CLINICAL TRIALS RESEARCH UNIT (CTRU)
UNIVERSITY OF LEEDS

FINAL
STATISTICAL ANALYSIS PLAN

PRESSURE2

V 2.0

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1 Introduction

1.1 Design

PRESSURE 2 is a randomised controlled trial involving up to 2954 patients comparing High Specification Foam (HSF) and Alternating Pressure Mattresses (APMs).

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

A maximum of 2954 consenting high risk patients from secondary and community in-patient facilities with evidence of acute illness will be randomised via minimisation 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 until the end of the treatment phase (up to a maximum of 60 days). 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 a maximum of 60 days. The treatment phase is defined as the period from randomisation to discharge or transfer 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 (-2/+7 days) from the end of the treatment phase.

The main trial will be supplemented with a Quality of Life (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 using International guidelines (1). 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.

1.2 Aim and objectives

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

1.2.1 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.

1.2.2 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.

1.2.3 Secondary validation objectives

1. To assess the responsiveness of the PU-QOL-Prevention (PU-QOL-P) instrument
2. To determine the extent of under and over-reporting of category 2 and above PUs
3. To assess the feasibility of using photographs for pressure ulcer assessment

1.3 Sample size and expected accrual

1.3.1 Original sample size and expected accrual

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 and above pressure ulcers between APM and HSF, assuming an incidence rate of 18% on APM 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.

The category 2 or above PU incidence rate for APM 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.

Pressure ulcer 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 greater than 5% then the trial will have sufficient power to stop early having demonstrated superiority (or inferiority) of the APM; if the difference is lower than 5% then the trial is likely to stop early for futility.

The first planned interim analysis to be conducted after 300 patients have developed a new category 2 or above pressure ulcer (~1508 patients overall) 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 second planned interim analysis, conducted after 445 patients have developed a new category 2 or above pressure ulcer (~2236 patients overall) 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)

1.3.2 Revised sample size and expected accrual

The PRESSURE2 trial recruited patients at a much slower rate than originally anticipated. An unplanned interim analysis was conducted in November/December 2015 at the request of the funder and the results of this analysis were reviewed by the DMEC. The DMEC and TSC supported a no-cost extension request which was submitted in June 2016 to continue recruitment until the end of November 2016 by which time approximately 1996 patients were expected to be recruited. A costed extension request to continue recruitment until the end of May 2017 was also supported by the TSC and DMEC. The funder approved the no-cost extension request in July 2016 and therefore the final sample size is 2030 (achieved November 2016).

1.3.3 Expected sample sizes for secondary validation objectives

1.3.3.1 To assess the responsiveness of the PU-QOL-Prevention (PU-QOL-P) instrument

The approximate sample size for the PUQoL-P sub-study will be 500 patients.

1.3.3.2 To determine the extent of under and over-reporting of category 2 and above PUs

A maximum of ~1653 photographs are expected for the central blinded review, which will enable Kappa to be estimated to within a precision of at least ±0.044 (corresponding to the half width of the 95% CI), assuming 65% of photographs are of Category 2 or above PUs and Kappa ≥0.5.

1.4 Planned analyses

The Data Monitoring and Ethics Committee (DMEC) will review the safety and ethics of the PRESSURE 2 trial at agreed intervals. The DMEC will be presented with detailed open and closed reports (containing aggregated overall data and unblinded data respectively) containing a summary of recruitment, data collection, mattress compliance, a review of adverse events (AEs), related & unexpected SAEs (RUSAEs) and other safety issues.

In addition to the above reports, interim analyses have been presented to the DMEC in strict confidence. This committee, in light of the interim data, and of any advice or evidence they wished to request, had the opportunity to advise the Trial Steering Committee (TSC) if there was proof beyond reasonable doubt that the trial should have been stopped in accordance with the planned stopping rules (Appendix F).

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

2. The second planned interim analysis, to be conducted after 445 events (~2236 patients) corresponded 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)

The final analysis was scheduled to take place after 588 events (~2954 patients) had occurred. A graphical representation of the double triangular group sequential design is provided in Appendix F.

Note that if a stopping boundary was crossed but the DMEC recommend continuing with the trial the stopping boundaries would be recalculated in EAST software assuming the first analysis had not been conducted (2). The overall power and type-I error rate of the trial will not change. This advice was provided by James Wason in response to a request for methodology assistance at the MRC Methodology adaptive designs hub.

This is the statistical analysis plan for the final analysis of the PRESSURE2 trial.

1.5 Unplanned analyses

As explained in section 1.3.2, recruitment has been slower than anticipated for a number of reasons. The trial team submitted a no cost extension request to recruitment in June 2015 to enable 1996 patients to be recruited by the end of November 2016. The HTA (funder) reviewed this request in August 2015 and asked the DMEC to request the CTRU to conduct an unplanned interim analysis as soon as possible; this was conducted in November and December 2015 and the HTA have since approved the no cost extension request to continue recruitment until the end of November 2016 and a final sample size of 2030 patients was achieved. No further formal interim analyses are planned before the final analysis.

2 Endpoints to be analysed

2.1 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.

2.2 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

2.3 Derivation of primary endpoint

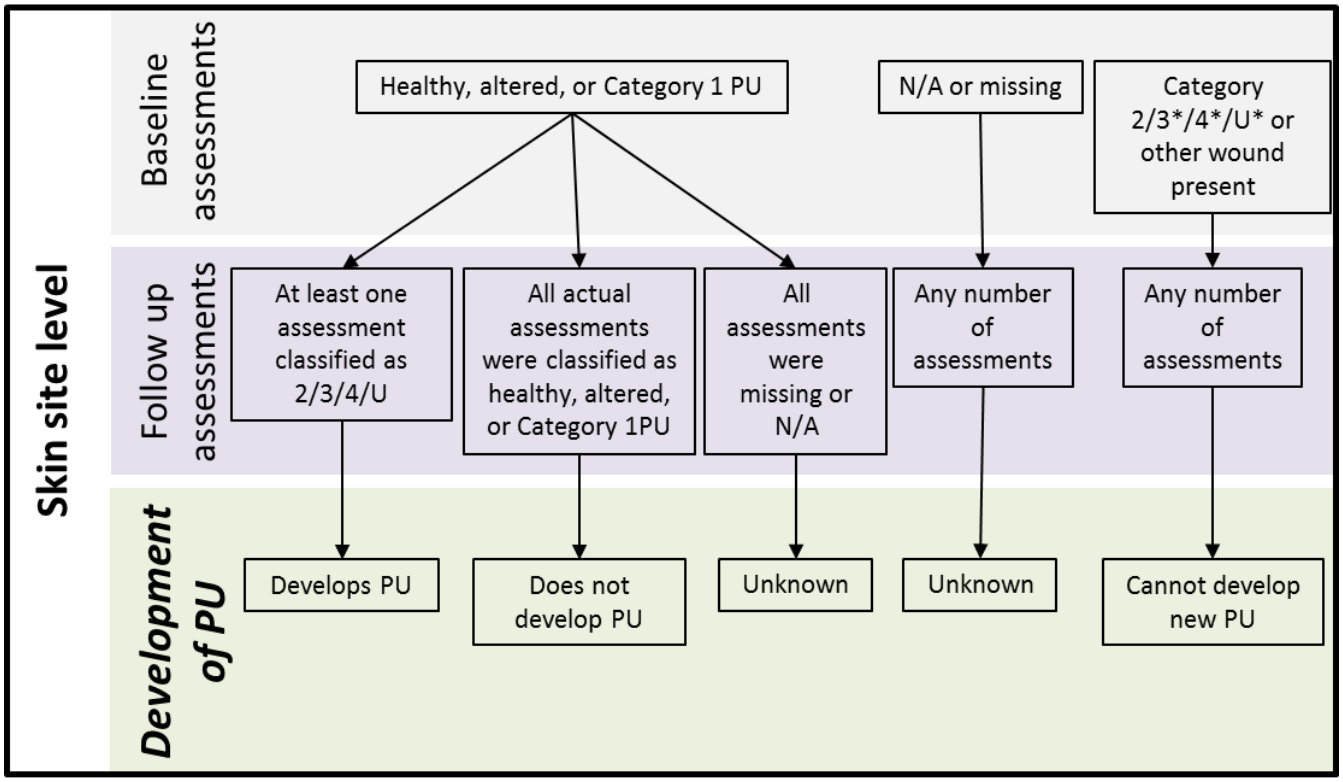
In order to derive the time to developing a new category 2 or above pressure ulcer the derivation of whether a participant has developed a new category 2 or above pressure ulcer at each skin site and follow-up assessment needs to be defined. Each participant will have a minimum of 14 pre-specified skin sites (Spine/back, sacrum, left and right buttocks, ischial tuberosities, trochanters (hips), heels, ankles, and elbows) assessed at baseline and every follow up assessment thereafter. There will be the option at each assessment to add other additional skin sites that have not been pre-specified on the CRF. At each assessment:

- If the skin site is assessed as healthy skin then a 0' is recorded.
- If the skin site has skin alterations then an 'A' is entered with the relevant sub category or description also entered (Appendix B).
- If there is pressure damage then the international pressure ulcer classification system is used to record the level of pressure ulceration (Appendix B).
- If the skin cannot be assessed, or there is another wound present, then the research nurse will enter 'N/A' for the skin assessment with the relevant sub category or description (Appendix B).

Note that the data collection process above leads to repeated measures for each skin site. Therefore, before deriving whether a patient has developed a new Category 2 or above pressure ulcer (and the time to development), the derivation of whether a new Category 2 or above pressure ulcer has developed since baseline needs to be defined on a **skin site basis (**Figure 1**)**. This will lead to a dataset that has one record per skin site. This data will then be used to derive the primary endpoint dataset which will have one record per patient that includes a variable denoting whether the patient developed a category 2 or above pressure ulcer at any skin site and the time to

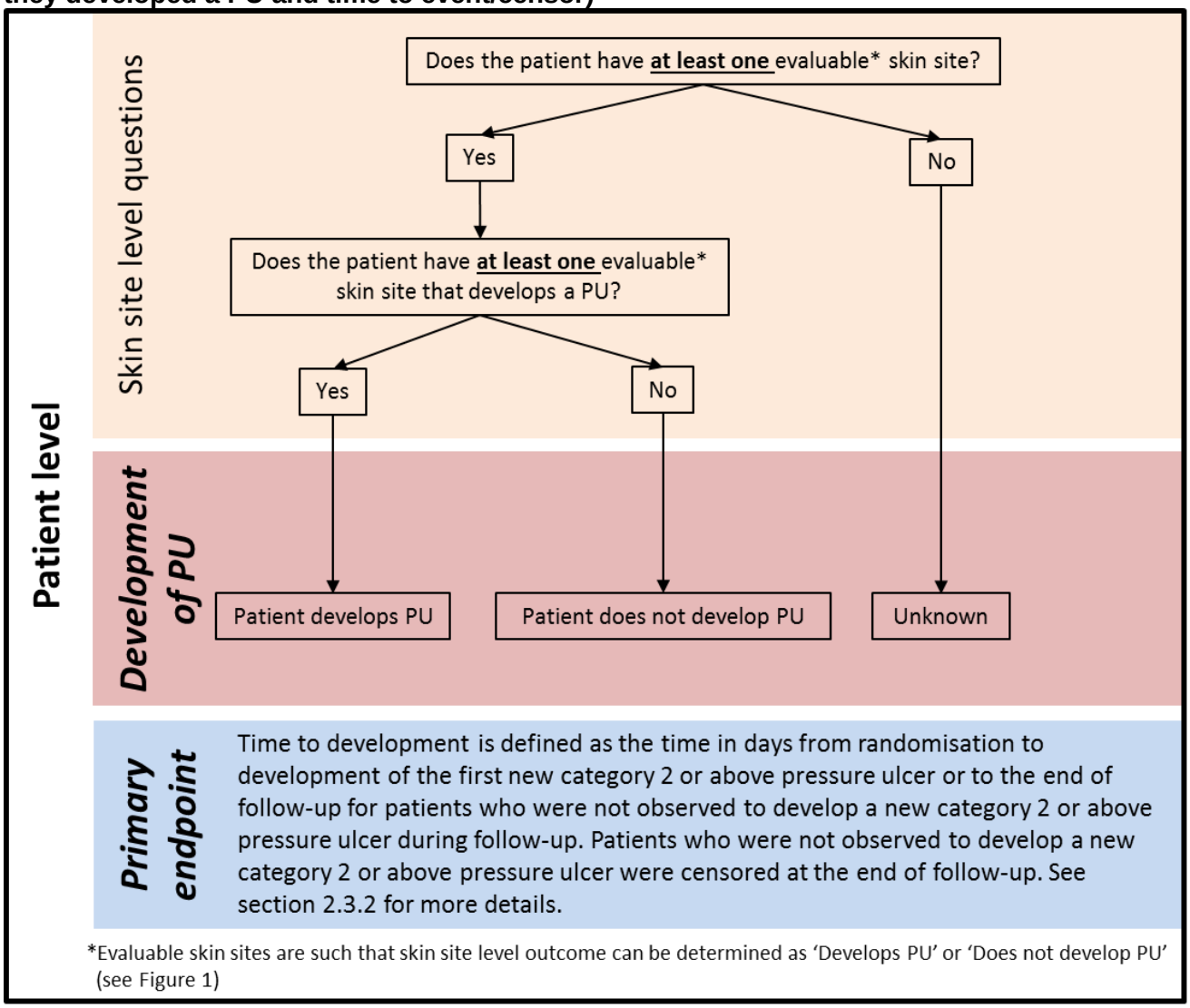
development of the first new pressure ulcer or censoring time. A summary of the derivation of the primary endpoint (time to first new Category 2 or above pressure ulcer on a patient level) is provided in Figure 2with justification for the derivations in Appendix C and Appendix D..

Figure 1 Derivation of PU development on a skin site level (one record per skin site per patient)



*Patients with a Category 3/4/U pressure ulcer should have been excluded from the trial according to the eligibility criteria, however they have been included in this derivation to account for patients that may have been incorrectly recruited to the trial.

Figure 2 Derivation of time to PU development (one record per patient including whether they developed a PU and time to event/censor)



Exceptions in the above derivation are where main skin sites are assessed as **N/A - device ulcer**. These will be reviewed centrally by the Chief Investigator by reviewing the skin assessment data entered on the database (the paper CRFs may also be referred to), without reference to the allocated mattress and may be assumed to be at least a category 2 pressure ulcer and if confirmed as a Category 2 or above PU will contribute to the primary endpoint in the primary analysis. The impact of this assumption will be assessed through a sensitivity analysis where these device ulcers are ***not*** assumed to be a Category 2 pressure ulcer in the derivation of the endpoint.

Further to this, the further descriptions for skin sites assessed as 'N/A' will be reviewed by the Chief Investigator and Clinical Co-ordinator(s) (without reference to mattress allocation) and the assessment 'N/A' may be changed to 'A', 'Category 1', or 'Category 2' for the purposes of a sensitivity analysis. This is to acknowledge the subjectivity that may arise in the assessment of pressure damage and that some skin sites assessed as N/A could have been misclassified.

2.3.1 Other skin sites

Other additional skin sites assessed at either the baseline and/or follow up visits will be reviewed without reference to the allocated mattress by the Chief Investigator (CI) and Clinical Co-ordinator/s as to their inclusion in the analysis (e.g. whether damage to the skin site could be pressure related). The skin site level endpoint (i.e. whether a skin site develops a category 2 or above pressure ulcer) for these other additional skin sites will be derived again (assuming a

healthy skin assessment at baseline, if the skin site was not recorded at baseline) for the purposes of a sensitivity analysis.

2.3.2 Time to development and censor variables

The time to development of a new category 2 or above pressure ulcer and the value of the censor variable (a variable denoting whether the participant was observed to develop a category 2 or above pressure ulcer or not) will be derived as detailed in table 1.

Table 1 Derivation of the event/censor variable and the number of days to developing a new category 2 or above pressure ulcer (on a patient basis)

Scenario	Number of days	Event/censor variable
Patient is observed to develop a new category 2 or above pressure ulcer(s) before end of follow up	Number of days between date of randomisation and date **first** new category 2 or above pressure ulcer was observed (i.e. date first recorded on CRF)	Event
Patient dies before end of follow-up not having developed a category 2 or above pressure ulcer	Number of days between date of randomisation and date of last evaluable skin assessment	Censored[α] at date of last evaluable skin assessment
Patient withdraws from the trial before end of follow-up not having developed a category 2 or above pressure ulcer	Number of days between date of randomisation and date of last follow up assessment where an assessment on an evaluable skin site was made	Patient is censored [α] at date of last evaluable skin assessment*
Patient is not observed to develop a new category 2 or above pressure ulcer before the end of follow up (including patients who were lost to follow-up)	Number of days between date of randomisation and date of last follow up assessment where an assessment on an evaluable skin site was made	Patient is censored at date of last evaluable skin site assessment

[α] Death and some withdrawals may be considered as competing risks as they prevent a pressure ulcer occurring, or being observed. The decision on whether specific reasons for withdrawal will be reviewed from a competing risks perspective by the CI blind to treatment allocation. See section 5.2.3.2 for more details.
* where patients were withdrawn due to clinical condition but a skin assessment was made on the same day the data used to derive the patients endpoint will be up until the assessment prior to the patient being withdrawn (i.e. the previous visit). This is due to ethical considerations around the patient's data being used if they had lost capacity or, for example, they were receiving palliative care. The decision over whether to censor these patients earlier is made in conjunction with the CI (or delegate) and is based solely on the reason for withdrawal, blind to mattress provision, skin status and time since entering the study.

2.4 Derivation of healing

A Category 2 PU will be classified as healed if the same skin site is later recorded as healthy or altered skin. The time to healing will be calculated as the number of days between date of randomisation and date first Category 2 PU is observed to heal, or patients will be censored at date of last evaluable assessment in line with Table 1.

2.5 Missing data

Attempts will be made to retrieve missing data via a thorough data cleaning process. Every effort will be made to obtain complete dates for all key data and missing dates will be monitored.

The levels of missing data and reasons for missing will be investigated, in addition to exploring the

pattern of missing data over time by treatment group. Exploratory work will be done comparing patients with complete data to those with missing data for various variables including baseline characteristics. This is in order to assess the level of imbalance and help assess the reason for missing. The quantity of missing data will be monitored by treatment group and a summary of the number of patients with missing primary endpoint data and the quantity of missing data by treatment group and centre will be reported.

Should key primary endpoint data (i.e. dates) be unavailable at the time of the final analysis, after all possible attempts to retrieve this missing data have been carried out, this data will be will be assessed (in the ways described above) and if assumed to be missing at random (MAR) will be imputed based on the date of the baseline visit and the visit number of the last evaluable skin assessment using the protocol visit schedule such as to comply with the intention-to-treat analysis principle (3). The baseline covariates that will be included in the primary analysis model consists the stratification factors used in the randomisation algorithm (Section 5.2.3) and as such there will be no missing data for these covariates. However, there will be some baseline covariates that will be included in the primary analysis and secondary analyses such as presence of pressure-related pain for which there may be missing data. If missing data exist for baseline data we will assess whether the missingness is correlated with the outcome and singly impute the baseline data according to White and Thompson (4).

2.5.1.1 Sensitivity analysis

A sensitivity analysis will be conducted to assess the robustness of the conclusions to the missing data assumptions. This will consist of a complete case analysis whereby patients with incomplete data for the corresponding analysis will be excluded and the conclusions from the analyses will be compared.

3 Populations

3.1 Eligibility

Eligibility criteria are detailed in the PRESSURE2 protocol (P:\CTRU\Projects\CHRD\Skin\PRESSURE II\TC\03_Protocol\3c_Current Protocol). Note that eligibility waivers are not permitted.

3.2 Intention to treat population

The intention to treat (ITT) population will include all patients randomised to treatment for whom consent to the main trial has been obtained. Allocation to treatment is by minimisation with respect to the following factors: centre, healthcare setting (Secondary care hospital, community hospital / intermediate care or rehabilitation facility), pressure ulcer status (no pressure ulcer/Category 1/Category 2), and consent (written/witnessed verbal/consultee agreement). Patients will be included in all statistical analyses using the correct data (i.e. using the data recorded on the randomisation CRF (F03) rather than the 24 hour system).

The ITT population will be analysed by allocated treatment.

3.3 Per protocol population

The per-protocol population will exclude all major protocol violators, this includes:

- Patients who do not fulfil all major eligibility criteria. Major eligibility criteria includes:
    - Patients must have evidence of acute illness

    - Patients must be at high risk of PU development
    - Patients must be on an electric profiling bed frame
    - Patients must not have previously participated in the trial
    - Patients must not have a current or previous category 3 PU at baseline
    - Patients must be within the acceptable weight limits
- Patients for whom consent to the main trial has not been obtained
- Patients whose date of consent to the main trial is after the date of randomisation
- Patients who do not receive their randomised mattress within 2 days of randomisation
- Patients who spend less than a pre-specified proportion (60%) of their follow up time on their allocated mattress

An analysis will be conducted on the per-protocol population by allocated mattress. Per-protocol violators will be monitored by centres who will complete the protocol deviation form (F42) and return it to the CTRU. The Trial Statistician will then present overall summaries of other protocol deviations at Internal Project Team meetings and Trial Management Group (TMG) meetings and a decision will be made over whether other deviations noted warrant exclusion from the per protocol population without reference to the endpoint data or treatment group allocation. Note that a compliance adjusted analysis has been considered with the TSC and DMEC but is not considered achievable with currently available methods (Appendix E).

3.4 Safety population

The safety population will be defined as all patients who were recruited into the PRESSURE 2 trial and will be used to summarise patient disposition during the trial. This population will be used to summarise any adverse events (AEs) and Related Unexpected Serious Adverse Events (RUSAEs) that occur and will be summarised by allocated mattress and actual mattress at the time of the AE.

3.5 Time to healing of category 2 PU population

The analysis of time to healing of pre-existing category 2 PUs will be conducted for the ITT population excluding all patients who did not have a category 2 PU at baseline.

3.6 Quality of life population

This will not be evaluated by the Trial Statistician and a separate analysis plan will be written for this population.

3.7 Blinded validation sub study populations

3.7.1 To assess over-reporting

To assess over-reporting a sensitivity analysis population will be defined. This will be the ITT population but skin assessments will be replaced with the outcome of the blinded central review where appropriate. That is, for skin sites assessed as category 2 or above by the research nurse, a photo should have been taken of the category 2 or above PU (providing consent has been provided by the participant) and sent for blinded review. The outcome of the central review will replace the skin assessment that took place closest to the date of the photo. If a photo was not taken (either because consent was not provided or because of a logistical reason such as the camera being unavailable) then the research nurse assessment of the category 2 or above PU will remain in the dataset and used in the sensitivity analysis.

3.7.2 To assess under-reporting

In addition to photos being taken of category 2 PUs, the CTRU will randomly identify 10% of patients from each centre for whom an independent TVTM at that centre (i.e. they are blind to the research nurse's skin assessments) will carry out a skin assessment of all 14 skin sites. In addition to these skin assessments the independent TVTM will also take photographs of 2 pressure areas (1 torso and 1limb/other) regardless of the PU status (note that if a PU is present then 1 photo will be of the PU and the second photo will be of a PU-free skin site), and providing the patient has given consent to have the photos taken. These 10% of participants will form the analysis population to assess under-reporting.

4 Data Handling

4.1 Data monitoring

Day to day monitoring for completeness and quality of trial data will be conducted centrally by the Trial Co-ordinator/Data Manager or their delegate. Every effort will be made to ensure that as much data as possible is available and that reasons for unobtainable data are obtained. Missing data, with the exception of participant reported data will be chased until it is received, confirmed as not available, or the study is at final analysis. In addition, the CTRU also monitor consent forms centrally. Any issues with data collection will be discussed at Internal Project Team meetings and, if appropriate, at Trial Management Group meetings.

The CTRU reserves the right to intermittently conduct source data verification exercises on a sample of participants. Source data verification will involve direct access to participant healthcare records and other relevant investigation reports at participating centres.

4.2 Data validation

The database validates most dates and specific data items in line with the pre-programmed validation rules in real time, as data are entered. The key data items relate to the data required for the primary endpoint. The key data items list (saved here: P:\CTRU\Projects\CHRD\Skin\PRESSURE II\TC\12_DataManagement\Key Data Item List\Key Data Item List.xlsx) for PRESSURE2 will be 100% checked for validation by the Trial Co-ordinator / Data Manager or their delegate.

SAS will be used to validate the data and check for any missing or inconsistent data. The data will be downloaded and read into permanent SAS data sets. The names and contents of the variables can be found on the annotated final database specifications in the Statistician's Trial File.

Other checks to be performed include:

- Checking eligibility of all randomised participants
- Checking for consistency between stratification factors provided to the 24hr randomisation system and the randomisation CRF (F03)
- Checking that participants allocated to the validation sub study have had the skin verification sub study CRF (F33) completed
- Checking that participants who have had a category 2 or above pressure ulcer reported have had the photography CRF (F32) completed for each category 2 or above pressure ulcer reported
- Checking that participants who have had a category 2 or above pressure ulcer reported at baseline have had the duration and area CRF (F34) sufficiently completed for each category 2 or above pressure ulcer reported at baseline
- Sequential dates
- Checks for unusual and outlying data
- Checks for inconsistent data
- Checks for missing data

- Other checks as deemed appropriate

Any suspicious or inconsistent data identified via these checks will be noted and an e-mail sent to the Trial Co-ordinator / Data Manager responsible for the study. The Clinical Co-Ordinator/Trial Co-Ordinator / Data Manager or their delegate will check such inconsistencies against the participant forms. If there has been an error in data input causing such inconsistencies this will be corrected on the database. If there has been no error in data input, a query requesting clarification will be sent to site. Details of corresponding changes will be documented.

5 Data Analysis

5.1 General calculations

Unless otherwise stated, all percentages will be calculated using the total number of patients or forms expected as the denominator (i.e. including all patients with missing data for that variable). All percentages, means, medians, interquartile ranges (where appropriate) and also ranges will be rounded to 1 decimal place (or 1 significant figure for numbers less than 1), whilst standard deviations will be rounded to 2 decimal places (or 2 significant figures for numbers less than 1). P-values will be rounded to 4 decimal places (those less than 0.0001 will be displayed as <0.0001), whilst parameter estimates, standard errors, hazard ratios and corresponding confidence intervals will be reported to 2 decimal places (or 2 significant figures for numbers less than 1). All analyses will be carried out using SAS unless otherwise stated.

5.2 Analysis

5.2.1 Screening summaries

Screening data, including age, gender, ethnicity and current mattress type will be summarised using frequencies and summary statistics. The screening process will be summarised using a flow diagram. If one of the screening questions, for example 'Eligibility assessed?', is missing and no further questions have been completed then it will be assumed that the answer to the corresponding screening question is 'No'. Else, if any subsequent screening questions have been completed then it will be assumed that the answer was 'Yes'.

The screening database and main database will be linked, where possible, using screening numbers and trial numbers. The screening logs will be monitored on an on-going basis to ensure that they are as accurate as possible, but it is anticipated that there will be some differences. Since the screening log is anonymised it would be very difficult to work out how to correct the differences, and so ball park figures will be given, i.e. if the screening log has identified 550 as being randomised, but there are actually 560 randomised participants then it will be assumed that these extra 10 participants are not on the screening log and will therefore be added to each stage of the screening process. Similarly if the screening log has identified 560 patients as being randomised, but there are actually 550 randomised participants then it will be assumed that these extra 10 patients on the screening log had consented but were not actually randomised.

5.2.2 Baseline characteristics

Baseline patient and clinical data as recorded on the randomisation (F03) and baseline assessment form (F02) will be tabulated using frequencies and summary statistics for each treatment group and overall. Missing or unobtainable data will be included as missing unless data are available from the 24-hour randomisation form. Summaries of the number of incorrect data on the 24-hour randomisation form compared to F03 will be produced.

5.2.3 Primary endpoint analysis

The Primary endpoint analysis will be conducted on both the ITT population and on the per-protocol population (Appendix 4).

The incidence rate of patients developing a new category 2 or above pressure ulcer will be summarised by treatment group together with the number of new category 2 or above pressure ulcers per patient and the location of new category 2 or above pressure ulcers. In addition, the incidence rate of new category 2 or above pressure ulcers will be summarised for each covariate planned to be included in the primary analysis using frequencies for each treatment group and overall.

After feedback from research nurses that Incontinence Associated Dermatitis (IAD) could be considered as skin alterations rather than 'N/A', summaries of whether the incidence rate of patients developing a new category 2 or above PU would change assuming IAD to be equivalent to skin alterations will be produced. It is not appropriate to conduct a sensitivity analysis on this data as IAD is often categorised in line with pressure ulcer reporting and may in fact be a category 2, and we do not collect this additional category data for IAD.

In addition, it is anticipated that there will be very few 'other' skin sites (see section 2.2.1.1) that are considered non-evaluable. Summaries on how the primary endpoint might change if these 'other' skin sites were included in the derivation of the endpoint.

5.2.3.1 Proportional hazards and no competing risks

If proportional hazards can be assumed and there are considered to be no (or minimal) competing risks then a
Cox Proportional Hazards (Cox PH) model will be fitted to the primary endpoint, with the following minimisation factors fitted as fixed effects: healthcare setting, pressure ulcer status and consent, in addition, the following covariates will also be fitted as fixed effects: presence of pain on a healthy, altered or category 1 skin site, 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.

The proportional hazards assumption and adequacy of the Cox PH model will be explored through examination of:

- Plot of Schoenfeld residuals versus time
- Plot of ln(cumulative hazard) versus time
- Formal test of whether treatment effect varies over time by fitting an interaction of treatment and ln(time)
- "Assess" statement in the SAS PHREG procedure

The probability of patients (using cumulative incidence functions) developing a Category 2 or above pressure ulcer over the length of trial participation in each group and adjusted confidence intervals corresponding to the nominal p-value will be presented.

Monitoring will also be conducted in East software and the analysis output will also be presented in a Double Triangular Group Sequential Design diagram to aid interpretation of the results.

5.2.3.2 Proportional hazards and competing risks

It is recognized that there may be competing risks, for example death or withdrawal from follow up which prevent the event of interest from occurring or being observed, and the reason for this may be such that the patients risk of developing a pressure ulcer has changed. These will be considered upon inspection of the data, by the CI who will be blind to treatment group, and if considered to be substantial, and the hazards of the cumulative incidence function are proportional then a Fine and Gray model (5) will be fitted to the primary endpoint, with the following minimisation factors fitted as fixed effects: healthcare setting, pressure ulcer status and consent, in addition, the following covariates will also be fitted as fixed effects: presence of pain on a healthy, altered or category 1 skin site, conditions affecting peripheral circulation. The effect of adding treatment group to this model will be assessed using the likelihood ratio test. Centre will be fitted as a random effect. The model assumptions will be checked according to (5).

In addition, for patients who have died or withdrawn, the number of days between the last evaluable assessment and the date of death/withdrawal will be summarised, by treatment arm.

5.2.3.3 Non proportional hazards and no competing risks

It is recognised that the proportional hazards assumption may not hold, therefore in this scenario if there are considered to be no (or minimal) competing risks then the Restricted Mean Survival Method (RMST) (6) will be used to compare the mean survival times between treatment groups. SAS software does not have an in built function to conduct this analysis therefore STATA will be used as described in (6, 7) and the relevant model assumptions will be checked.

5.2.3.4 Non proportional hazards and competing risks

If competing risks are considered to be substantial and the proportional hazards assumption does not adequately hold for the Fine and Gray model then the methods for dealing with this data are limited. In this scenario we will conduct Gray's test which is an analogue of the log rank test to compare two or more groups in the presence of competing risks (8). The disadvantage to this method is that it will not provide an estimate of the treatment effect, but we will explore whether there are confounding variables that may affect the proportional hazards assumption in order to conduct an analysis that provides an estimate of the treatment effect. We will also conduct the analyses described in sections 5.2.3.2 and 5.2.3.3 as sensitivity analyses.

5.2.3.5 Sensitivity analysis based on treatment phase

The time to pressure ulcer development within the treatment phase only will be derived (i.e. ignoring the 30 day post treatment phase visit) and a sensitivity analysis will be conducted on this endpoint to evaluate whether there is evidence of a treatment effect within the treatment phase. The analysis will be conducted as in line with sections 5.2.3.1 to 5.2.3.4.

5.2.3.6 Sensitivity analysis for non-evaluable participants

The analysis conducted on the primary endpoint will be repeated to assess the robustness of the missing data assumptions for participants who did not have an evaluable endpoint and were included in the primary analysis through imputation of dates; A complete case analysis will be conducted where patients will be excluded if the date of their last evaluable skin assessment is missing.

5.2.3.7 Moderator & mediator analyses:

5.2.3.7.1 Moderator analyses

Moderator analyses will explore whether the treatment effect depends on baseline characteristics of the patient. These will be conducted by building separate models for each of the following potential predictors of response (time to developing Category 2 or above pressure ulcer):
pre-existing pressure ulcers

- Category A skin status
- diabetes
- age
- mobility
- sensory perception
- macro and micro circulatory function
- nutritional status
- skin moisture

Each of these models will take the form of the primary analysis model with the addition of the potential moderator and the interaction of the treatment variable with the moderator. If the interaction is observed to be statistically significant in the model then the variable will be said to moderate the treatment effect, although the exploratory nature of these analyses will be recognised in the interpretation of the results.

5.2.3.7.2 Mediator analyses

Mediator analyses will explore the relationship between treatment group and the following potential mediator variables:

- length of stay
- time on allocated mattress
- patient turning*
- use of specialist cushions*
- heel protectors*
- protective dressings*

The data for the above variables indicated by * have been collected in a simple way and therefore there is a query over the validity and reliability of these data. Further, the length of stay and time on allocated mattress may be dependent on outcome (e.g. stay and time on allocated mattress may be longer/shorter if the patient develops a PU). Therefore the data will first be summarised by source (e.g. patient reported/records), by centre and by PU outcome to explore whether there are any systematic differences. If there are considered to be systematic differences then further analysis of these data will not be conducted because of the risk of bias. If there do not appear to be systematic differences that the Baron and Kenny method (9) will be used to explore whether any mediators exist.

5.2.4 Secondary endpoint analysis

5.2.4.1 Time to developing a PU of at least Category 3

The time to development of a category 3 or above PU will be derived in line with the derivation of the primary endpoint but adjusted for the development of a more severe pressure ulcer (i.e.

Category 3, see Appendix G) rather than a Category 2. The analysis on this endpoint will be conducted in line with the analysis outlined in section 5.2.3

5.2.4.2 Time to developing a PU of at least Category 1

The time to development of a category 1 or above PU will be derived in line with the derivation of the primary endpoint but adjusted for the development of a less severe pressure ulcer (i.e. Category 1, see Appendix H) rather than a Category 2. The analysis on this endpoint will be conducted in line with the analysis outlined in section 5.2.3.

5.2.2.3 Time to healing of pre-existing Category 2 pressure ulcers

The time to healing of pre-existing Category 2 pressure ulcers will be analysed in line with the analysis methods described in section 5.2.3.

Note that for this endpoint patients who do not have their Category 2 PU heal during the intervention period and by 30 days post trial completion will be censored at 30 days post trial completion, or else at the date of withdrawal, death or loss to follow-up, accounting for competing risks in the same way as described in section 2.3.2.

The incidence rate of healing of pre-existing category 2 PUs will be summarised by treatment group together with the number of healed pre-existing category 2 PUs per patient and the location of healed pre-existing category 2 PUs. In addition the incidence rate of healing of pre-existing category 2 PUs will be tabulated for each covariate to be included in the analysis using frequencies and summary statistics for each treatment group and overall.

5.2.4.3 Safety

AEs and SAEs classified as related to the mattress or resulting from administration of any research procedures will be listed and summarised by allocated mattress and mattress at the time of the AE.

5.2.5 Validation sub study analysis

5.2.5.1 Compliance

The consent rates for having photographs taken of skin sites will be summarised, at baseline and during follow up, by treatment arm, by centre and overall.

Compliance with sending photographs will be summarised by treatment arm, by centre and overall and will include how frequently photographs were:

- unable to be assessed by the central review team (for example because they were blurry or the grey scale card was not present)
- not taken by the research team for logistical or research team reasons
- not sent to the CTRU for logistical or research team reasons.

5.2.5.2 Assessing risk of over-reporting (Photographs of all Category 2 PUs)

A sensitivity analysis on the primary endpoint will be conducted such that the model used in the primary analysis will be applied to the population defined in section 3.7.1.

5.2.5.3 Assessing risk of under-reporting (10% sample)

For each skin site assessed by the independent TVTM, 2 by 2 tables will be produced by arm and overall to summarise whether the skin assessments made by the PI and the skin assessments made by the research nurse/registered health care professional (RHCP), agree on the category 2 or above PU status. In addition, a 2 by 2 table summarising the agreement overall skin sites (i.e. on a patient basis) will be produced. The following statistics will be reported for each of these tables: Kappa and Prevalence and Bias Adjusted Kappa.

5.2.5.4 Reliability of photographs

Summaries, by arm and overall, of the outcome of the blinded central review of photographs compared to the clinical skin assessment made by either the research nurse or independent TVTM will be produced, and corresponding agreement statistics (Kappa and Prevalence and Bias Adjusted Kappa) will be reported for each of the following cases:

- Assessments drawn from the photographs (via blinded central review) and the skin assessments made by the independent TVTM, for each skin site for which a photograph was taken and overall area (i.e. torso/limb)
- Assessments drawn from the photographs taken by the research nurse/RHCP because a Category 2 or above PU was observed and the skin assessments made by the research nurse/RHCP for each skin site for which a photograph was taken.

Where poor agreement is observed the data will be explored, for example the number of days between the photograph taken by the independent TVTM and the clinical assessment made by the research nurse/RHCP will be summarised because these may not have been conducted on the same day and skin appearance can change quickly. Any additional skin descriptors (for N/A or alterations) will also be examined.

5.2.6 Patient Disposition

The number of patients who completed the study, died, withdrawn (with reasons where available), and who were lost to follow-up will be presented by centre, treatment arm and overall. The length of treatment phase and length of overall time in the study will also be summarised by treatment arm and overall.

5.2.7 Protocol violators/deviations

Protocol violations and protocol deviations will be described by treatment arm and overall. This includes those found not to satisfy the eligibility criteria after randomisation and those who do not receive their randomised mattress throughout the treatment phase. Reasons for those violating the eligibility criteria will be summarised by treatment arm and overall.

5.2.8 Mattress compliance

A summary of the time to receiving allocated mattress, reasons for not receiving mattress on the day of randomisation (day 0) and the number of mattress changes together with reasons will be summarised by treatment arm and overall. The number of days and the proportion of time spent on the randomised mattress during the treatment phase will be summarised using descriptive statistics and frequency distributions by treatment arm and overall. In addition, for those allocated to APM, a summary of the number of times the mattress is observed to not be working correctly together with reasons will be presented.

5.2.9 CONSORT diagram

The CONSORT diagram (10) will be produced to summarise the course of patients throughout the study and the analysis populations included reasons for exclusion from analyses (e.g. derivation of the per-protocol population).

6 Reporting and dissemination of the results

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.

7 Approval of Analysis Plan

Clinical Trials Research Unit (CTRU)

The following final analysis plan, February 2017, for the PRESSURE 2 study has been approved by the following personnel. Any signed amendments to the plan will be filed with this document.

Trial Statistician: _____

Date: _____

Supervising Statistician: _____

Date: _____

Data Manager: _____

Date: _____

Trial Co-ordinator: _____

Date: _____

Clinical Co-ordinator: _____

Date: _____

Clinical Co-ordinator: _____

Date: _____

Clinical Co-ordinator: _____

Date: _____

CTRU Project Delivery Lead: _____

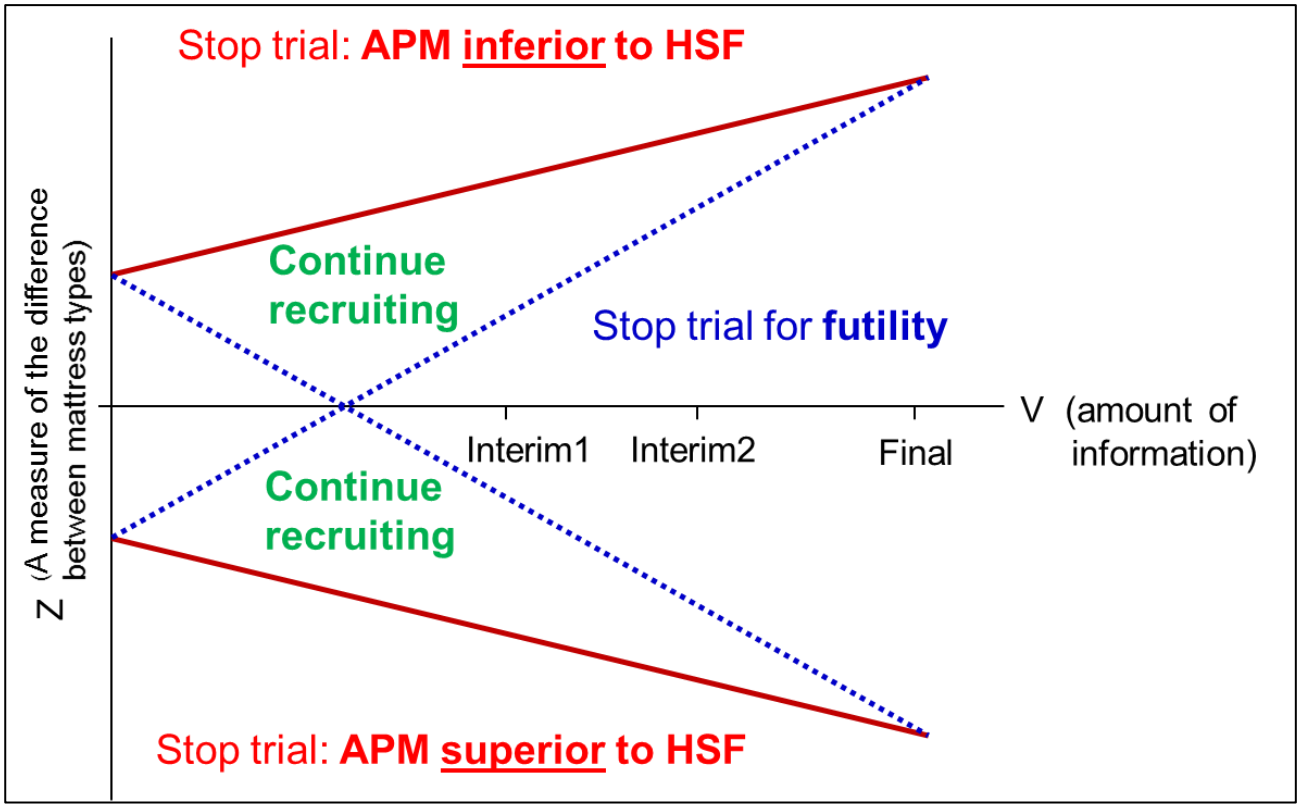
Date: _____

Chief Investigator: _____

Date: _____

Additional information:

Appendix A. Graphical representation of trial design



Appendix B. Skin classification incorporating the NPUAP/EPUAP PU Classification System

Category	Description	
Category 0 Healthy intact skin	No skin changes	
Category A Alterations to intact skin	*Alterations to intact skin. Please specify with sub-category code:*	
	001 = Blanching redness which persists	011 = Papery thin
	002 = Bruising – red hue	012 = Cracks/calloused
	003 = Bruising – purple hue	013 = Spongy
	004 = Scar	014 = Macerated
	005 = Oedema	015 = Scratches
	006 = Cellulitis	016 = Rash
	007 = Lymphodema	017 = Scab
	008 = Discoloration – ischaemia	018 = Induration
	009 = Discoloration – cyanosis	019 = Heat
	010 = Dry/flaky	999 = None of the above, please describe
Category 1 Non-blanchable erythema of intact skin	Intact skin with non-blanchable erythema of a localised area usually over a bony prominence. Discoloration 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.	
Category N/A Not applicable	*Specify with sub-category code:*	
	001 = Amputation	007 = Device-related ulcer
	002 = Bandage in situ	008 = Surgical wound/bruising
	003 = Cast in situ	009 = Traumatic wound/bruising
	004 = Dressing in situ	010 = Dermatological skin condition e.g. eczema
	005 = Incontinence associated dermatitis	011 = Unable to assess
	006 = Other chronic wound	999= None of the above, please describe

Appendix C. Derivation of skin site level outcome

Table 2 Derivation with justification of whether a new category 2 or above pressure ulcer develops on a skin site basis (i.e. for each separate skin site)

Scenario	Baseline skin assessment	Follow up skin assessments	New category 2 or above pressure ulcer?	Reasoning
1	Category 0, 1 or A	No follow up	Unknown	No follow up assessments to identify whether the skin site does or doesn't develop a new category 2 or above pressure ulcer
4	Category 0,1, or A	**At least one** follow up assessment is category 2 or above	Yes	The skin site was assessed as healthy, altered or a category 1 pressure ulcer at baseline. A category 2 or above pressure ulcer is reported during follow up and therefore we conclude that a new category 2 or above pressure ulcer has developed.
3	Category 0, 1 or A	**All** "actual" follow up assessments are category 0,1, or A (although some could be 'N/A' or missing)	No	There has been at least one follow up assessment from which we could say no new category 2 or above pressure ulcer developed
5	Category 0,1, A	**All** follow up assessments are 'N/A' or missing	Unknown	There are no follow up assessments to determine whether or not this skin site develops a new category 2 or above pressure ulcer
2	Category 2 or above	Any number of follow up skin assessments have taken place	N/A	The baseline skin assessment shows the skin site to have an existing category 2 or above pressure ulcer therefore a new category 2 or above pressure ulcer cannot develop at this skin site
6	N/A	Any number of follow up skin assessments have taken place	Unknown	The baseline assessment cannot inform whether this skin site develops a new category 2 or above pressure ulcer

Exceptions in the above derivation are where main skin sites are assessed as having a device ulcer. These will be reviewed centrally without reference to the allocated mattress and may be assumed to be at least a category 2 ulcer and could contribute to the primary endpoint in the primary analysis.

Appendix D. Derivation of patient-level outcome

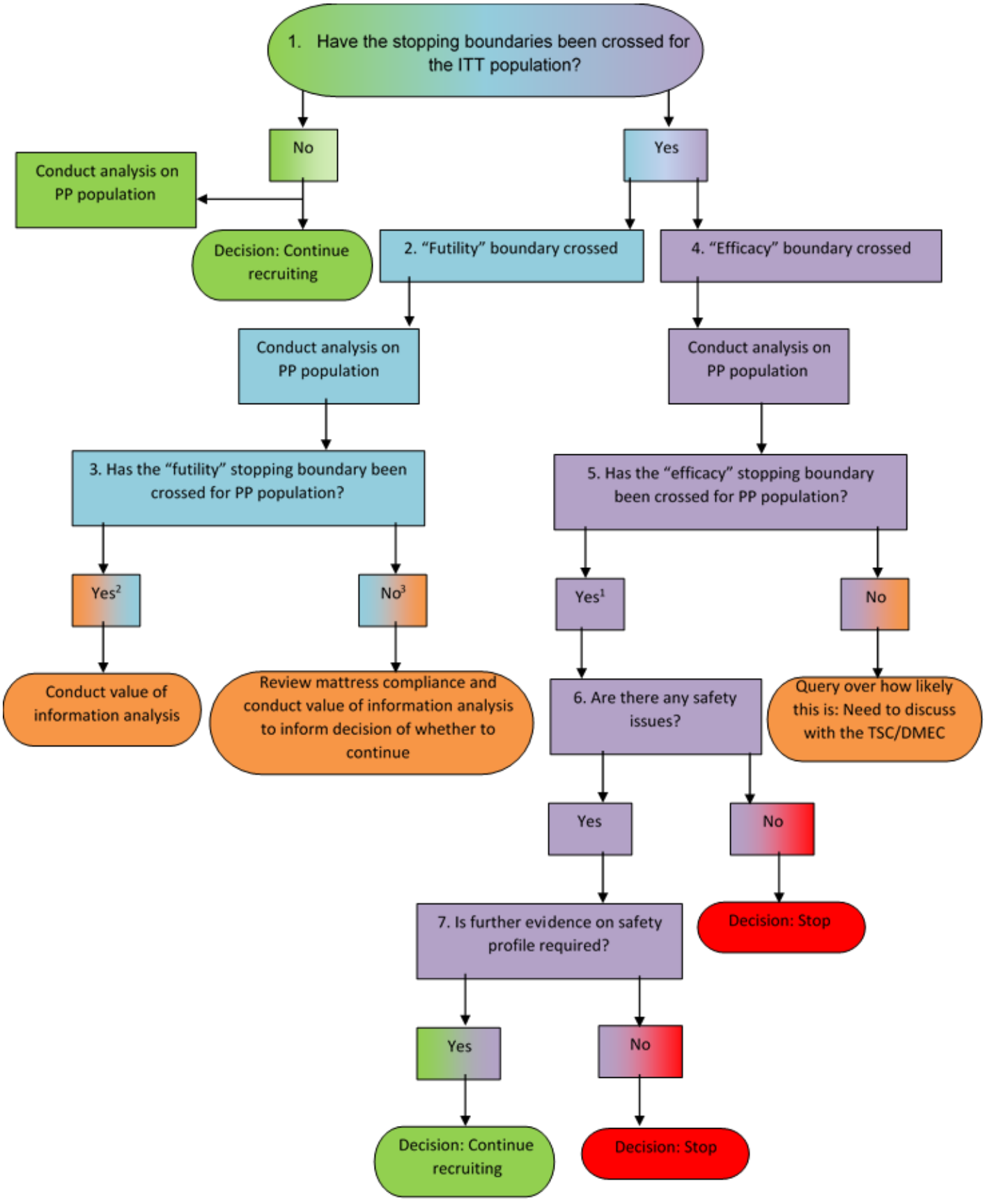
Table 3 Derivation with justification of whether a participant develops a new category 2 or above pressure ulcer

New category 2 or above pressure ulcer on a skin site level basis?	New category 2 or above pressure ulcer on a participant level basis?	Reasoning
Unknown or N/A (for all skin sites)	Unknown	Participant has no evaluable skin sites (e.g. there were either no follow up assessments or the baseline skin assessments were insufficient)
At least one yes	Yes	Participant develops a new category 2 or above pressure ulcer on at least one skin site
No (for all skin sites)	No	Participant does not develop new category 2 or above pressure ulcer during follow up at any skin site
No's and unknown's	No	Based on the evaluable skin sites the participant did not develop a new category 2 or above pressure ulcer

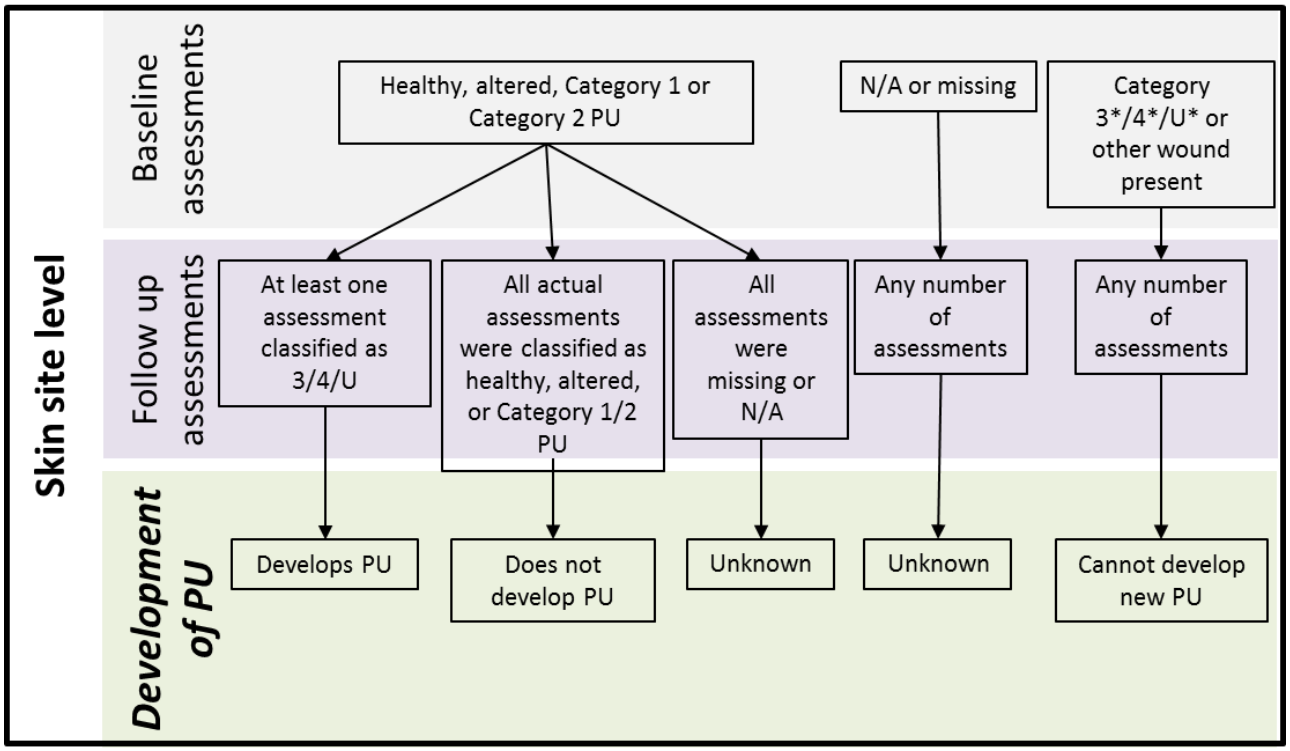
Appendix E. Compliance adjusted analyses

The TSC and DMEC have previously recommended conducting analyses in addition to the per protocol analysis whereby the causal effect of the two mattresses are assessed taking into account compliance with allocated mattress and respecting the randomisation process. However, because PRESSURE2 is a pragmatic trial where the trial interventions are used in practice there are multiple considerations in terms of 'treatment switching'. These include situations where the patient could receive their allocated mattress; switch to the alternative trial mattress or a non-trial mattress and, switch back again to their allocated mattress multiple times. This can be due to ward transfers or the patients' level of risk changing for example. This complex level of mattress compliance has been discussed with methodologists including Ian White who was previously contacted regarding how to deal with mattress compliance in the original PRESSURE1 trial (11) and they were unable to find a solution. Ian White is keen to explore this again with the PRESSURE2 data but it is deemed to be infeasible to do for this unplanned interim analysis. A pragmatic solution at this stage is to include patients who have spent a minimum proportion of their treatment phase spent on their allocated mattress in the per protocol population.

Appendix F. Scenarios to consider at interim analysis

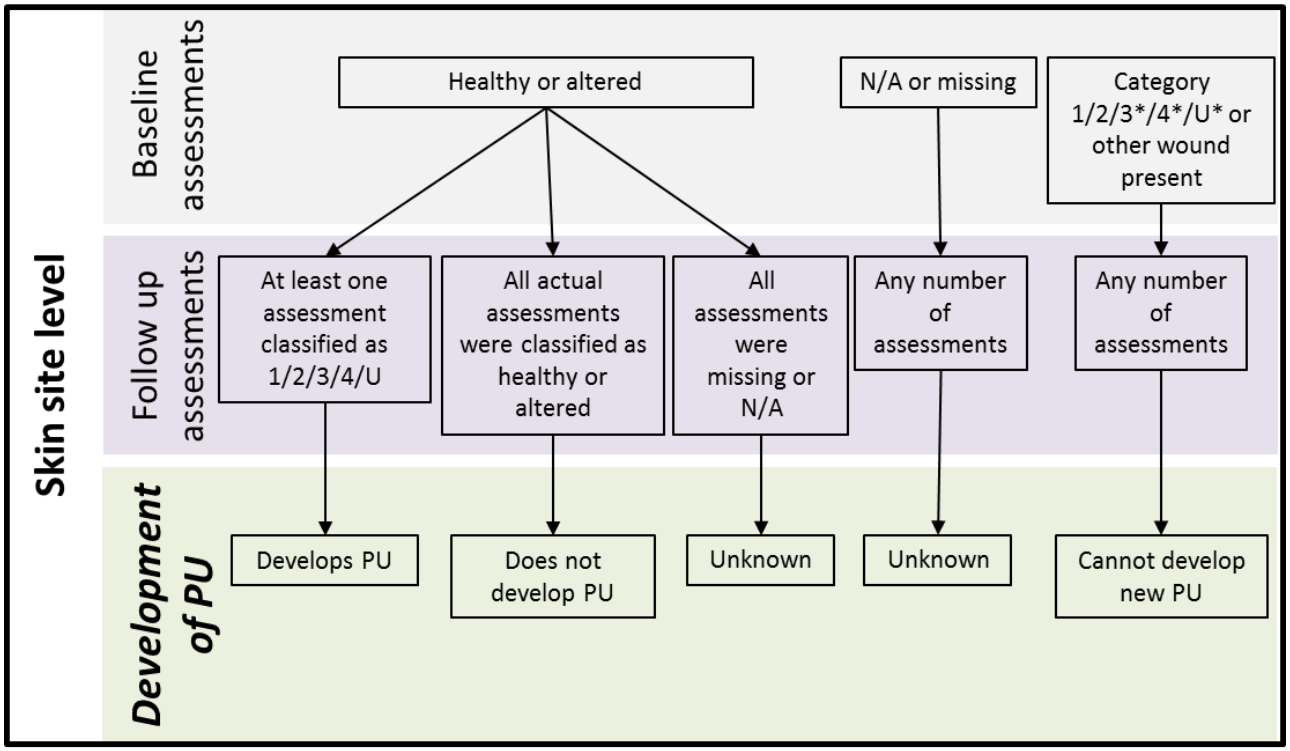


Appendix G. Derivation of Category 3 PU development on a skin site level



*Patients with a Category 3/4/U pressure ulcer should have been excluded from the trial according to the eligibility criteria, however they have been included in this derivation to account for patients that may have been incorrectly recruited to the trial.

Appendix H. Derivation of Category 1 PU development on a skin site level



*Patients with a Category 3/4/U pressure ulcer should have been excluded from the trial according to the eligibility criteria, however they have been included in this derivation to account for patients that may have been incorrectly recruited to the trial.

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Analysis Plan Amendment and Deviation Log

Current Version Number	New Version Number *	Section	Description and Reason for Amendment or Deviation	Trial Statistician Name & Date	Supervising Statistician Name & Date
2.0		3.3	The minimum compliance for the per protocol population derivation is defined as 60% of their follow-up time on their allocated mattress. This definition has been updated for the purposes of the final analysis to: "Patients who are on their allocated mattress for less than 60% of their follow up time defined as the time until they develop a Category 2 PU or they complete the treatment phase, whichever happens first" This is because in the case where a patient is on their allocated mattress for say, 7 days, develops a PU and then changes mattress for the remaining 51 days of their treatment phase they would be excluded from the per protocol population in the original definition because they have spent 12.1% of their treatment phase on their allocated mattress but at the point of their event they were 100% compliant. Therefore the original definition would have biased the results by excluding patients who might have changed mattress *because* they experienced the event of interest.	Isabelle Smith 14/03/2017	Sarah Brown 14/03/2017
2.0		2.4	The derivation of time to healing was originally based on the earliest date a pre-existing Category 2 PU was observed to heal. This was changed on the basis of clinical opinion to the date the latest pre-existing ulcer was observed to heal.	Isabelle Smith 02/11/2017	Sarah Brown 02/11/2017
2.0		2.5	All baseline covariate data were categorical and missing data were entered into the model as a separate category.	Isabelle Smith 02/11/2017	Sarah Brown 02/11/2017

* If the analysis plan is amended, note the new version number. If a deviation is made from the analysis plan within the analysis, leave blank.

2.0		5.2.3.7.1	Consent type was included as an additional moderator	Isabelle Smith 02/11/2017	Sarah Brown 02/11/2017
2.0		5.2.3.7.2	Mediator analysis could not be conducted as planned due to existing methods being unsuitable for the competing risks setting. Details are provided in the methods chapter of the monograph.	Isabelle Smith 02/11/2017	Sarah Brown 02/11/2017
2.0		5.2.4.3	The model for the analysis of PU healing did not include the presence of pain at baseline or skin status (because all patients had a pre-existing ulcer at baseline).	Isabelle Smith 02/11/2017	Sarah Brown 02/11/2017
2.0		5.2.5.2	A sensitivity analysis on the primary endpoint could not be conducted using photographic assessment because the data were derived on a longitudinal basis and photographs were only taken at one point in time.	Isabelle Smith 02/11/2017	Sarah Brown 02/11/2017
2.0		5.2.5.4 & 5.2.5.3	Comparisons on a skin site level of photographs have not been possible at this stage because of the broad labelling of grey scale cards, e.g. “sacrum and buttocks” or “heel” instead of “Left heel”. This will be explored in more detail for a separate paper.	Isabelle Smith 02/11/2017	Sarah Brown 02/11/2017

Summaries specified in the analysis plan but not included in the monograph, or included on the amendment log have been conducted and are available if required.

