clinical tests.

A Serious Adverse Event (SAE) is defined in general as an untoward (unfavourable) event which is:

- fatal or life threatening*
- requires or prolongs hospitalisation
- is significantly or permanently disabling or incapacitating
- constitutes a congenital anomaly or a birth defect
- may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

* The term life-threatening in the definition of a SAE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

A SAE occurring to a patient which, in the opinion of the Chief Investigator, is Related and Unexpected (RUSAE) will be reported to the main Research Ethics Committee (main REC).

The National Research Ethics Service (NRES) defines related and unexpected SAEs as follows:

- 'related' – that is, it resulted from administration of any research procedures; and
- 'unexpected' – that is, the type of event is not listed in the protocol as an expected occurrence.

12.2 Operational Definition & Reporting AEs/SAEs

Expected AE/SAEs – Not Reportable

This is a randomised controlled trial in a patient population with high levels of morbidity and co-morbid diseases and as such in this patient population, acute illness resulting in hospitalisation, new medical problems and deterioration of existing medical problems are expected.

In recognition of this, events fulfilling the definition of an adverse event or serious adverse events will not be reported in this study unless they are classified as 'related'.

Expected AEs/SAEs– Standard Reporting

The following AEs and SAEs are expected within the patient study population and will be reported during the 90 day post randomisation period on standard Case Report Forms (CRFs):

• Death (SAE)
• Hospital re-admission (SAE)

• Institutionalisation (AE)
- Device related ulcers which may be considered to be related to the mattress (AE/SAE) such as plaster cast ulcers.
- Falls (AE/SAE).

As these events are expected within the study population they will not be subject to expedited reporting to the main REC.

12.3 Recording & Reporting RU SAEs

Related & Unexpected SAEs – Expedited Reporting
All Related & Unexpected SAEs (related to the mattress) which occur from randomisation to trial completion must be recorded on the Related & Unexpected Serious Adverse Event Form and faxed to the CTRU **within 24 hours** of the TVT becoming aware of the event. Once the event has been resolved, the original form should also be posted to the CTRU, and a copy retained on site.

For Related & Unexpected SAEs the following information will be collected:
- full details in medical terms with a diagnosis, if possible
- its duration (start and end dates if applicable)
- action taken
- outcome
- causality (i.e. relatedness to investigation), in the opinion of the investigator
- whether the event would be considered expected or unexpected

Any follow-up information should be faxed to the CTRU as soon as it is available. Events will be followed up until the event has resolved or a final outcome has been reached. All Related & Unexpected SAEs will be reviewed by the Chief Investigator and subject to expedited reporting to the Sponsor and the main REC by the CTRU on behalf of the Chief Investigator within 15 days.

12.4 Responsibilities

Principal Investigator / Authorised individual:

- Checking for SAEs during the treatment phase.
- Judgement in assigning:
  - Seriousness
  - Relatedness
  - Expectedness

- To ensure all R/U SAEs are recorded and reported to the CTRU within 24 hours of becoming aware and to provide further follow up information as soon as available.
- To report R/U SAEs to local committees in line with local arrangements.

Chief Investigator or delegate:

- Assign relatedness and expected nature of SAEs where it has not been possible to obtain local assessment.
- Undertake SAE review
- Review all events assessed as Related/Unexpected in the opinion of the local investigator. In the event of disagreement between local assessment and the Chief

Investigator, local assessment may be upgraded or downgraded by the Chief Investigator prior to reporting to the main REC.

CTRU:

- Expedited reporting of Related/Unexpected SAEs to the main REC and Sponsor within required timelines.
- Preparing annual safety reports to main REC and periodic safety reports to TSC and DMEC as appropriate.
- Notifying Investigators of Related/Unexpected SAEs which compromise participant safety.

TSC:
In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMEC regarding safety issues.

DMEC:
In accordance with the Trial Terms of Reference for the DMEC, periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

13. HEALTH RELATED QUALITY OF LIFE (HRQoL) EVALUATION

We are using the SF12 instrument to assess HRQoL, on the basis of evidence from a systematic review of QoL measures for chronic wounds (including PUs) [31] and practical issues relating to the patient population.

There are a large number of generic QoL measures with evidence of validity and reliability; however, only six studies have previously investigated QoL in patients with PUs using three generic measures: Ferrans and Powers QoL Index (QLI), the Medical Outcomes 36-item Short-Form Health Survey (SF36) and the Medical Outcomes 12-item Short-Form Health Survey (SF12) [31]. Even though all three generic measures include 6 of the 13 conceptual issues important to patients with PUs [32], the QLI has only been used once with a spinal cord injured population where some of the sample had PUs, compared to five studies that used the SF36 or SF12 to measure changes in HRQL in people with PUs; all apart from one study indicating reductions in HRQL for patients with PUs compared to those without.

Use of the SF-36 was considered for inclusion however it was decided by the project team that it was too long for use with patients with PUs (e.g. these patients are largely elderly, highly dependent, and/or with high levels of co-morbidity including acute and chronic illness). Instead, the SF-12, a short version of the SF-36, was selected to reduce respondent burden. The SF-12 is a generic instrument that assesses eight QoL domains: physical functioning, role-physical, body pain, general health, energy/fatigue, social functioning, role-emotional and mental health. A Physical Component Summary (PCS) and a Mental Component Summary (MCS) score are generated. An acute version of the SF12 is available that incorporates a 1 week recall period which for this condition has been found to be relevant [33]. It takes 2 minutes to administer and has been validated for researcher-administration. Even though the SF12 has not specifically been validated for use with people with PUs, it has wide-spread use in other chronic wounds and dermatological conditions to assess changes in QoL between groups; has been used with other chronic-skin wound conditions to validate their corresponding disease-specific QoL instruments; and has been validated for

use with elderly people. The acute SF12 has therefore been chosen as the best available QoL instrument for the primary trial analysis at this stage.

In PRESSURE 1 we identified the need for the development of a PU specific patient reported QoL outcome measure and associated health utility measure and this work has been taken forward through the NIHR PURPOSE Programme Grant (RP-PG-0407-10056: 2008). We have completed the PU QoL-P Instrument (PU- QoL-P) development and psychometric evaluation [33] and propose to incorporate the final responsiveness validation within PRESSURE 2 as a sub-study. We have adopted this approach previously [34] and believe that this can be achieved in a sub sample of patients within this trial. A sub-sample of patients have completed the PU-QoL-P at baseline, weeks 1 and 3, and at 30 days from the end of treatment phase.

The SF-12 QoL questionnaire will be administered at baseline and also:

- twice during treatment phase: week 1 (visit 2) and week 3 (visit 6)
- 30 days from end of treatment phase.

14. ECONOMIC EVALUATION

Primary objective: to assess the incremental cost effectiveness of APM compared to HSF in the prevention of Category 2 and above PUs in high risk patients at 30 days post treatment phase, from the perspective of the health and social care sectors.

Secondary objective: to assess the long term incremental cost effectiveness of APM compared to HSF in the prevention of Category 2 and above PUs in high risk Patients, from the perspective of the health and social care sectors.

Tertiary objective: in the event of an early stopping signal for futility; to assess the value of continuing with the trial from the NHS decision making perspective, via an *Expected Value of Sample Information Analysis*, to inform the deliberations of the Data Safety and Monitoring Committee.

Methods 1: Within trial economic evaluation
The primary economic evaluation will be a within trial analysis. We will estimate the expected costs and outcomes for each intervention for each arm of the trial up to 90 days post randomization; based upon the observed outcomes and resource utilization collected during the trial. The outcome measure used in the primary economic evaluation will be the Quality Adjusted Life Year, using utilities taken from the EQ-5D. A secondary analysis will use PUQoL-UI, a condition-specific utility measure derived from the PU-QoL-P measure. The research required to generate the PUQoL-UI is currently being undertaken as part the NIHR PURPOSE Programme Grant (RP-PG-0407-10056: 2008).

The resource use data collection will focus on those incurred by the NHS including length of stay in hospital, use of hospital outpatient facilities, contact with community based health care services and utilization of supported living such as care and nursing homes. Unit costs will be obtained from national databases such as the NHS Reference costs and the PSSRU Costs of Health and Social Care. Other costs will be estimated in consultation with the finance departments of centers' recruiting to the trial. We will calculate the within trial QALYs and within trial resource cost for a sub sample of trial participants. Due to the short time horizon for the within trial analysis, discounting will not be required. We will use the non-parametric bootstrap to estimate the expected costs and outcomes for each group and the associated incremental cost effectiveness ratio for APM vs. HSF. The results of the

bootstrap will be used to construct a Cost Effectiveness Acceptability Curve, using a range of values of willingness to pay per incremental QALY.

Methods 2: Long term cost effectiveness of APM vs. HSF in Prevention of PUs in High Risk Patients.

A long term cost effectiveness analysis of APM vs. HSF will be undertaken. The exact structure of the cost effectiveness model will be established in discussions with the clinicians on the study team. It is likely that the model will be a Markov or semi-Markov state model. As far as possible the transition rates for the model will be estimated from the clinical trial data. Model parameters for which data could not be collected within the trial we will follow recommended best practice in identifying and synthesising the best available evidence in the literature [35,36].
. Costs and outcomes will be discounted at 3.5% p.a. in line with the NICE recommendations [35]. Probabilistic Sensitivity Analysis will be undertaken. Results will be reported as a Cost Effectiveness Acceptability Curve which represents the probability an intervention is cost-effective for a range of willingness to pay per incremental QALY threshold values (Lambda). Sub-group analyses will report the expected cost effectiveness where analyses of the clinical outcome data suggest a substantial difference in absolute benefit from in a priori identifiable groups..

The EQ-5D and PUQoL-UI questionnaires will be administered for all participants:

- at baseline
- twice during treatment phase: week 1 (visit 2) and week 3 (visit 6)
- 30 days from the end of treatment phase.

The health and social care resource utilisation questionnaire will be administered for all participants:

- twice during treatment phase: week 1 (visit 2) and week 3 (visit 6)
- 30 days from the end of treatment phase.

The primary cost effectiveness analysis will use Quality Adjusted Life Years as the outcome measure, based on utilities generated from the EQ-5D. A secondary analysis will be conducted based on the PUQoL-UI condition-specific utility values. Unit costs will be obtained from national sources such as the NHS Reference costs, PSSRU Unit costs of health and social care.

15. ENDPOINTS

The following endpoints relating to the development or healing of pressure ulcers will be derived based on the assessments recorded by the clinical research nurse/registered healthcare professional.

15.1 Primary Endpoint

The primary endpoint is time to developing a new Category 2 or above PU from randomisation to 30 days from the end of the treatment phase (maximum of 90 days). If participants do not develop a new category 2 or above PU then their time to developing a new category 2 or above PU will be censored at the time of trial completion.

15.2 Secondary Endpoints

- Time to developing a PU of Category 3 or above from randomisation to trial completion.
- Time to developing a PU of Category 1 or above from randomisation to trial completion.
- Time to healing of pre-existing Category 2 pressure ulcers from randomisation to trial completion
- Health-related quality of life using SF-12 instrument.
- Incremental cost effectiveness of APM compared to HSF
- Mattress change during the treatment phase.
- Adverse events

16. STATISTICAL CONSIDERATIONS

16.1 Sample Size

A maximum of 588 events (patients developing a new Category 2 or above PU), corresponding to 2954 patients, are required for the study to have 90% power for detecting a difference of 5% in the incidence of ≥ Category 2 PUs between APM and HSF, assuming an incidence rate of 18% on APM [20] and 23% on HSF, (corresponding to a hazard ratio of 0.759), 2-sided significance level of 5%, and accounting for 6% loss to follow-up [20].

The Category 2 or above PU incidence rate for alternating pressure mattress of 18% was estimated on the ITT population for PRESSURE 1 and hence the sample size estimate incorporates the effect of non-compliance. The sample size accounts for multiplicity in the interim analyses using Lan-DeMets α and β spending functions [37].

For comparison, a fixed design with the same parameters would require 554 events and a corresponding 2786 patients. Therefore, although conducting a group sequential trial does increase the maximum sample size required compared to a conventional fixed design, these stopping boundaries will also allow for an increased chance of stopping early.

PU incidence rates cannot be estimated accurately for the HSF and the maximum sample size estimate is based on the detection of the smallest relevant difference of 5% (clinical opinion). If the difference is >5% then the trial will have sufficient power to stop early having demonstrated superiority (or inferiority) of the APM; if the difference is <5% then the trial is likely to stop early for futility.

Table 1 demonstrates that there is a low probability of stopping the trial at the first interim analysis if the difference between treatment groups is 5% (power of only 29.2%), which is in line with the conservative stop/continue criteria of the Lan DeMets stopping boundaries [37]. However, if the difference between groups is as high as 8%, then the trial has a much greater probability of stopping early for superiority at the first interim analysis (power of 85.0%). Table 1 also demonstrates that the probability of stopping for futility at the first interim is low even when there is no difference between treatment groups (probability of 18.6%). However, if there is no difference between treatment groups by the second interim analysis, then the trial has a much greater chance of stopping early (probability of 77.8%).

Table 1 Probability of crossing the efficacy and futility boundaries at the interim and final analyses

Interim /final analysis	Numb-er of events	Spac-ing of interim analyses	**Probability of crossing the efficacy boundary[a]**		**Probability of crossing the futility boundary[a]**		
			5% difference (HSF 23% & APM18%; HR=0.759)	**9% difference** (HSF 27% & APM18%; HR=0.631)	**0% difference** (HSF 18% & APM 18%; HR=1.0)	**2% difference** (HSF 20% & APM 18%; HR=0.889)	**4% difference** (HSF 22% & APM 18%; HR=0.799)
Interim 1 Interim 2 Final	300 445 588	51.0% 75.7% 100%	29.2% 71.6% 90.0%	85.0% 99.5% 99.9%	18.6% 77.8% 95.0%	12.0% 48.2% 73.8%	3.5% 12.8% 25.9%

[a]Probabilities for crossing the efficacy and futility boundaries were obtained by a running simulation of 10,000 trials in the software East v5.3.

16.2 Planned Recruitment Rate

We plan to involve 10 large and 10 medium NHS Trusts (comprising approximately 30 hospital sites). We estimate that we will need to screen 15,000 patients of whom ~40% (6000) will be eligible and ~50% (3000) of those eligible will consent. Accrual estimates are: 7 patients per month in 3 large Trusts for 33 months; 6 patients per month in 7 large Trusts for 30 months and 3.5 patients per month in 10 medium Trusts for 30 months, enabling recruitment of 3003 patients.

17. STATISTICAL ANALYSIS

17.1 General considerations

Statistical analysis is the responsibility of the CTRU Statistician. A full statistical analysis plan will be finalised and signed off before any data analyses are conducted.

The primary analysis will be on an intention-to-treat (ITT) basis where patients will be analysed according to treatment group randomised to receive. A per-protocol population will also be defined, which will include all eligible randomised participants according to the treatment received but will exclude major protocol violations. This population will be defined in agreement with the Data Monitoring and Ethics Committee (DMEC) and the Trial Steering Committee (TSC) members. Results from both the ITT and the per-protocol analyses will be presented.

17.2 Frequency of Analysis

Statistical monitoring of safety data will be conducted throughout the trial and reported at agreed intervals to the DMEC. Two formal interim analyses are planned (see section 17.3).

17.3 Interim Analyses and Stopping Rules

Interim analyses will be presented to the DMEC in strict confidence, at the intervals specified below. This committee, in light of the interim data, and of any advice or evidence they wish to request, will advise the Trial Steering Committee if there is proof beyond reasonable doubt that the trial should be stopped in accordance with the planned stopping rules.

The trial will have a maximum of three planned analyses (using Lan-DeMets α and β spending functions [37]) with unequally spaced reviews at event driven coherent cut points.

1. The first analysis conducted after 300 events (~1508 patients) corresponds to the earliest time point at which the trial can be stopped for demonstrating overwhelming evidence of efficacy or futility, and also corresponds to the minimum number of events required for conducting the economic evaluation. The futility boundaries are constructed as non-binding in order for the DMEC to overrule a decision of stopping early for futility in the event that a futility boundary is crossed. In the event of the DMEC recommending that the trial is stopped for futility using the pre-defined stopping criteria, an *Expected Value of Sample Information Analysis* will be undertaken to assess the value of additional sample information on the effectiveness parameter, to establish whether continuing the trial would be valuable from the NHS decision makers' perspective

2. The second analysis, conducted after 445 events (~2236 patients) corresponds to the number of expected events required for trial termination under futility (with 434 corresponding to the number of events required for demonstrating superiority or inferiority of APM to HSF)

3. The final review will be conducted after 588 events (~2954) have occurred.

At each interim analysis, the primary analysis of the primary endpoint, time to developing a Category 2 or above PU, will be conducted on both the ITT and per protocol population. The test statistic for the treatment effect from the Cox proportional hazards model, adjusting for the minimisation factors and covariates (specified in the primary endpoint analysis), will be used to test for a difference between treatment groups. The hazard ratio for the treatment effect and adjusted confidence interval corresponding to the nominal p-value will be presented.

Table 1 shows the precision within which the hazard ratio can be estimated at each interim and final analysis [38].

Table 1 Precision of the hazard ratio at the interim and final analyses

Interim /final analysis	**Number of events**	**Precision about the Hazard Ratio (HR)**	**Example scenarios: Confidence interval for the HR at the corresponding nominal α-level**	
			HR=1 (under H_0)	**HR=0.759** (under H_A: APM is superior to HSF)
Interim 1	300	27.0%	0.730, 1.370	0.554, 1.040
Interim 2	445	17.0%	0.830, 1.205	0.630, 0.915
Final	588	12.5%	0.875, 1.143	0.664, 0.868

PUQoL-P sub-study

The purpose of the validation sub-study is to assess the PU-QoL-P instruments' responsiveness to changes in HRQL outcomes over time. A sub-study analysis will be performed to examine the PU-QoL-P instrument responsiveness. Effect sizes [39] and standardised response means (SRM) [40] will be calculated between two time points (before and after mattress allocation). We will also examine the ability of the PU-QoL-P instrument to distinguish between patients whose PUs deteriorate (e.g. progress from Category 1 to 2, or Category 2 to 3) or heal (e.g. reduce from category 2 to category 1, using unpaired t tests with a standard threshold for significance (0.05).

17.4 Primary Endpoint Analysis

Primary analysis

A Cox proportional hazards model will be fitted to the primary endpoint, with adjustment for the minimisation factors: centre, healthcare setting, PU status and consent and covariates: presence of pain on a healthy, altered or Category 1 PU skin site and conditions affecting peripheral circulation. The effect of adding treatment group to this model will be assessed using a likelihood ratio test. Centre will be fitted as a random effect. The hazard ratio for the treatment effect and adjusted confidence interval corresponding to the nominal p-value will be presented.

Patients who do not develop a ≥Category 2 PU during the treatment phase or by 30 days post treatment follow-up will be censored at the date of their 30 days post treatment follow-up visit, or else at the date of withdrawal, death or loss to follow-up.

The probability of patients (using Kaplan-Meier estimates) developing a Category 2 or above PU over 90 days in each group and adjusted confidence interval corresponding to the nominal p-value will be presented.

Moderator & mediator analyses:

Potential predictors of response (time to developing Category 2 or above PU) will be explored using baseline measurements: pre-existing pressure ulcers, Category A skin status, diabetes, age, mobility, sensory perception, macro and micro circulatory function, nutritional status, skin moisture and presence of pain at pressure area skin site by assessing potential predictor by treatment group interactions in the model. In addition, the relationship between potential moderator and mediator variables (including length of stay, time on allocated mattress, patient turning, and use of specialist cushions, heel protectors and protective dressings) and treatment effect will be modeled.

17.5 Secondary Endpoint Analysis

Time to developing a PU of at least Category 1 and time to developing a PU of at least Category 3

The secondary endpoints, time to developing a PU of at least Category 1, and time to developing a PU of at least Category 3, will be analysed using Cox proportional hazards modelling adjusting for the minimisation factors: centre (if appropriate), healthcare setting, pre-existing pressure ulcer(s) and consent procedure. The following covariates will be considered for inclusion into the model: age, mobility, Category A skin status, sensory perception, diabetes, macro and micro circulatory function, nutritional status, skin moisture, presence of pain at pressure area skin site and treatment group.

Time to healing of pre-existing Category 2 pressure ulcers

A Cox proportional hazards model will be fitted to the outcome time, from randomisation, to healing of pre-existing Category 2 PUs. The following covariates will be considered for inclusion into the model: centre (if appropriate), healthcare setting, duration and size of PU, age, sensory perception, diabetes, macro and micro circulatory function, nutritional status, skin moisture, presence of pain at pressure area skin site and treatment group.

Quality of life
QoL domains and subscales for the SF12 will be compared using multi-level repeated measures modeling (allowing for time, mattress type, mattress type by time interaction, adjusting for baseline QoL, all fixed effects), patient and patient by time (random effects) and pattern mixture multi-level models.

Safety
Adverse events and serious adverse events classified as related to the mattress, resulting from administration of any research procedures, and falls and device related events during the treatment phase and follow-up will be listed and summarised by treatment group.

17.6 Validation sub study analysis

Assessing risk of over-reporting

A sensitivity analysis will be conducted. The model to be fitted will be the same model outlined in the primary endpoint analysis however; the primary end point will be replaced by the primary end point that would have been derived if the assessment made by the blinded central endpoint review had been used. That is, for all category 2 or above pressure ulcers that were reported by the clinical research nurse/registered healthcare professional, these assessments will be replaced with the assessments made by the blinded central endpoint review. The primary end point will remain the same for skin sites that were not assessed as category 2 or above by the clinical research nurse/registered healthcare professional.

Assessing risk of under-reporting

For a skin site assessed by the local Principal Investigator (or delegate), a 2 by 2 table will be produced to summarise whether the skin assessments made by the local Principal Investigator (or delegate) and the skin assessments made by the clinical research nurse/registered healthcare professional, agree on the category 2 PU status. In addition, there will be a 2 by 2 table summarising the agreement overall skin sites.

For the skin sites photographed by the local Principal Investigator (or delegate), 2 by 2 tables will be produced for each skin site and overall to summarise the agreement on the category 2 PU status for each of the comparisons below:

- Skin assessments made by the local Principal Investigator (or delegate) and the skin assessments made by the clinical research nurse/registered healthcare professional.
- Assessments drawn from the photographs and the skin assessments made by the clinical research nurse/registered healthcare professional.
- Assessments drawn from the photographs and the skin assessments made by the local Principal Investigator (or delegate).

The following statistics will be reported for each of these tables: Kappa and Prevalence and Bias Adjusted Kappa.

17.7 Trial Monitoring

A Trial Monitoring Plan will be developed and a Meeting Group Monitoring Schedule including primary endpoint and safety data will be defined and agreed by the Trial Management Group (TMG), Trial Steering Committee and Data Monitoring and Ethics Committee.

18. DATA MONITORING

18.1 Data Monitoring

Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until it is received, confirmed as not available or the trial is at analysis. However missing data items will not be chased from participants (although missing questionnaires sometimes are). The CTRU/Sponsor will reserve the right to intermittently conduct source data verification exercises on a sample of participants, which will be carried out by staff from the CTRU/Sponsor. Source data verification will involve direct access to patient notes at the participating secondary and community Trusts and the on-going central collection of copies of consent forms and other relevant investigation reports.

18.2 Clinical Governance and Issues

The University of Leeds will take on sponsorship and will delegate responsibilities as appropriate to the Chief Investigator, CTRU and local research centers' through a Research Sponsorship Agreement. All approvals including NHS Permissions and ethical approvals will be in place at participating centres prior to patient enrolment.

19. QUALITY ASSURANCE AND ETHICAL CONSIDERATIONS

19.1 Quality assurance

The study will be conducted in accordance with the principles of Good Clinical Practice in clinical trials as detailed by the Medical Research Council (1998), the NHS Research Governance Framework (*and Scottish Executive Health Department Research Governance Framework for Health and Social Care 2006 for studies conducted in Scotland)* and through adherence to CTRU Standard Operating Procedures (SOPs).

19.2 Serious Breaches

Investigators are required to promptly notify the CTRU of a serious breach (as defined in the latest version of the National Research Ethics Service (NRES) SOP) A 'serious breach' is defined as a breach of the protocol or of the conditions or principles of GCP (or equivalent standards for conduct of non-CTIMPs) which is likely to affect to a significant degree the safety or physical or mental integrity of the trial subjects, or the scientific value of the research. In the event of doubt or for further information, the Investigator should contact the Senior Trial Co-ordinator at the CTRU

19.3 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. A large proportion of patients suffering from pressure ulcers/at risk of pressure ulcers have receptive or comprehension or language difficulties. They may also have general cognitive impairment affecting their understanding and/or dementia. Cognition impacts upon compliance with repositioning and self care in the use of the electric profiling functionality is an integral component of the intervention package (profiling bed plus mattress) and it is important that the trial population is representative of the normal NHS patient population. To ensure that the study population is representative of the clinical population assessed in the course of usual care, recruitment procedures will facilitate consultee or nearest relative/Guardian/welfare attorney (Scotland agreement.

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/registered healthcare professionals, that is, members of the local TVT to assess patients.

There are also ethical issues associated with photography of Category ≥2 pressure ulcers and skin areas at 'high risk' of PU development, due to the body positions associated with PU development (sacrum and buttocks). For this reason patients will be able to opt out of pressure ulcer/skin photography at initial written consent/consultee or nearest relative/Guardian/welfare attorney (Scotland) agreement at each assessment where photography may be indicated verbal agreement from the patient will be obtained.

The trial 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, 1996. Informed written consent will be obtained from the patients prior to randomisation into the study. The right of a patient to refuse participation without giving reasons must be respected. The participant must 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.

Records will be kept for 5 years from the end of the last patient follow-up.

20. CONFIDENTIALITY

All information collected during the course of the trial will be kept strictly confidential. Information will be held securely on paper and electronically at the Clinical Trials Research Unit (CTRU). The CTRU will comply with all aspects of the 1998 Data Protection Act and operationally this will include:

- consent from participants for site to record personal details including name, date of birth, address and telephone number, NHS number, hospital number, GP name and address and Consultant name and address
- consent from participants for a letter to be sent to their GP and Consultant to let them know they are taking part in a research study.
- consent from patients for the CTRU to receive their consent form (which includes their name and signature) and NHS number to check that they have not been previously randomised

- consent from patients to photograph Category ≥2 pressure ulcers/high risk skin sites (where indicated) and for electronic transfer of these images (with identifiers study number, initials and date of birth)
- appropriate storage, restricted access and disposal arrangements for participant personal, clinical details and photographs.
- consent from participants for access to their medical records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to trial participation
- consent from participants for the data collected for the trial to be used to evaluate safety and develop new research.
- all data collection forms that are transferred to or from the CTRU will be coded with a study number and will include two identifiers, usually the patient's initials and date of birth
- where anonymisation of documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to CTRU

If a participant withdraws consent from further trial treatment and / or further collection of data their data will remain on file and will be included in the final study analysis.

20.1 Archiving

At the end of the study, data will be securely archived in line with the Sponsor's procedures for a minimum of 5 years. Data held by the CTRU will be archived in the Leeds Sponsor archive facility and site data and documents will be archived at site. Following authorisation from the Sponsor, arrangements for confidential destruction will then be made.

21. STATEMENT OF INDEMNITY

This study is sponsored by the University of Leeds and the University of Leeds will be liable for negligent harm caused by the design of the study. The NHS has a duty of care to patients treated, whether or not the patient is taking part in a clinical study and the NHS remains liable for clinical negligence and other negligent harm to patients under this duty of care.

22. STUDY ORGANISATIONAL STRUCTURE

22.1 Individuals and Individual Organisations

Chief Investigator - as defined by the NHS Research Governance Framework, is responsible for the design, management and reporting of the study.

Trial Sponsor – The Sponsor is responsible for trial initiation management and financing of the trial as defined by NHS Research Governance Framework. These responsibilities are delegated to the CTRU as detailed in the trial contract

Clinical Trials Research Unit – The CTRU will have responsibility for conduct of the study in accordance with the Research Governance Framework and CTRU SOPs. The CTRU will provide set-up and monitoring of trial conduct to CTRU SOPs, and MRC GCP including main REC, Site Specific Assessment and NHS Permissions submissions, randomisation design and service, database development and provision, protocol development, CRF design, trial design, monitoring schedule, statistical analysis for the trial, clinical set-up, ongoing

management including training, monitoring reports and promotion of the trial. The CTRU will be responsible for the day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting and all statistical analyses.

22.2 Oversight / Trial Management Groups

Trial Management Group - The TMG, comprising the Chief Investigator, Co-applicants and the CTRU team, will be assigned responsibility for the clinical set-up, on-going management, promotion of the trial, and for the interpretation and publishing of the results. Specifically the TMG will be responsible for (i) protocol completion, (ii) CRF development, (iii) obtaining approval from the main REC and supporting applications for Site Specific Assessments, (iv) completing cost estimates and project initiation, (v) nominating members and facilitating the TSC and DMEC, (vii) reporting of serious adverse events, (viii) monitoring of screening, recruitment, treatment and follow-up procedures, (ix) auditing consent procedures, data collection, trial end-point validation and database development.

Trial Steering Committee – The Trial Steering Committee, with an independent Chair, will provide overall supervision of the trial, in particular trial progress, adherence to protocol, participant safety and consideration of new information. It will include an Independent Chair, not less than two other independent members and a consumer representative. The Chief Investigator and other members of the TMG may attend the TSC meetings and present and report progress. The Committee is expected to meet 6 monthly.

Data Monitoring and Ethics Committee (DMEC): The DMEC will include independent membership and will review the safety and ethics of the trial by reviewing interim data during recruitment. As a minimum the Committee will meet prior to recruitment and at each planned interim analyses.

23. PUBLICATION POLICY

The trial will be registered with an authorised registry, according to the ICMJE Guidelines, prior the start of recruitment.

The success of the trial depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributorship. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

- conception and design, or acquisition of data, or analysis and interpretation of data
- drafting the article or revising it critically for important intellectual content
- and final approval of the version to be published
- and that all these conditions must be met (www.icmje.org).

In light of this, the Chief Investigator, co-applicants and relevant senior CTRU staff will be named as authors in any publication. In addition, all collaborators will be listed as contributors for the main trial publication, giving details of roles in planning, conducting and reporting the trial.

To maintain the scientific integrity of the trial, data will not be released prior to the first publication of the analysis of the primary endpoint, either for trial publication or oral presentation purposes, without the permission of the Trial Steering Committee. In addition, individual collaborators must not publish data concerning their participants which is directly

relevant to the questions posed in the trial until the first publication of the analysis of the primary endpoint.

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