PROTOCOL KCE-16012

THE USE OF A SILICONE ADHESIVE MULTILAYER FOAM DRESSING AS AN ADJUVANT PROPHYLACTIC THERAPY FOR PRESSURE ULCER PREVENTION: A MULTICENTRE RANDOMISED OPEN LABEL PARALLEL GROUP MEDICAL DEVICE TRIAL IN HOSPITALISED PATIENTS AT RISK OF PRESSURE ULCER DEVELOPMENT

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GENERAL INFORMATION

FULL TITLE OF THE STUDY

The use of a silicone adhesive multilayer foam dressing as an adjuvant prophylactic therapy for pressure ulcer prevention: a multicentre randomised open label parallel group medical device trial in hospitalised patients at risk of pressure ulcer development.

SHORT STUDY TITLE

Silicone adhesive multilayer foam dressings to prevent pressure ulcers.

PROTOCOL VERSION NUMBER AND DATE

Version 2.0, 11 Jan 2018

RESEARCH REFERENCE NUMBERS

EudraCT Number:	Not Applicable
KCE Number:	KCE-16012

SIGNATURE PAGE

Title: The use of a silicone adhesive multilayer foam dressing as an adjuvant prophylactic therapy for pressure ulcer prevention: a multicentre randomised open label parallel group medical device trial in hospitalised patients at risk for pressure ulcer development.

This medical device Clinical Trial Protocol has been reviewed and approved by the sponsor, the Chief Investigator and the Statistician. The undersigned agree to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the GCP guidelines, the Belgian law of May 7th 2004 regarding experiments on the human person, the Sponsor's SOPs, and other regulatory requirements.

The undersigned agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

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

FOR AND ON BEHALF OF THE STUDY SPONSOR		
Signature:		Date: ...../...../.....
Frank Hulstaert, MD		
CHIEF INVESTIGATOR		
Signature:		Date: ...../...../.....
Prof. Dimitri Beeckman		
STATISTICIAN		
Signature:		Date: ...../...../.....
Mr. Filip Deforce		

SIGNATURE PAGE – INVESTIGATOR

Title: The use of a silicone adhesive multilayer foam dressing as an adjuvant prophylactic therapy for pressure ulcer prevention: a multicentre randomised parallel group open label medical device clinical trial in hospitalised patients at risk for pressure ulcer development

I, the undersigned, confirm that the following protocol has been agreed and accepted and that the study will be conducted in compliance with the approved protocol and will adhere to the principles outlined in the GCP guidelines, the Belgian law of May 7th 2004 regarding experiments on the human person, the Sponsor's SOPs, and other regulatory requirements.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

_____	_____	_____
Investigator Name	Signature	Date

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	• A representative from a participating site • Up to two representatives of patients or the public

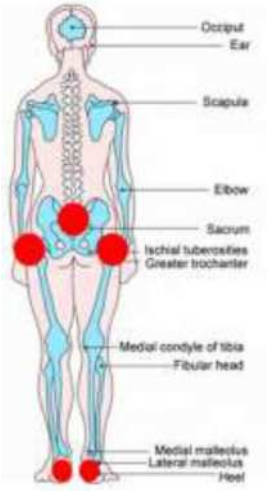
▪ STUDY SUMMARY

Study Title	The use of a silicone adhesive multilayer foam dressing as an adjuvant prophylactic therapy for pressure ulcer prevention: a multicentre randomised open label parallel group medical device trial in hospitalised patients at risk for pressure ulcer development.
Protocol version and Date	Version 2.0, 11 Jan 2018
Internal ref. no. and short title	KCE-16012: Silicone adhesive multilayer foam dressings to prevent pressure ulcers.
Objective	The objective of this study is to determine if silicone adhesive multilayer foam dressings applied to the sacrum, heels and greater trochanter in addition to standard prevention reduce pressure ulcer incidence category II, III, IV, Unstageable, and Deep Tissue Injury (DTI) compared to standard pressure ulcer prevention alone in at risk hospitalised patients. *Note: Medical device related pressure ulcers are out of the scope of this trial.*
Primary endpoint	The primary endpoint of this study is the incidence rate during the study period of the patient (during maximum 14 days) of at least one new pressure ulcer category II, III, IV, Unstageable, Deep Tissue Injury (DTI) (briefly referred to as pressure ulcers category II or worse) on sacrum, heels and greater trochanter as judged on site.
Study Design	• Multicentre randomised controlled open label parallel group medical device trial in approximately 8 hospitals in Belgium. • Patients will be randomly allocated to three study arms based on a 1:1:1 allocation: - **Study arm 1:** ▪ Patients at risk for pressure ulcer category II, III, IV, Unstageable, and Deep Tissue Injury (DTI) development will receive standard pressure ulcer prevention strategies (as described in the hospital protocol) which include ongoing risk assessment, regular repositioning and skin care. ▪ Skin sites (restricted to sacrum, heel right/left and greater trochanter right/left) will be treated with silicone adhesive multilayer foam dressings by Smith & Nephew (Allevyn® brand). - **Study arm 2:** ▪ Patients at risk for pressure ulcer category II, III, IV, Unstageable, and Deep Tissue Injury (DTI) development will receive standard pressure ulcer prevention strategies (as described in the hospital protocol) which include ongoing risk assessment, regular repositioning and skin care. ▪ Skin sites (restricted to sacrum, heel right/left and greater trochanter right/left) will be treated with silicone adhesive multilayer foam dressings by Mölnlycke Health care (Mepilex® brand). - **Study arm 3:** ▪ Patients at risk for pressure ulcer category II, III, IV, Unstageable, and Deep Tissue Injury (DTI) development will receive standard pressure ulcer prevention strategies (as described in the hospital protocol) which include ongoing risk assessment, regular repositioning and skin care.

	▪ No silicone adhesive multilayer foam dressings will be applied on the skin sites of interest for this trial (sacrum, heel right/left, greater trochanter right/left). • Skin sites (restricted to sacrum, heel right/left, greater trochanter right/left) of patients at risk for pressure ulcer category II, III, IV, Unstageable, and Deep Tissue Injury (DTI) development will be assessed daily for a maximum period of 14 days.
Statistical analyses	• **Primary analysis:** - Patients in study arms 1 and 2 will be pooled as the treatment group and the incidence rate of pressure ulcers category II or worse as judged on site will be compared between the treatment group and the usual care group as per randomisation scheme. - The primary evaluation will be performed on the basis of the Intention to Treat (ITT) set consisting of all patients randomised. A sensitivity analysis will be performed on the Per Protocol (PP) set. • **Exploratory analyses:** - Comparison (both on the ITT and PP sets) of incidence rates (primary endpoint) between the experimental investigational devices (arms 1 and 2). - Analysis (both on the ITT and PP sets) of the primary endpoint based on the central reading of the images. - Sensitivity analysis of the primary endpoint (both on the ITT and PP sets) using time to event approach (cox proportional hazard) and logistic mixed models.
Hospital eligibility	In most hospitals in Belgium no dressings are currently used in the prevention of pressure ulcers. Those hospitals where dressings are currently used in the prevention of pressure ulcer in smaller or larger at risk groups as part of the standard of care cannot participate to this trial and need to discontinue their participation to the trial if the hospital introduces such practice. The use of dressings for routine care prevention of pressure ulcers in participating hospitals will therefore remain limited to exceptional cases. and, if known in advance, such patients will not be eligible for trial participation.
Inclusion and exclusion criteria	**Inclusion criteria:** 1. At risk for pressure ulcer development based on Braden risk assessment (Braden score ≤17). 2. Admitted to hospital within the previous 48 hours. *Note: Not more than 25% of patients per site should be recruited at ICU wards.* 3. Skin at sacrum is assessable and there is no clinically relevant incontinence- associated dermatitis (IAD*) or another skin condition that would be a contra-indication for the application of the devices under study, and there is no pressure ulcer category II or worse present. **clinically relevant IAD is defined as any of the 4 categories described in the publication http://users.ugent.be/~dibeeckm/globiadnl/nlv1.0.pdf* 4. For at least 3 of the following 4 skin sites (heel left, heel right, greater trochanter left, greater trochanter right) one of the following two conditions should apply: ○ A study dressing can be applied as prevention of a pressure ulcer category II or worse at that skin site (there is no contra-indication) **OR**

	There is already a pressure ulcer category II or worse at that skin site. 5. Written informed consent by the patient or his/her legal representative. **Exclusion criteria:** 1. Aged < 18 years. 2. The length of stay counting from first day of admission in one or (if the patient is transferred to another ward) more participating wards is < 7 days. 3. Both heels amputated 4. Previously known/documented allergy for substances used in the devices under study. 5. A clinical condition not allowing participation in a clinical study. 6. Participation in another interventional clinical trial. 7. Patients who exceptionally receive or are planned to receive a dressing for the prevention of pressure ulcers at sacrum, heels and trochanters based on best medical judgment and outside of the surgery setting.
Sample Size	The following assumptions were applied to calculate the sample size: • The incidence rate of pressure ulcers category II, III, IV, Unstageable and DTI at sacrum, heels and greater trochanter is 6% in the control group (Schoonhoven, Bousema & Buskens, 2007). • The treatment groups will have a 50% reduction in pressure ulcer incidence category II, III, IV, Unstageable and DTI incidence on sacrum, heels and greater trochanter (Demarré, Beeckman, Vanderwee, Defloor & Grypdonck, 2012; Nixon, Cranny, Iglesias, Nelson, Hawkins et al., 2006). • In order to have 80% power to show superiority, data should be available for 1578 patients in total of which 526 are allocated to the control group and 1052 are allocated to the treatment group. • Considering approximately 5% dropout, a total of 1662 patients are to be randomised to ensure that sufficient patients complete the study without compromising the study power.
Treatment	**Experimental arms:** • Patients in an experimental arm will: - be cared for on the available support surfaces of the hospital (mattresses, cushions) for the duration of their hospital admission. - receive standard pressure ulcer prevention strategies (as described in the hospital protocol) which include ongoing risk assessment, regular repositioning and skin care. • Silicone adhesive multilayer foam dressings will be applied on to dry intact skin on sacrum, heel right/left, greater trochanter right/left, in addition to standard pressure ulcer prevention. • Dressings will not be applied in skin areas affected by clinically relevant incontinence- associated dermatitis (IAD) or other skin conditions that are a contra-indication for the application of the dressing. • Emollients or other skin barrier products will not be applied to prevent adhesion issues of the dressing to the skin site. • The procedure for dressing application and frequency of re- application be followed is as described by the manufacturer. Dressings will be maintained on the treatable skin sites throughout the conduct of the trial and changed if they become soiled or dislodged. • The skin beneath the dressing will be inspected daily.

	The maximum treatment duration is 14 days. **Control arm:** • Patients in the control arm will: - be cared for on the available support surfaces of the hospital (mattresses, cushions) for the duration of their hospital admission. - receive standard pressure ulcer prevention strategies (as described in the hospital protocol) which include ongoing risk assessment, regular repositioning and skin care. • No silicone adhesive multilayer foam dressings will be applied on any skin sites to prevent pressure ulcer development. • The skin on sacrum, heel right/left, trochanter right/left will be inspected daily. The maximum observation period under study is 14 days.
Planned Study Period	Accrual: estimated at 9 months, starting Q1 2018, data cleaning: 3 months, analysis and reporting: 6 months
Investigational Devices	• Silicone adhesive multilayer foam dressings by Smith & Nephew (Allevyn® brand, type: Allevyn® Life, Allevyn® Life Sacrum and Allevyn® Life Heel) • Silicone adhesive multilayer foam dressings by Mölnlycke Health care (Mepilex® brand, type: Mepilex® Border, Mepilex® Border Sacrum, Mepilex® Border Heel) *Note: Changes to the investigational dressings' design (but keeping the same range of* indications*) and marketing driven relabelling of the current investigational devices may occur and will be discussed by the trial steering committee (TSC). After approval by the TSC, these dressings will be allowed in the trial. An ad hoc TSC meeting may be needed in order not to put the study on hold at any time for this reason.*

Application of the Investigational Devices	The investigational dressings will be applied on the sacrum (upper, back part of the pelvic cavity, between the two wings of the pelvis), the heels (large bony prominence connecting with the talus and cuboid bones), and the greater trochanter of the femur (large, irregular, quadrilateral bony prominence) The investigational dressings will only be applied on dry intact skin sites 

FUNDING

FUNDER	FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN
BELGIAN HEALTH CARE KNOWLEDGE CENTRE, Administrative Centre Botanique (Doorbuilding) Boulevard du Jardin Botanique 55 1000 Brussels, Belgium	

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Trial Management and Oversight Committees

Following trial management and oversight committees will be involved in the set-up, management and monitoring of the clinical study:

- **Project Team (PT)**

  The Project Team (PT) is responsible for the day-to-day management of the study. It is composed of the Chief Investigator (CI) team and project management team from DICE/DRC.

- **Trial Steering Committee (TSC)**

  The Trial Steering Committee (TSC) shall oversee the performance of the study and discuss important topics in relation thereto. The TSC shall meet every 4 months as required and send reports to the study funder. It is composed of the following members:

  - Dimitri Beeckman (chair)
  - Frank Hulstaert
  - Marianne Devis
  - Mieke Denys
  - Bénédicte Manderlier
  - Filip Deforce
  - A representative from a participating site
  - Up to two representatives of patients or the public

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KEY WORDS:	Pressure ulcer, prevention, multilayer foam dressings, multicentre randomised controlled parallel group medical device trial.

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ADE	Adverse Device Effect
AE	Adverse Event
APR	Annual Progress Report
AR	Adverse Reaction
ASADE	Anticipated Serious Adverse Device Effect
CA	Competent Authority
CE	Conformité Européenne
CI	Chief Investigator
CMH	Cochran-Mantel-Haenszel
COS	Core Outcome Set
CRF	Case Report Form
CRO	Contract Research Organisation
DSUR	Development Safety Update Report
DTI	Deep Tissue Injury
EC	Ethics Committee
EDC	Electronic Data Capture
EU	European Union
GCP	Good Clinical Practice
IAD	Incontinence-associated dermatitis
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
ICU	Intensive Care Unit
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
ISF	Investigator Site File
ITT	Intent to treat
KCE	Belgian Healthcare Knowledge Centre
MDI	Medical Device Incident
MRI	Magnetic Resonance Imaging
MS	Member State
NIMP	Non-Investigational Medicinal Product
PI	Principal Investigator
PIS	Patient Information Sheet
PP	Per Protocol

PU	Pressure Ulcer
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSI	Site Specific Information
USADE	Unanticipated Serious Adverse Device Effect
TSC	Trial Steering Committee
TMF	Trial Master File

1 INTRODUCTION

1.1 BACKGROUND

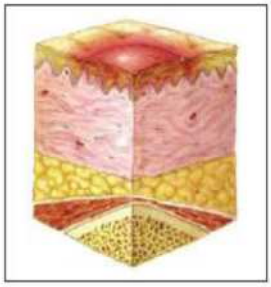
A pressure ulcer is defined as a **localized injury to the skin and/or underlying tissue usually over a bony prominence**, as a result of pressure, or pressure in combination with shear (National Pressure Ulcer Advisory Panel, 2014). The NPUAP/EPUAP classification system distinguishes four categories of pressure ulcers: non-blanchable erythema of the intact skin (category I), partial thickness loss of dermis (category II), full thickness tissue loss (category III) and full thickness tissue loss with exposed bone, tendon or muscle (category IV). Also unstageable pressure ulcers and deep tissue injuries can be recognised (National Pressure Ulcer Advisory Panel, 2014). Pressure ulcers are **associated with prolonged exposure to an applied external mechanical load**. This load comprises all types of external forces applied to the patient's skin and underlying tissue due to contact with support surfaces. The extent of skin and/or tissue damage depends on the **duration and magnitude of the applied load** (pressure and shear).

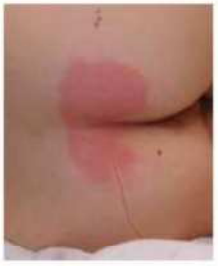
Medical device related pressure ulcers are out of the scope of the current trial. These pressure ulcers result from the use of devices designed and applied for diagnostic or therapeutic purposes. The resultant pressure ulcer generally conforms to the pattern or shape of the device.

Category/Stage I: Nonblanchable Erythema

Intact skin with non-blanchable redness of a localized area usually over a bony prominence. Darkly pigmented skin may not have visible blanching; its color may differ from the surrounding area.

The area may be painful, firm, soft, warmer or cooler as compared to adjacent tissue. Category/Stage I may be difficult to detect in individuals with dark skin tones. May indicate "at risk" individuals (a heralding sign of risk).



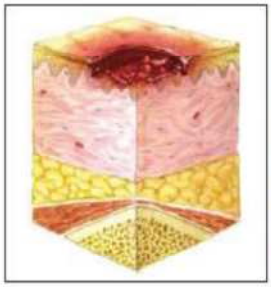


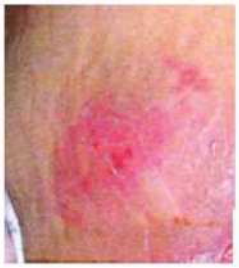
Category/Stage II: Partial Thickness Skin Loss

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-filled blister.

Presents as a shiny or dry shallow ulcer without slough or bruising.* This Category/Stage should not be used to describe skin tears, tape burns, perineal dermatitis, maceration or excoriation.

**Bruising indicates suspected deep tissue injury.*

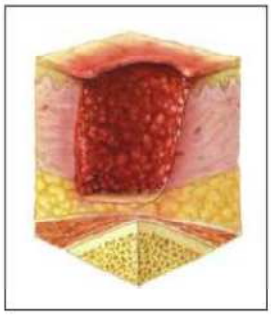


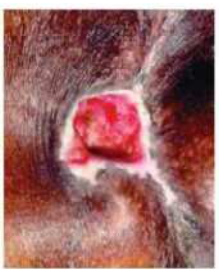


Category/Stage III: Full Thickness Skin Loss

Full thickness tissue loss. Subcutaneous fat may be visible but bone, tendon or muscle are not exposed. Slough may be present but does not obscure the depth of tissue loss. May include undermining and tunneling.

The depth of a Category/Stage III pressure ulcer varies by anatomical location. The bridge of the nose, ear, occiput and malleolus do not have subcutaneous tissue and Category/Stage III ulcers can be shallow. In contrast, areas of significant adiposity can develop extremely deep Category/Stage III pressure ulcers. Bone/tendon is not visible or directly palpable.





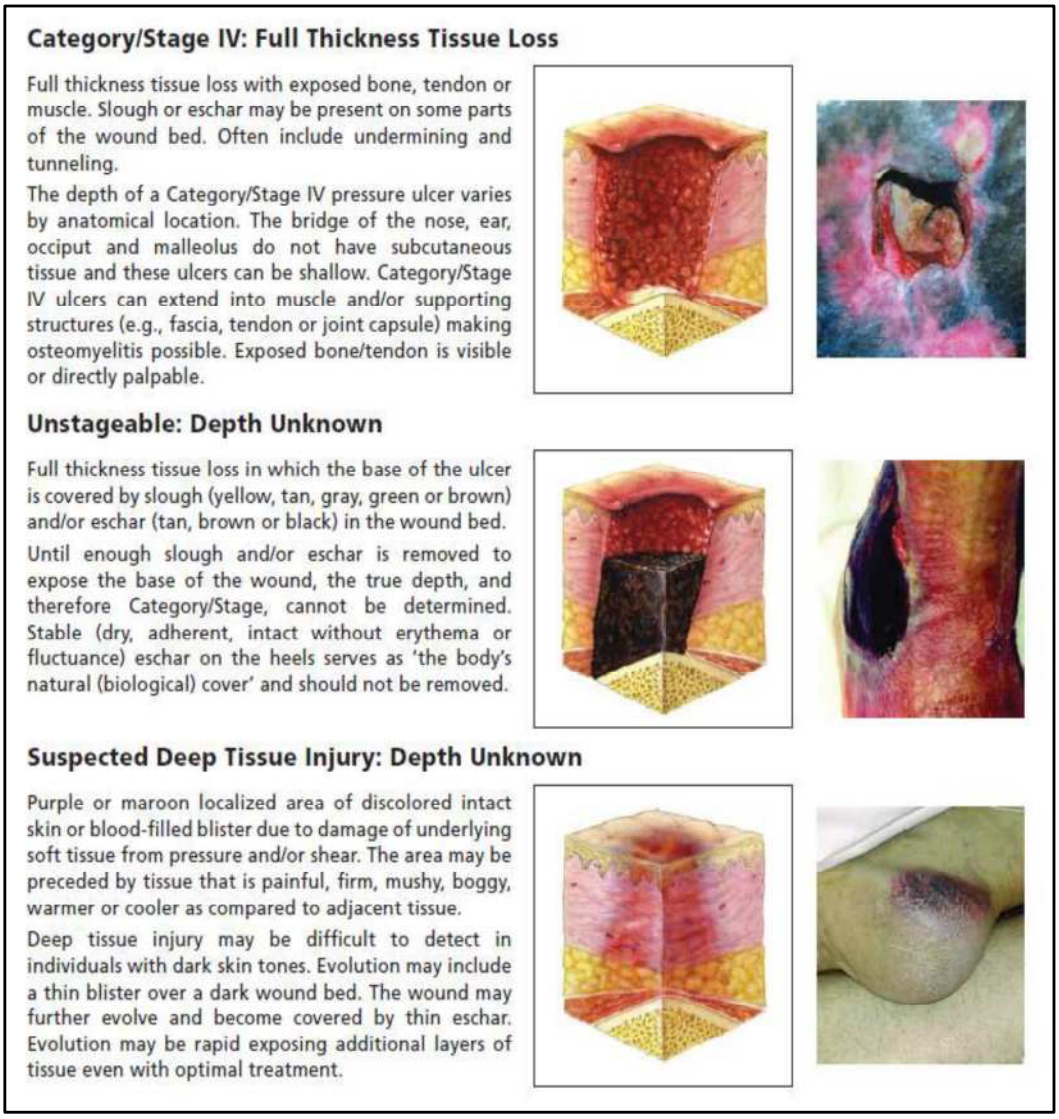


Figure 1: Pressure ulcer categories National Pressure Ulcer Advisory Panel (2014)

Pressure ulcers may occur on all body locations covering a bony prominence. However, two large scale studies, one in Belgium (Vanderwee, Defloor, Beeckman, Demarré, Verhaeghe et al., 2011) (n= 19968), and one in the Netherlands (Schoonhoven et al., 2007) (n=1229), reported that prevalence of pressure ulcers varies according to body location. Both studies determined that most of the category II-IV pressure ulcers occur in the sacral/ischial tuberosity/coccyx area (45.0% - 51.7%), and the heels (26.7% - 40.7%), followed by the greater trochanter (1.8% - 2.6%).

Table 1: Prevalence of pressure ulcer category II-IV

Location	PU prevalence (Cat. II-IV)	
	Vanderwee et al. (2011) n = 1676*	Schoonhoven et al. (2007) n = 172*
Sacral/ischial tuberosity/coccyx area	754 (45.0%)	89 (51.7%)
Heel area	682 (40.7%)	46 (26.7%)
Greater trochanter	44 (2.6%)	3 (1.8%)
Other (elbows, spine, ankle)	196 (11.7%)	34 (19.8%)

* Total number of observed pressure ulcers (Cat. II – IV) in the study

To prevent the development of pressure ulcers, the KCE clinical practice guideline recommends to reduce both the amount and the duration of pressure and shear (Beeckman, Matheï, Van Lancker, Van Houdt, Vanwalleghem et al., 2013). This includes the application of appropriate **support surfaces** (such as mattresses or cushions), combined with correct **patient repositioning** on a continuous basis. Heels should be free of all pressure permanently. A general comment of the authors was the limited available RCT evidence concerning preventive measurements or evidence based on studies with methodological weaknesses (Beeckman et al., 2013). Alternative approaches to achieving modification of applied mechanical loads (such as the use of multilayer foam dressings) were not considered in these practice guidelines.

Currently, interest is growing in the application of **multilayer foam dressings** (initially being used for wound treatment) as an **adjuvant prophylactic therapy for pressure ulcer prevention**. A multilayer foam dressing aims to act as an absorbent cushion on the skin. The foam dressing aims to promote the **redistribution of pressure and shearing forces** over a larger area and reduce the amount of pressure over the bony prominence (e.g. sacrum). In addition, it is suggested that the presence of multiple layers **reduces shearing forces**. Furthermore, the foam structure of the dressing aims to promote the **moisture absorbing capacity** of the dressing, which is assumed to be beneficial for the moisture balance on the skin (microclimate) (Clark, Black, Alves, Brindle, Call et al., 2014; Davies, 2016; Santamaria et al., 2015). Referring to the KCE clinical practice guideline described above, multilayer foam dressings focus on the reduction of the amount of pressure and shear (not on the duration of the applied load on the tissue).

The **biomechanical efficacy** of dressings in preventing heel ulcers has been recently studied by the research group of Amit Gefen (Levy, Frank, & Gefen, 2015; Levy & Gefen, 2016). For this purpose, a 3D computational model was derived from medical imaging (MRI). The researchers measured the exposure of the soft tissues at the patients' heels to compression, tension and shear without any dressing, with a single layer dressing and a multilayer dressing. The use of the multilayer dressing consistently and considerably reduced soft tissue exposures to strains due to compression or combined compression and shear on various support surfaces (Levy et al., 2015). Furthermore, the exposure to elevated strains was also reduced in diabetic tissue conditions (Levy & Gefen, 2016). According to the authors, these results suggest that a multilayer foam dressing provides a **cushioning effect** to the soft tissues of the heel, and **tempers tissue deformation** and the consequent risk for pressure ulcer development (Levy & Gefen, 2016). **Randomised controlled clinical trials were recommended** to examine the clinical effectiveness of dressings for the prevention of heel pressure ulcers (Levy et al., 2015).

The clinical effectiveness of a multilayer foam dressing as a preventative intervention for pressure ulcers has been summarized in **three systematic reviews** (Clark et al., 2014; Davies, 2016; Moore & Webster, 2013). In addition, a consensus panel formulated recommendations based on a literature search (Black, Clark, Dealey, Brindle, Alves et al., 2015).

A **first (Cochrane) systematic review**, including four randomised controlled trials and 561 participants, concluded that the use of dressings (foam dressings or a hydrocolloid dressing) was associated with a significant decrease in pressure ulcer incidence (Moore & Webster, 2013) (relative risk 0.21, 95% confidence interval 0.09-0.51). Foam dressings were tested in three RCT's including patients undergoing back surgery (Jing, Guizhi, Aimin et al., 2011), ICU patients (Kalowes, Carlson, Carr, Llantero, Lukaszka et al., 2013), and neurosurgical patients (Qiuli, 2010). For two trials, little information was found on the methods used (Jing, 2011; Kalowes et al., 2013). The authors reported **unclear or high risk of bias** for all included studies (e.g. small sample sizes, short follow-up periods) and **recommended** further **well-designed trials** addressing important clinical, and economic outcomes based on the incidence of the problem and the high costs associated with PU management.

A **second systematic review**, including 4 RCT's, 7 cohort studies and 11 case studies, suggested that the introduction of a dressing as part of pressure ulcer prevention may help reduce pressure ulcer incidence, especially in immobile intensive care patients (Clark et al., 2014). **The authors found no evidence that one dressing type was more effective than another.** The quality of the RCT's and cohort studies ranged from low to moderately high. Only one RCT (Santamaria, Gerdtz et al., 2015) compared foam dressings with the use of no dressings. This RCT determined a significant reduction in pressure ulcer incidence using a soft silicone foam dressing. Common failings of the RCT's and cohort studies concerned lack of randomisation, small sample size, blinding of treatment allocation and outcome assessment, and insufficient reporting of statistical data. The authors **recommended large scale studies**, similar to the RCT from Santamaria, Gerdtz (Santamaria, Gerdtz et al., 2015), to ascertain the most appropriate patient populations, and anatomical locations for the use of multilayer foam dressings as a preventative intervention for pressure ulcers.

A **third systematic review** was restricted to studies examining the benefits of multilayer foam dressings with Safetec® technology: 3 RCTs, 6 non-randomised trials with concurrent controls, 17 non-randomised trials with historical controls, 4 case series without controls, and 10 reviews. The reviewers concluded that the **use of a multi-layer foam dressing can reduce the occurrence of PUs on anatomical locations such as the sacrum and the heel, and underneath medical devices**. The RCT's identified (Black et al., 2015; Levy & Gefen, 2016; Moore & Webster, 2013) were similar to those included in the reviews above. It is important to address that **no quality assessments of the included studies** were reported.

A 2016 best practice document recommends the use of multilayer foam dressings combined with standard preventive interventions for pressure ulcer prevention in emergency care, intensive care and during surgery (WUWHS, 2016). The recommendations were based on one RCT (Santamaria, Gerdtz et al., 2015) and three cohort studies (Brindle & Wegelin, 2012; Chaiken, 2012; Walsh, Blanck, Smith, Cross, Andersson et al., 2012). The development of the document was funded by Mölnlycke Healthcare and was not based on a systematic review of original studies. None of the primary studies was subjected to a quality assessment of the research methods. The experts expressed the need for comparative studies in other patient groups.

One single centre non- blinded RCT on the effectiveness of foam dressings was found which was adequately powered (Santamaria, Gerdtz et al., 2015). This study was performed in a specific population of **440 trauma patients and critically ill patients**. A five-layer silicone foam dressing was applied to the sacrum and a three-layer foam dressing was applied to heels. Significantly less patients from the intervention group developed pressure ulcers at the sacrum (2/219 vs. 8/221, $p = 0.001$) and at the heels (5/219 vs. 19/221, $p = 0.002$). A reduction in pressure ulcer incidence of 10.0% (3.1% versus 13.1%) was determined. Data about pressure ulcer severity/grading were not reported. The authors recommended future multicentre studies, not restricted to critically ill patients to confirm their results and to **enhance generalizability**. Mölnlycke Healthcare provided a research grant and the dressings for this trial.

The RCT mentioned in above paragraph was the only study which also examined the cost effectiveness of multi-layered foam dressings to prevent sacral and heel pressure ulcers (Santamaria, Liu et al., 2015). The study was performed from a health care sector's perspective in one Australian hospital. The costs were derived from dressing material costs and labour costs. The authors concluded that **the costs of the dressings and the time for dressing application were largely exceeded by the costs associated with pressure ulcer treatment in critically ill patients**. Costs associated with a prolonged length of hospital stay were not taken into account because in these particular patient group, pressure ulcers were not assumed to prolong the hospital stay. Follow-up of patients undergoing pressure ulcer treatment, after transferring from intensive care to at least other hospital wards, has been recommended for a more accurate calculation of treatment costs (Santamaria, Liu et al., 2015).

Currently, **two single centre studies on the use of foam dressings are in progress**. One study examines the effectiveness of two silicone dressings for sacral and heel pressure ulcer prevention in critically ill patients (ClinicalTrial.gov: NCT02295735). Data are collected between June 2015 and December 2017 in one teaching hospital in Germany. The other study examines the effectiveness of a polyurethane foam for sacral pressure ulcer prevention in elderly people with hip fractures (ClinicalTrial.gov: NCT02692482). Data are collected between March and August 2016 in an Italian hospital. The results of this trial are not yet published.

By conducting this randomised controlled trial, we aim to gain insight into the effectiveness of silicone adhesive multilayer foam dressings, as an adjuvant prophylactic therapy for pressure ulcer prevention. The study will be performed on a large scale, including 1662 hospitalised patients at risk of pressure ulcer development. The study will be executed in different wards in both teaching hospitals and general hospitals in Belgium to increase the likelihood of an appropriate case mix and thus generalizability of the conclusions.

The following silicone adhesive multilayer foam dressings will be included in this study:

- Silicone adhesive multilayer foam dressings by Smith & Nephew (Allevyn® brand, type: Allevyn® Life, Allevyn® Life Sacrum and Allevyn® Life Heel)
- Silicone adhesive multilayer foam dressings by Mölnlycke Health care (Mepilex® brand, type: Mepilex® Border, Mepilex® Border Sacrum, Mepilex® Border Heel)

Note: Changes to the investigational dressings' design (but keeping the same range of indications*) and marketing driven relabeling of the current investigational devices may occur and will be discussed by the trial steering committee (TSC). After approval by the TSC, these dressings will be allowed in the trial. An ad hoc TSC meeting may be needed in order not to put the study on hold at any time for this reason.*

1.2 RATIONALE

In 2012 and 2013, the Belgian Healthcare Knowledge Centre (KCE) and the CI of the current application published two practice guidelines for the prevention and treatment of pressure ulcers (Beeckman et al., 2013; Beeckman et al., 2013). Pressure ulcers are (and remain) a common problem for healthcare. A large scale Belgian prevalence study in 2008 (n = 19968) reported a pressure ulcer prevalence of 12.1% in hospitals (Vanderwee et al., 2011). Since 2008, many international studies have been published about pressure ulcer epidemiology and all of them showed similar results in both primary and secondary healthcare (Gorecki, Brown, Nelson, Briggs, Schoonhoven et al., 2009). The consequences of pressure ulcers for patients include pain, discomfort, a decrease in quality of life and an increase in morbidity and mortality (Gorecki et al., 2009; Hopkins, Dealey, Bale, Defloor, & Worboys, 2006). Besides, treatment of pressure ulcers is associated with an increase in health care expenditures, as a consequence of supplementary work load, wound care products, hospitalisation or prolonged hospitalisation (Demarré, Verhaeghe, Annemans, Van Hecke, Grypdonck et al., 2015; Schuurman, Schoonhoven, Defloor, van Engelshoven, van Ramshorst et al., 2009; Severens, Habraken, Duivenvoorden & Frederiks, 2002). According to Demarré et al. (2015), the mean costs for pressure ulcer treatment in Belgian hospitals varies between 2.34 EURO and 77.36 EURO per patient per day. Internationally, the cost of pressure ulcer prevention per patient per day varied between 2.65 EURO to 87.57 EURO across all settings. The cost of pressure ulcer treatment per patient per day ranged from 1.71 EURO to 470.49 EURO across different settings. The methodological heterogeneity among studies was considerable, and encompassed differences regarding type of health economic design, perspective, cost components, and health outcomes (Demarré et al., 2015).

Based on the literature review, we can conclude that there is **limited and not generalizable evidence on prophylactic dressings for preventing pressure ulcers**. The current evidence on effectiveness and cost effectiveness of prophylactic dressings is

limited to individuals requiring critical care/intensive care, with dressings generally applied on first contact with health professionals (e.g. in the emergency department). **The evidence mainly focuses on one specific dressing (Mepilex®, Mölnlycke Health Care)**. This dressing comprises five layers: a backing film which faces the support surface, an airlaid layer, a nonwoven layer, a polyurethane foam layer and a Safetec® layer that adheres to the skin and minimises trauma on dressing removal (Levy & Gefen, 2016). In clinical practice, **a broad range of foam dressings are currently being applied**, varying in composition, size, adhesion to the skin, and whether or not designed to fit specific anatomical locations (e.g. sacrum, heels). The available dressings are mainly applied for the treatment of pressure ulcers (or other skin lesions) rather than for the prevention of pressure ulcers.

Since the prevalence of pressure ulcers remains high (Vanderwee et al., 2011) and the treatment of pressure ulcers is associated with considerable costs (Demarré et al., 2015), high quality research on additional interventions for the prevention of pressure ulcers is urgently needed. (Multilayer) foam dressings seem to be promising as an additional prophylactic intervention. However, evidence demonstrating that the clinical and cost effectiveness of foam dressing for pressure ulcer prevention in a heterogeneous patient population is lacking.

The control intervention is defined as pressure ulcer prevention according to the current national prevention guidelines. Current practice in hospitals in Belgium reflect the KCE guidelines for prevention and treatment of pressure ulcers (Beeckman et al., 2013; Beeckman et al., 2013) and the 2014 international guidelines (National Pressure Ulcer Advisory Panel, 2014). In summary, current practice includes:

- The application of a structured approach for **risk assessment** at the first contact with the patient. Reassessment is performed at regular time intervals and if there is any change in the patient's medical condition.
- The conduct of a **comprehensive head-to-toe skin assessment** with special attention to vulnerable areas.
- The introduction and documentation of a **tailored repositioning plan** (including specifications about posture and frequency) for each patient at risk for pressure ulcer development.
- The use of appropriate **pressure redistributing devices** (low-tech constant low pressure surfaces or high-tech support surfaces) for individuals at risk of pressure ulcers development. Decisions about which pressure redistributing device to use are based on an overall assessment of the individual including level of risk, comfort and general health state.
- The use of devices to ensure that **heels are free of the support surface**
- Monitoring of the **nutritional status** of individuals as part of a general assessment procedure

Pressure ulcers may occur on all bony prominences and prevalence figures vary depending on body location. In addition, silicone adhesive multilayer foam dressings are expensive. In this randomised controlled clinical trial, silicone adhesive multilayer foam dressings will be used on sacrum, heels, and greater trochanter. The specific skin sites cover the vast majority of all body locations at risk for pressure ulcer development (Vanderwee et al., 2011; Schoonhoven et al., 2007).

1.2.1 Assessment and management of risk

This study is considered a low risk clinical study. The silicone adhesive multilayer foam dressings are CE-marked and available on the Belgian market. They will be used in accordance with the product insert. Furthermore, all investigator teams will be trained by the dressing suppliers in the application and use of their respective dressings. The study will be conducted and monitored according to GCP guidelines.

2 OBJECTIVE AND PRIMARY ENDPOINT

2.1 Objective

The objective of this study is to determine if silicone adhesive multilayer foam dressings applied to the sacrum, heels and greater trochanter in addition to standard prevention reduce pressure ulcer incidence category II, III, IV, Unstageable and Deep Tissue Injury (DTI) compared to standard pressure ulcer prevention alone, in at risk hospitalised patients. In particular, this trial extends previous trial results obtained in ICU setting. **Therefore, only a maximum of 25% of patients will be recruited from ICU settings.**

The **hypothesis** is: 'The use of silicone adhesive multilayer foam dressings as adjuvant prophylactic therapy for pressure ulcer prevention is more effective in reducing pressure ulcer category II, III, IV, Unstageable, and Deep Tissue Injury (DTI) incidence rate on sacrum, heels and greater trochanter, compared to standard pressure ulcer prevention alone.'

The **null hypothesis** is: 'The use of silicone adhesive multilayer foam dressings as adjuvant prophylactic therapy for pressure ulcer prevention is not more effective in reducing pressure ulcer category II, III, IV, Unstageable, and Deep Tissue Injury (DTI) incidence rate on sacrum, heels and greater trochanter, compared to standard pressure ulcer prevention alone.'

2.2 Primary Endpoint

The primary endpoint of this study is the incidence rate during the study period of the patient (during maximum 14 days) of at least one new pressure ulcer category II, III, IV, Unstageable, Deep Tissue Injury (DTI) (briefly referred to as pressure ulcers category II or worse) on sacrum, heels and greater trochanter as judged on site.

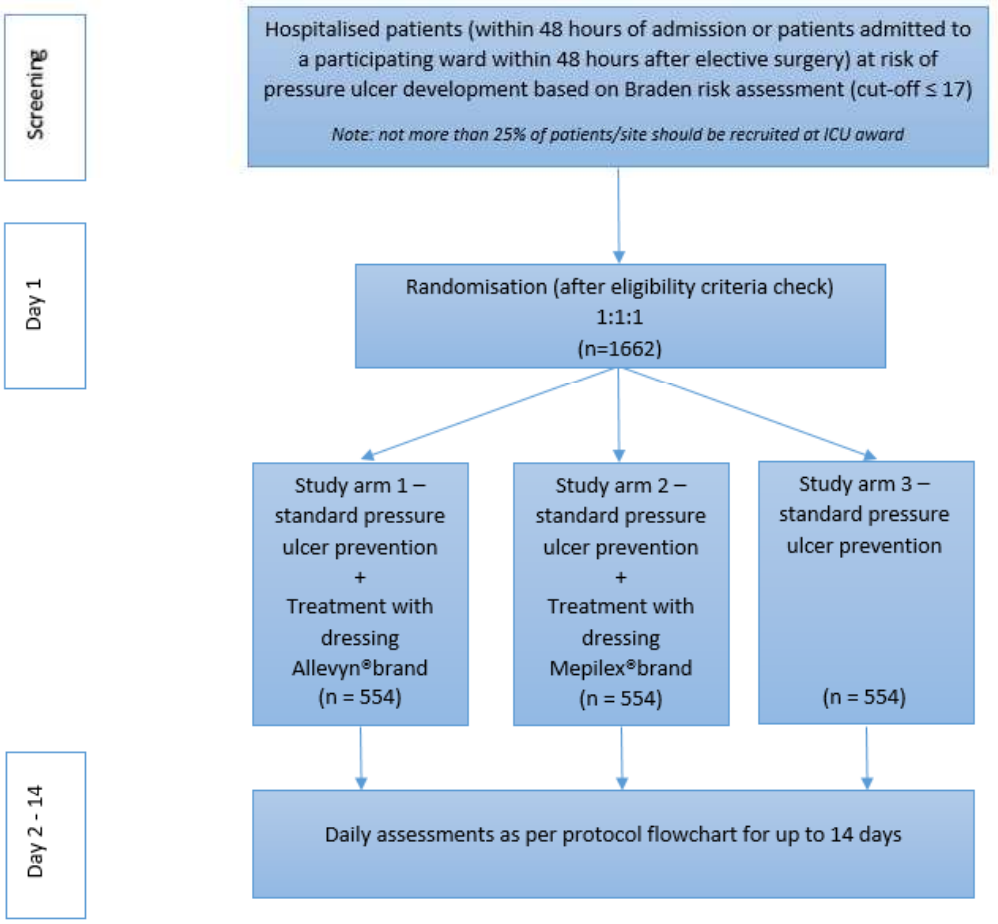
3 INVESTIGATIONAL PLAN

3.1 Study Design

Multicentre, randomised, open label, parallel group medical device trial in approximately 8 hospitals in Belgium.

3.2 Investigation Population

The investigational population includes hospitalised patients at risk for pressure ulcer development in teaching and general hospitals.



Note that most (about 70%) patients admitted to the participating wards are not at risk for pressure ulcer development according to Braden score cut-off used in this study (<= 17). In addition, about 15% of patients at risk will likely not meet all eligibility criteria.

3.2.1 *Hospital eligibility.*

In most hospitals in Belgium no dressings are currently used in the prevention of pressure ulcers. Those hospitals where dressings are currently used in the prevention of pressure ulcer in smaller or larger at risk groups as part of the standard of care cannot participate to this trial and need to discontinue their participation to the trial if the hospital introduces such practice. The use of dressings for routine care prevention of pressure ulcers in participating hospitals will therefore remain limited to exceptional cases. and, if known in advance, such patients will not be eligible for trial participation.

3.2.2 *Patient Eligibility criteria*

3.2.2.1 *Inclusion criteria*

Following inclusion criteria will be applied:

1. At risk for pressure ulcer development based on Braden risk assessment (Braden score ≤17).

2. Admitted to hospital within the previous 48 hours.

   Note: Not more than 25% of patients per site should be recruited at ICU wards.

3. Skin at sacrum is assessable and there is no clinically relevant incontinence-associated dermatitis (IAD) or another skin condition that would be a contra-indication for the application of the devices under study, and there is no pressure ulcer category II or worse present.
   **clinically relevant IAD is defined as any of the 4 categories described in the publication http://users.ugent.be/~dibeeckm/globiadnl/nlv1.0.pdf*

4. for at least 3 of the following 4 skin sites (heel left, heel right, greater trochanter left, greater trochanter right) one of the following two conditions should apply:

   - A study dressing can be applied as prevention of a pressure ulcer category II or worse at that skin site (there is no contra-indication)

     OR

   - There is already a pressure ulcer category II or worse at that skin site.

5. Written informed consent by the patient or his/her legal representative.

3.2.2.2 Exclusion criteria

Following exclusion criteria will be applied:

1. Aged < 18 years.
2. The length of stay counting from first day of admission in one or (if the patient is transferred to another ward) more participating wards is < 7 days.
3. Both heels amputated
4. Previously known/documented allergy for substances used in the devices under study.
5. A clinical condition not allowing participation in a clinical study.
6. Participation in another interventional clinical trial.
7. Patients who exceptionally receive or are planned to receive a dressing for the prevention of pressure ulcers at sacrum, heels and trochanters based on best medical judgment and outside of the surgery setting.

3.2.3 Prohibition and restrictions

Following instructions will be followed regarding the admission of patients within the Clinical Investigation.

Study arm 1:

- Patients will be cared for on the available support surfaces of the hospital (mattresses, cushions) for the duration of their hospital admission.
- Patients will receive standard pressure ulcer prevention strategies (as described in the hospital protocol) which include ongoing risk assessment, regular repositioning and skin care.
- Silicone adhesive multilayer **foam dressings by Smith & Nephew** (Allevyn® brand, type: Allevyn® Life, Allevyn® Life Sacrum and Allevyn® Life Heel) will be applied on to dry intact skin on sacrum, heel right/left, greater trochanter right/left, in addition to standard pressure ulcer prevention.
- Dressings will not be applied to skin areas affected by clinically relevant incontinence-associated dermatitis (IAD) or other skin conditions that are a contra-indication for the application of the dressing and there is no pressure ulcer category II or worse present
- Emollients or other skin barrier products will not be applied to prevent adhesion issues of the dressing to the skin site.

- The procedure for dressing application and frequency of re- application will be followed as described by the manufacturer.
- Dressings will be maintained on the treatable skin sites and changed if they become soiled or dislodged.
- The skin beneath the dressing will be inspected on a daily basis.

Study arm 2:

- Patients will be cared for on the available support surfaces of the hospital (mattresses, cushions) for the duration of their hospital admission.
- Patients will receive standard pressure ulcer prevention strategies (as described in the hospital protocol) which include ongoing risk assessment, regular repositioning and skin care.
- Silicone adhesive multilayer **foam dressings by Mölnlycke Health care** (Mepilex® brand, type: Mepilex® Border) will be applied on to dry intact skin on sacrum, heel right/left, greater trochanter right/left, in addition to standard pressure ulcer prevention.
- Dressings will not be applied in skin areas affected by clinically relevant incontinence-associated dermatitis (IAD) or other skin conditions that are a contra-indication for the application of the dressing and there is no pressure ulcer category II or worse present.
- Emollients or other skin barrier products will not be applied to prevent adhesion issues of the dressing to the skin site.
- The procedure for dressing application and frequency of re- application will be followed as described by the manufacturer.
- Dressings will be maintained on the treatable skin sites and changed if they become soiled or dislodged.
- The skin beneath the dressing will be inspected on a daily basis.

Study arm 3:

- Patients will be cared for on the available support surfaces of the hospital (mattresses, cushions) for the duration of their hospital admission.
- Patients will receive standard pressure ulcer prevention strategies (as described in the hospital protocol) which include ongoing risk assessment, regular repositioning and skin care.
- **No silicone adhesive multilayer foam dressings** will be applied on any skin sites to prevent pressure ulcer development.
- The skin on sacrum, heel right/left, trochanter right/left will be inspected on a daily basis.

3.2.4 Discontinuation of study

Patients will be informed prior to study entry that they are free to withdraw from the study at any time and for any reason, without jeopardizing their clinical care. Patients withdrawing from the study before Day 14 will be encouraged (if possible) to complete the assessments as listed for Day 14 (see section 4.4.4).

The study for the patient will be discontinued for any of the following reasons:

- The patient is no longer at risk of pressure ulcer development according to the Braden scale (Braden score >17).
- The sponsor closes the study
- The patient wishes to withdraw from the study*
- Discharged from the hospital
- Moved to a non-participating ward
- Death

*In case the patient or their legal representative withdraws consent, it should be documented whether the data collected from that patient can still be kept in the study and used for the analysis which will be the default assumption.

3.2.5 *Discontinuation of study intervention.*

The investigator *may* discontinue the study intervention for any of the following reasons:

- Non-compliance with study procedures
- Life-threatening AE or serious adverse event (SAE) that places the patient at immediate risk if the study intervention would be continued
- The patient shows a worsening of his/her medical condition, which in the investigator's opinion requires a discontinuation of the study intervention
- Patient's best interest

However, the investigator should continue the collection of patient data and study endpoints as long as possible up to study day 14 (see section 4.4.4) if the patient is still on a participating ward and still at risk for pressure ulcer development (Braden score <=17).

The intent to treat principle

Despite the fact that at one or more body location dressings are not or no longer applied because of incontinence- associated dermatitis or for whatever reason, the daily assessments of the body locations under study and recording of any new pressure ulcers category II or worse should continue as long as the patient is considered at risk for the development of pressure ulcers or until the patient is discharged from the participating wards or until study day 14, whatever comes first. Any such new pressure ulcers of category II or worse will be included in the ITT analysis, but may be excluded from the PP analysis if a major protocol violation was detected.

In case the patient or their legal representative withdraws consent, it should be documented whether the data collected from that patient can still be kept in the study and used for the analysis which will be the default assumption.

3.3 Investigational products

3.3.1 Identity of the investigational devices

Two silicone adhesive multilayer foam dressings will be tested in this study: (1) Allevyn® Life (Smith & Nephew) and (2) Mepilex® Border (Mölnlycke Health care). Both are available on the Belgian market. The different shapes and sizes of the dressings are shown below.

3.3.1.1 Allevyn® Life – Smith & Nephew

Smith & Nephew developed the Allevyn® range of absorbent foam dressings for the treatment and prevention of wounds. The Allevyn® range is divided into the Allevyn® Classic products, such as Allevyn® (non-)Adhesive and Allevyn® Gentle (Border), and the Allevyn® Life, an advanced layered dressing used for treatment and prevention of pressure ulcers. An overview of the different sizes and shapes are presented in the table below. The procedure for dressing application and frequency of re- application should be followed as described by the manufacturer.

Allevyn® Life 12.9 X 12.9	
Allevyn® Life Sacrum 21.6 x 23	
Allevyn® Life Heel 25 x 25.2	

3.3.1.2 Mepilex® Border – Mölnlycke Health care

Mölnlycke Health care developed foam dressings for the treatment and prevention of wounds under the brand name Mepilex®. Different foam dressings are available on the Belgian market e.g. adhesive and non-adhesive. The prevention of pressure ulcers has been studied using the Mepilex® Border. An overview of the different sizes and shapes are presented in the table below. The procedure for dressing application and frequency of re-application should be followed as described by the manufacturer.

Mepiplex® Border 15x15	
Mepilex® Border Sacrum 22 X 25	
Mepilex® Border Heel 22 X 23	

3.3.2 Product insert

The study devices will be used in accordance with their insert in this study. All devices used in this study are CE-marked. The CE certificate numbers are CE 01965 (Mepilex® foam dressings), and CE 00356 (Allevyn® foam dressings). Both the Allevyn® and Mepilex® Border are silicone adhesive multilayer foam dressings. The two technologies are described below.

3.3.2.1 *Allevyn® (Smith & Nephew)*

The Allevyn® Life dressings consist of 5 layers: (1) the top layer consists of a breathable film of polyurethane film with an acrylic adhesive (Opsite®), (2) a protective layer consisting of polyester, (3) a hyperabsorbent padding layer consisting of cellulose and polyacrylate, (4) an absorbent hydrocellular polyurethane foam and (5) the layer in contact with the skin consisting of a polyurethane film coated with a silicone gel adhesive. The Allevyn® Life products do not contain latex, colophony and PVC.

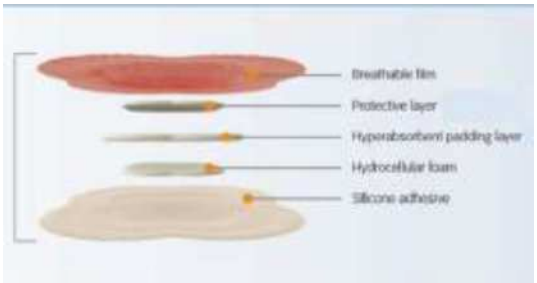


Figure 2: Allevyn® Life technology

3.3.2.2 *Mepilex® (Mölnlycke Healthcare)*

The Mepilex® dressings consists of a 5-layer absorbent foam structure including the Safetac® technology (see figure below). Safetac® is the adhesive layer of the dressing, which gently adheres to the skin, minimizing damage and trauma to the skin.

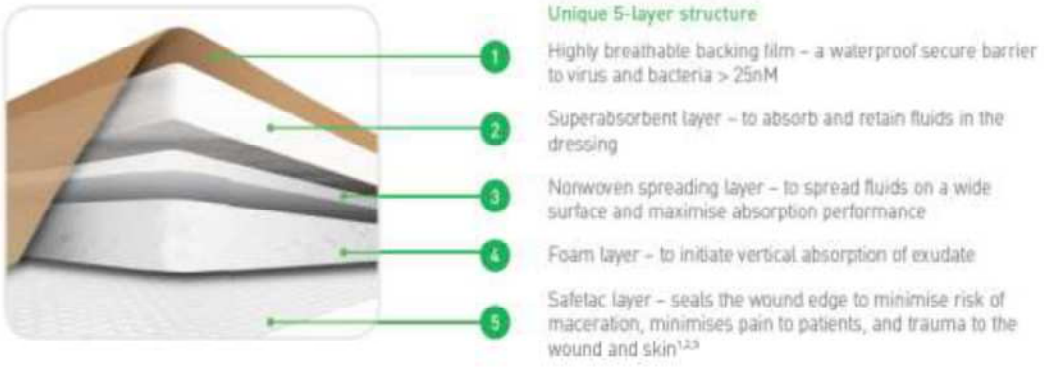


Figure 3: Mepilex® Safetac® technology

3.3.3 *Device storage and supply*

The silicone adhesive multilayer foam dressings need to be stored in a dry location at room temperature, and away from sunlight. The devices will be delivered to the hospital pharmacy.

3.3.4 *Contra-indications for use*

3.3.4.1 *Allevyn® (Smith & Nephew)*

According to the product label, do not use ALLEVYN® Life dressing with oxidising agents such as hypochlorite solutions (e.g. EUSOL) or hydrogen peroxide, as these can break down the absorbent polyurethane component of the dressing

Do not use on infected wounds.

In addition, as per inclusion criterium 3, do not use on skin site with clinically relevant IAD.

3.3.4.2 Mepilex® (Mölnlycke Healthcare)

According to the product label, do not use in conjunction with oxidizing agents such as hypochlorite solutions or hydrogen peroxide.

Do not use on infected wounds

In addition, as per inclusion criterium 3, do not use on skin site with clinically relevant IAD.

3.3.5 Concomitant medication/devices

During the study period, all other care provided is at the discretion of the attending clinical team.

4 STUDY ASSESSMENTS

4.1 Flowchart

	Assessments (Day)														
Procedure	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14***
	Pre-randomisation baseline data	**Randomisation and after randomisation**													
Informed consent	X														
Demographics (date of birth, gender, weight, length, BMI, diabetes, …)	X														
Applied PU prevention (support surface, repositioning, heel elevation)	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Braden Risk assessment (including sub-scores)	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Pre-existing pressure ulcer category I	X														
Visual inspection of the skin sites	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Check in- and exclusion criteria	X														
Ward type	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Skin moisture	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of life (EQ5D)	X			X											(x*)
Randomisation		X													
Dressings application		X	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)
Number of dressing changes between assessments			X	X	X	X	X	X	X	X	X	X	X	X	X
Pressure ulcer Cat. II, III, IV, Unstageable, Deep Tissue Injury (DTI)			(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)
Photograph of new pressure ulcer Cat II and above			(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)
Photograph on last day in trial															(x)*
Safety evaluation		(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)
Early discontinuation of intervention (including reason)			(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)

X = obligatory, (x) = if appropriate, * If the study duration of the patient is shorter than 14 days, these assessments will be done on the last day of the study participation of the patient.

4.2 Assessments

Pre-randomisation
• Possible eligible patients will be identified at ward level based on an initial assessment of pressure ulcer risk and estimated length of stay in the hospital (taking into account possible transfer to non- participating wards during hospital admission). • The initial risk assessment will be performed using the risk assessment procedure of the hospital.
• The trial nurse will evaluate how many new patients that can be enrolled in the trial (based on workload) and will select those patients from the list with the highest pressure ulcer risk profile (evaluation based on hospital procedures) for further screening.
• The trial nurse will visit possible eligible patients and will check all criteria for participation (including risk assessment according to Braden). If a patient is deemed eligible for inclusion, information about the trial procedures will be provided and the patient or the legal representative will be invited to sign the informed consent documents.
• The trial nurse will collect all pre- randomisation data (see section 4.4.1) and performs all data input using eCRF.
• The skin sites of interest (sacrum, heels right/left and greater trochanter right/left) will be assessed by the trial nurse.
• Skin sites being affected at baseline by a pressure ulcer category II, III, IV, Unstageable, DTI will be treated according to hospital standard care and followed-up by the local wound care team and ward nurses according to hospital procedures. These particular skin sites will not be treated nor be followed- up for the purpose of this trial.

Randomisation and post- randomisation
• After informed consent has been obtained, the patient will randomly be assigned (based on eCRF allocation information) to one of the study arms.
• For patients in the experimental group (study arms 1 and 2), the investigational dressings will be applied on the sacrum (upper, back part of the pelvic cavity, between the two wings of the pelvis), the heels (large bony prominence connecting with the talus and cuboid bones), and the greater trochanter of the femur (large, irregular quadrilateral bony prominence).
• The dressings will only be applied on dry intact skin sites. The procedure for dressing application be followed is as described by the manufacturer.
• The trial nurse will collect post- randomisation data (see section 4.4.2) and performs all data input using eCRF.

Daily assessments (Day 2 – 14 or end of study)*
• The trial nurse will collect follow- up data (see section 4.4.3) and performs all data input in the eCRF.
• Quality of life data will be collected on day 3 and day 14 (or when the patient has a last daily assessment before day 14, at this time). *
• The skin sites of interest (sacrum, heels right/left and greater trochanter right/left) will be assessed by the trial nurse. In the experimental arms, the dressing will be lifted and re-applied to allow daily skin assessment.
• The occurrence of a new pressure ulcer category II, III, IV, Unstageable, DTI will be recorded. Photographs will be taken whenever a new category II, III, IV, Unstageable, DTI is observed. All photographs will be transferred to the CI for blinded central endpoint review. Guidelines on the taking and transfer of photographs can be found in the trial guidelines.

• Any newly occurred pressure ulcer will be treated according to hospital standard care and followed- up according to hospital procedures by the local wound team and ward nurses.
• Particular skin sites affected by a pressure ulcer category II or worse will no longer be treated within the trial. A high quality photograph will be taken of each pressure ulcer that occurred during the trial period at end of treatment of the location. All photographs will be transferred to the CI for blinded central review. *
• Other skin sites (not affected with a pressure ulcer category II or higher or clinically relevant IAD) will still be treated with trial intervention and followed- up for the purpose of the trial.
• For patients in the experimental group (study arm 1 and study arm 2), the procedure for dressing application and frequency of re- application be followed is as described by the manufacturer.
• Dressings will be changed if exudate is visible at the edge of the dressing (saturated dressing), when the dressing is no longer able to adhere fully, dislodged, rolled at the edges, wrinkled, creased or damaged, soiled or compromised in some other way. Each dressing change will be documented (including a justification). Each dressing change between two follow-up visits will be documented by the trial nurse in the eCRF.

* If patient prematurely discontinues trial intervention then these assessments should be performed on the last day of trial participation

End of study evaluation
• The trial nurse will collect end of study evaluation data (see section 4.4.4) and performs all data input using eCRF.

4.3 Recruitment

4.3.1 Patient identification

Eligible patients will be identified on participating wards, based on the inclusion and exclusion criteria. If a risk assessment tool other than the Braden scale is used on admission (e.g. Norton scale), this tool will be maintained to identify patients. Each day, the trial nurse will evaluate how many new patients that can be enrolled in the trial (based on workload) and will select those patients from the list with the highest pressure ulcer risk profile (evaluation based on hospital procedures) for further screening.

Eligible patients will be provided information concerning informed consent (see section 11.2).

After a patient is considered eligible according to the pressure ulcer risk assessment using the Braden score (Braden score $\leq$ 17), informed consent will be obtained for each patient. In addition, sacrum, heels, and greater trochanter will be assessed for the presence of pressure ulcers category II, III, IV, Unstageable, DTI and clinically relevant IAD or other skin conditions that are a contra-indication for the application of the study dressings.

4.3.2 *Braden Scale*

SENSORY PERCEPTION ability to respond meaningfully to pressure-related discomfort	**1. Completely Limited** Unresponsive (does not moan, flinch, or grasp) to painful stimuli, due to diminished level of consciousness or sedation OR limited ability to feel pain over most of body.	**2. Very Limited** Responds only to painful stimuli. Cannot communicate discomfort except by moaning or restlessness OR has a sensory impairment which limits the ability to feel pain or discomfort over ½ of body.	**3. Slightly Limited** Responds to verbal commands, but cannot always communicate discomfort or the need to be turned OR has some sensory impairment which limits ability to feel pain or discomfort in 1 or 2 extremities.	**4. No Impairment** Responds to verbal commands. Has no sensory deficit which would limit ability to feel or voice pain or discomfort.
MOISTURE degree to which skin is exposed to moisture	**1. Constantly Moist** Skin is kept moist almost constantly by perspiration, urine, etc. Dampness is detected every time patient is moved or turned.	**2. Very Moist** Skin is often, but not always moist. Linen must be changed at least once a shift.	**3. Occasionally Moist** Skin is occasionally moist, requiring an extra linen change approximately once a day.	**4. Rarely Moist** Skin is usually dry, linen only requires changing at routine intervals.
ACTIVITY degree of physical activity	**1. Bedfast** Confined to bed.	**2. Chairfast** Ability to walk severely limited or non-existent. Cannot bear own weight and/or must be assisted into chair or wheelchair.	**3. Walks Occasionally** Walks occasionally during day, but for very short distances, with or without assistance. Spends majority of each shift in bed or chair.	**4. Walks Frequently** Walks outside room at least twice a day and inside room at least once every two hours during waking hours.
MOBILITY ability to change and control body position	**1. Completely Immobile** Does not make even slight changes in body or extremity position without assistance.	**2. Very Limited** Makes occasional slight changes in body or extremity position but unable to make frequent or significant changes independently.	**3. Slightly Limited** Makes frequent though slight changes in body or extremity position independently.	**4. No Limitation** Makes major and frequent changes in position without assistance.
NUTRITION usual food intake pattern	**1. Very Poor** Never eats a complete meal. Rarely eats more than ⅓ of any food offered. Eats 2 servings or less of protein (meat or dairy products) per day. Takes fluids poorly. Does not take a liquid dietary supplement OR is NPO and/or maintained on clear liquids or IVs for more than 5 days.	**2. Probably Inadequate** Rarely eats a complete meal and generally eats only about ½ of any food offered. Protein intake includes only 3 servings of meat or dairy products per day. Occasionally will take a dietary supplement OR receives less than optimum amount of liquid diet or tube feeding.	**3. Adequate** Eats over half of most meals. Eats a total of 4 servings of protein (meat, dairy products) per day. Occasionally will refuse a meal, but will usually take a supplement when offered OR is on a tube feeding or TPN regimen which probably meets most of nutritional needs.	**4. Excellent** Eats most of every meal. Never refuses a meal. Usually eats a total of 4 or more servings of meat and dairy products. Occasionally eats between meals. Does not require supplementation.
FRICTION & SHEAR	**1. Problem** Requires moderate to maximum assistance in moving. Complete lifting without sliding against sheets is impossible. Frequently slides down in bed or chair, requiring frequent repositioning with maximum assistance. Spasticity, contractures or agitation leads to almost constant friction.	**2. Potential Problem** Moves feebly or requires minimum assistance. During a move skin probably slides to some extent against sheets, chair, restraints or other devices. Maintains relatively good position in chair or bed most of the time but occasionally slides down.	**3. No Apparent Problem** Moves in bed and in chair independently and has sufficient muscle strength to lift up completely during move. Maintains good position in bed or chair.	

Figure 4: The Braden Scale for Predicting Pressure Sore Risk (Bergstrom, Braden, Laguzza & Holman, 1987). Copyright. Barbara Braden and Nancy Bergstrom, 1988. Reprinted with permission. All Rights Reserved.

4.4 Variables to be collected

4.4.1 *Pre-randomisation*

- Did the patient sign informed consent?
- What is the Braden score (including sub-scores)?
- How many skin sites at risk for pressure ulcer development are dry and intact (free of skin damage, including incontinence- associated dermatitis), treatable and assessable?
- Is there a pre-existing pressure ulcer category I (non-blanchable erythema) present on the sacrum, heels right/left, greater trochanter right/left?
- Skin assessment of all 5 sites (pre-existing pressure ulcer, skin condition such that a dressing could potentially be applied, the skin condition is such that no dressing should be applied, skin site missing/not assessable, presence of another dermatological condition, presence of a pre-existing category I pressure ulcer – can answer more than 1 answer)
- Are there any known allergies to substances used in the investigational devices?
- What was the date of admission to hospital?
- What was the date of elective surgery (if any)?
- What is the expected length of stay on the participating wards?

- Is the skin at sacrum assessable and likely to remain assessable during the follow- up period?
- On which ward is the patient at the time of assessment?
- What is the date of birth of the patient?
- What is the gender of the patient?
- Quality of life: EQ-5D-5L subscales (mobility, self-care, daily activities, pain and discomfort, anxiety and depression, self-reported general health) completed by the patient or if the patient is not able completed by a proxy. In case the patient is unconscious a standard value will be used.
- If a skin site comes in contact with moisture: what is the type of moisture (sweat, urine, diarrhoea)?
- What is the patient's weight?
- What is the patient's length/height?
- What is the patient's Body Mass Index (calculated automatically)?
- Does the patient have diabetes?
- What type of support surface is used?
- Are the heels elevated from the bed?
- What is the frequency of repositioning (every 2 hours or more often, every 3-4 hours, every 5-6 hours or every 6 hours or longer)?

4.4.2 Randomisation and post- randomisation

- If randomised to an experimental group (study arms 1 and 2):
  - What is the type, shape and size of dressings used on the sacrum, heels right/left, greater trochanter right/left?

4.4.3 Daily assessments (as of the day after randomisation)

- On which ward is the patient at the time of assessment?
- What is the Braden score (including sub-scores)?
- If a skin site comes in contact with moisture: what is the type of moisture (sweat, urine, diarrhoea)?
- What was the number of re- applications of investigational devices since the last patient visit (and reason for change, type and shape)?
- Is there a pressure ulcer category II, III, IV, Unstageable, DTI present on the sacrum, heels right/left, greater trochanter right/left since the last patient visit?
- Has a photograph being taken if a pressure ulcer category II, III, IV, Unstageable, DTI present on the sacrum, heels right/left, greater trochanter right/left developed since the last patient visit?
- Did any Adverse Device Effect occur or was any Device Deficiency observed since the last patient visit?
- What type of support surface is used?
- Are the heels elevated from the bed?
- What is the frequency of repositioning (every 2 hours or more often, every 3-4 hours, every 5-6 hours or every 6 hours or longer)?
- If the patient completes/stops the study before Day 14: what was the reason for stopping prematurely (reasons have to be specified)?
- Only on Day 3: Quality of life: Consciousness status of the patient and EQ-5D-5L subscales (mobility, self-care, daily activities, pain and discomfort, anxiety and depression, self-reported general health) completed by the patient or if the patient is not able completed by a proxy. In case the patient is unconscious a standard value will be considered for the analysis.

4.4.4 *End of study evaluation: day 14 or day when a patient ends study*

- On which ward is the patient at the time of assessment?
- What is the Braden score (including sub-scores)?
- If a skin site comes in contact with moisture: what is the type of moisture (sweat, urine, diarrhoea)?
- What was the number of re- applications of investigational devices since the last patient visit (and reason for change)?
- Is there a pressure ulcer category II, III, IV, Unstageable, DTI present on the sacrum, heels right/left, greater trochanter right/left since the last patient visit?
- Is a photograph being taken if a pressure ulcer category II, III, IV, Unstageable, DTI present on the sacrum, greater trochanter right/left, heels right/left developed since the last patient visit?
- Is a photograph being taken of all pressure ulcer category II, III, IV, Unstageable, DTI on the sacrum, heels right/left, greater trochanter right/left developed during the study period?
- What type of support surface is used?
- Are the heels elevated from the bed?
- What is the frequency of repositioning (every 2 hours or more often, every 3-4 hours, every 5-6 hours or every 6 hours or longer)?
- Did any Adverse Device Effect occur or was any Device Deficiency observed since the last patient visit?
- If the patient completes/stops the study before Day 14: what was the reason for stopping prematurely (reasons have to be specified)?
- Quality of life: Consciousness status of the patient and EQ-5D-5L subscales (mobility, self-care, daily activities, pain and discomfort, anxiety and depression, self-reported general health) completed by the patient or if the patient is not able completed by a proxy. In case the patient is unconscious a standard value will be considered for the analysis.

4.4.5 *Image acquisition*

Trials nurses will be trained to take photographs of pressure ulcers. This will be described in the trial guidelines.

5 END OF STUDY

The end of Clinical Investigation is 30 days after last patient last visit. The sponsor will notify the central EC of the end of the study within 90 days of database lock for the primary endpoint.

6 SAFETY REPORTING

This section is structured in the following way. First of all definitions are given of the different events that might occur during a study. These definitions are structured along two axis: seriousness of the event and if the event is related to the device or not. Secondly it described what information is collected during this study. **Only events related to the medical device will be collected.** Thirdly it is explained what must be reported, who needs to report and how this reporting needs to be done.

6.1 Definitions

Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in patients, users or other persons whether or not related to the investigational medical device.
NOTE 1: This definition includes events related to the investigational device.
NOTE 2: This definition includes events related to the procedures involved.
NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

Serious Adverse Event (SAE)

Adverse event that:
a) Led to a death, injury or permanent impairment to a body structure or a body function
b) Led to a serious deterioration in health of the patient, that either resulted in:
   - as life-threatening illness or injury, or
   - a permanent impairment of a body structure or a body function, or
   - requires in-patient hospitalisation or prolongation of existing hospitalisation, or
   - in medical or surgical intervention to prevent life threatening illness
c) Led to foetal distress, foetal death or a congenital abnormality or birth defect.

NOTE 1: Planned hospitalisation for a pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered a serious adverse event.

Adverse Device Effect (ADE)

Adverse event related to the use of an investigational medical device.

NOTE 1- This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.
NOTE 2- This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE)

A Serious Adverse Device Effect of which the nature or severity is not consistent with the applicable product information (e.g. Instructions for Use as compiled by the manufacturer). Reports which add significant information on the specificity, increase of occurrence, or severity of a known, already documented serious adverse reaction constitute unexpected MDIs.

NOTE: Anticipated SADE (ASADE): an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

Device deficiency

Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

Medical Device Incident (MDI)

Any malfunction or deterioration in the characteristics and/or performance of a device (i.e. any device deficiency), as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health.

6.2 Events Reportable by the PI

For this study only ADEs, SADEs (i.e. AE/SAEs considered related to the study intervention being the study dressings and their application) and device deficiencies will be recorded in the eCRF.

They will be recorded between the first usage of the study dressings and the last study related intervention for that patient for ADEs and till 30 days after last study related intervention for SADEs/MDIs.

ADE's

ADEs, i.e. AEs considered related to the trial intervention, will be recorded in the eCRF by the PI, which in practice means:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with device use/application or procedures;
- the event involves a body-site or organ that
  - the device or procedures are applied to
  - the device or procedures have an effect on
- the event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/ exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the patient is due to error in use;

Ultimately it will be left to the investigator's clinical judgement to determine whether an adverse event is related or not.

Device deficiencies.

Any device deficiencies have to be recorded in the eCRF by the PI.

6.3 Events Reportable by the Sponsor or its delegate

Any SADE is considered as an INCIDENT and must be reported by the Sponsor to the Competent Authorities. Such events meet all three-basic reporting criteria A-C listed below

A. An event has occurred
B. The Device is suspected to be a contributory cause of the event
C. The event led, or might have led, to one of the following outcomes:
   - Death of a patient, user or other person
   - Serious deterioration in state of health of a patient, user or other person.
     Serious deterioration can include (non-exhaustive list):
     a) Life threatening illness
     b) Permanent impairment of body function or permanent damage
     c) Condition necessitating medical or surgical intervention to prevent a) or b)
     d) Foetal distress, foetal death or any congenital abnormality or birth defect

Conditions where reporting under the medical device vigilance system is not usually required are:

- Deficiency of a device found by user prior to its use
- Event caused by patient conditions
- Service life or shelf-life of the device exceeded
- Protection against fault functioned correctly
- Expected and foreseeable side effects
- Negligible likelihood of occurrence of death or serious deterioration in state of health

Medical Device Incidents

Any medical device incidents and have to be reported by the Sponsor or its delegate.

6.4 Reportable Information by the PI and the Sponsor

For each ADEs the following information will be collected:

- description of the event
- severity (mild, moderate, severe)
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- whether the event would be considered expected or unexpected.

For each Device deficiency, the following information will be collected:

- details in medical terms
- start and end dates, if applicable
- Relationship to any ADE/SADE (i.e. whether the event is an MDI).

6.5 How to report

6.5.1 "Principal Investigator (PI):

Checking for ADEs and device deficiencies during follow-up.

- Uses medical judgement in assigning seriousness, causality and expectedness
- Ensuring that all SADEs and device deficiencies are recorded and reported to the Pharmacovigilance department (pharmacovigilance@archemin.eu) as quickly as possible using the quickest means possible after becoming aware of the event and provide further follow-up information as soon as available.

Each ADE and device deficiency should be recorded in the eCRF. For SADEs and medical device incidents a report with the above mentioned information (section 6.4) on the event will be sent **by mail to** pharmacovigilance@archemin.eu.

Ludwig Everaert, Archemin BVBA, Lange Nieuwstraat 1, B-2800 Mechelen
Tel: +32 (0)15 28 74 11; Mobile: +32 (0)476 41 51 35

6.5.2 "Sponsor" or its delegate

The sponsor will transmit to the Federal Agency for Medicines and Health Products the following incidents:

- Any dysfunction or any change of the characteristics and/or performance of a device, and any inadequacy in the labelling or instructions, which might lead to or have led to death or serious relapse in the state of health of a patient, a user or a third party.
- Any technical or medical reason related to the characteristics or performance of a device for reasons shown in the previous paragraph and having led to the systematic withdrawal from the market by a manufacturer of devices of the same type.

The sponsor will transmit to Federal Agency for Medicines and Health Products and the Ethics Committee the following incidences:

- An unexpected SADEs or incident which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients, users or other persons or new finding to it: immediately, but not later than 2 calendar days after awareness by sponsor
- Any other reportable events (USADEs and medical device incidents) as described in section 6.3 or a new finding/update to it: immediately, but not later than 7 calendar days following the date of awareness by the sponsor.

The sponsor informs the sites, appropriate manufacturers if applicable.

7 BIOSTATISTICAL ASPECTS

7.1 Trial design and hypothesis.

This is a randomised, open label, parallel group, superiority, multicentre post-marketing release study.

Patients will be randomised in a 1:1:1 ratio to the Allevyn®, Mepilex® and control group and stratified by

- Hospital
- ICU vs non- ICU ward

For all analyses, both treatment groups will be pooled into one group unless specified otherwise. The sample size calculation is based on this assumption.

The primary objective is to compare the incidence rate of occurrence of at least one new pressure ulcer category II, III, IV, Unstageable, and DTI pressure ulcer at sacrum, heels and greater trochanter in both treatment arms versus the control arm.

The primary hypothesis is that the incidence rate of new pressure ulcer category II, III, IV, Unstageable, and DTI at sacrum, heels and greater trochanter will be lower in the treatment groups compared to the standard of care group. Superiority will be concluded if the primary variable is significantly different in the treatment groups compared to the standard of care group, based on a two sided test at 5% level of significance.

Exploratory efficacy analysis will compare the effectiveness of the two treatments: Allevyn® and Mepilex®. The null hypothesis is that there is no difference between Allevyn® and Mepilex®. The alternative hypothesis is that there is a difference between the treatment groups. The difference will be tested two- sided at 5 % level of significance.

7.2 Sample size calculation

The sample size calculation is based on the results of a number of randomised trials with data about pressure ulcer category II, III, IV, Unstageable, and DTI incidence.

- The pressure ulcer category II, III, IV, Unstageable, and DTI incidence rate on sacrum, greater trochanter and heels is 6% in the standard of care group (Schoonhoven et al., 2007)
- The treatment groups will have a 50% reduction in pressure ulcer incidence category II, III, IV, Unstageable, and DTI incidence on sacrum, greater trochanter and heels. (Demarré et al., 2012; Nixon et al., 2006)

In order to have 80% power to show superiority, data should be available for 1578 patients in total of which 526 are allocated to the control group and 1052 are allocated to the treatment group. Considering approximately 5% drop a total of 1662 patients are to be randomised to ensure that sufficient patients complete the study without compromising the power of the study.

7.3 Analysis set

The following analysis sets will be considered:

Total Set:	All patients who consented to participate in the study.
Intent-to-treat (ITT) Population:	All patients of the Total set who were randomised and who did not explicitly ask to have their data excluded from the analysis.
Per Protocol (PP) Population:	All patients of the ITT Population who received the study treatment according to the protocol, without any major protocol deviation impacting the primary efficacy assessment.
Safety Population:	All patients of the ITT population who entered into the observation period. and, for the patients in study arms 1 and 2, who were applied at least once study treatment.

For the ITT Population patients will be considered in the treatment group as randomised (as foreseen by the attributed randomisation number). For the other analysis sets patients will be considered in the treatment group as treated.

The exclusion of patients from the analysis sets will be discussed during a data review meeting that will be held before database lock.

The efficacy analyses will primarily be performed for the ITT Population and supportively for the PP Population.

7.4 Methods of statistical analysis.

The statistical methods outlined in the protocol will be detailed in the statistical analysis plan which will be created and finalised before database lock.

7.4.1 General statistical considerations

The statistical analysis will be performed using the SAS statistical package, version 9.2 or later. Unless otherwise stated, summary statistics for quantitative variables will include the mean, standard deviation, 95% confidence interval on the mean, minimum, 1st quartile, median, 3rd quartile, maximum, number of observations, and number of missing values. For categorical variables absolute counts (n) and percentages (%) of patients with data will be presented. For key categorical variables exact 95% confidence intervals will be presented for each treatment group and for the difference or ratio between the groups. The inferential statistical analysis will consist of:

For the primary efficacy variable:

- Comparison of the treatment group (Allevyn® & Mepilex® pooled) versus the control group (incidence rate is frequency at which patients develop one or more such new pressure ulcers over the study period as judged on site) by means of the CMH test controlled for type of ward (ICU/Non-ICU).

For the explorative analysis, the same analysis techniques will be used as for the primary efficacy analysis. Superiority tests will be performed two-tailed, at the 5% level of significance.

7.4.2 Demographics and baseline characteristics.

A description will be given of key patient characteristics recorded at the baseline visits, for all patients and broken down by treatment group.

7.4.3 Efficacy evaluation

7.4.3.1 Primary efficacy variable

Primary analysis:
Patients in study arms 1 and 2 will be pooled as the treatment group and the incidence rate of pressure ulcers category II or worse as judged on site will be compared between the treatment group and the usual care group as per randomisation scheme, by means of the CMH test controlled for type of ward (ICU/Non-ICU). An intention to treat (ITT) analysis including all patients randomised as well as a per protocol (PP) analysis will be performed.

Exploratory analyses.

- Comparison (ITT and PP) of incidence rates (primary endpoint) between the experimental investigational devices (arms 1 and 2).
- Analysis (ITT and PP) of the primary endpoint based on the central reading of the images

Sensitivity analysis of the primary endpoint using time to event approach (cox proportional hazard) and logistic mixed models.

The primary endpoint of this study is the incidence rate during the study period of the patient (during maximum 14 days) of at least one new pressure ulcer category II, III, IV, Unstageable, Deep Tissue Injury (DTI) (briefly referred to as pressure ulcers category II or worse) on sacrum, heels and greater trochanter as judged on site. The primary analysis of the primary efficacy variable is a superiority analysis that compares the incidence rate in the pooled treatment groups versus the control group, on the ITT population by means of the CMH test controlled for type of ward (ICU/Non-ICU). Superiority will be concluded if the

estimated impact of the treatment (Allevyn® and Mepilex® versus standard of care) is significant based on a 2 sided test at 5% significance level. A sensitivity analysis will be done using logistic regression and Cox proportional hazard models. A sensitivity analysis will be conducted in the ITT and PP populations based on the reviewed photographs of the PU, based on the review by the CI team. This variable will be included in the database before database lock.

7.4.3.2 Exploratory efficacy variables

A comparison between the efficacy of the two treatments will be made by defining a contrast in the logistic mixed model. A difference between the two treatments will be concluded if there is a significant difference between the two treatments based on 2 sided testing at the 5% significance level.

7.4.3.3 Further exploratory analyses

Any further exploratory analyses will be detailed in a statistical analysis plan.

7.4.4 Safety evaluation

Safety analyses will be performed on the basis of the Safety Set and will be descriptive. Statistical comparisons will be for exploratory purposes only.

7.5 Randomisation

Patients eligible to participate in the study will be randomly assigned to one of the following arms:

- Experimental study arm 1
- Experimental study arm 2
- Control study arm 3

Description of the different arms to be based on the description in section 4.

The randomisation plan is based on allocation of ratio 1:1:1. Randomisation will be stratified by:

- Hospital
- ICU vs. non- ICU

The randomisation will be based on a permuted-block randomisation with varying block sizes used to reduce the probability to predict the next treatment assignment.

For each ward (ICU versus non-ICU), the randomisation schedule will ensure balance of the three intervention arms at the intended number of randomised patients. The permuted-block randomisation will also allow balance at the end of each block

7.6 Interim and final analysis

The analyses will be done after database lock. There are no interim analyses planned.

8 MATERIAL

8.1 Data collection tools and source document identification

- Following source data will be used:
  - Data collection forms, to be used during observations
- Secondly, data will be entered in an electronic data capture (EDC) system

8.2 Trial Master File

The sponsor representative will set up a Trial Master File (TMF) at the beginning of the study and will manage the collection/storage of essential trial documents during the course and at the end of the study. The list of essential documents (the Master TMF List) will be in accordance with the GCP-guidelines and will specify which essential study documents are created and which are kept electronically and/or in paper. Additionally, the Master TMF List will identify where all the potential documentation, part of the Master TMF, is located as the Master TMF will include documents across different parties/departments other than clinical operations, such as Data Management, Statistics, Medical Writing, Pharmacovigilance, device supplies, Pharmacy, Legal, Regulatory Affairs. Provisions will be made to identify these documents and retain them as part of the TMF for the required retention period, even if stored separately from the main TMF itself.

Any documentation which has been created during the study and that helps reconstruct and evaluate the study conduct must be filed in the TMF.

The TMF is composed of:
- a Sponsor TMF, held by DRC/Sponsor/Sponsor's Subcontractors and
- an investigator TMF held by the investigator(s). The investigator TMF is referred to as the Investigator Site File (ISF).

The TMF held by sponsor representative will be established following a hybrid model, i.e. will contain both paper and electronic records:
- The eTMF is a cloud-based document management system (VEEVA vault).
- The paper-based documents will be filed in study binders in a secure but accessible manner for authorized people.

9 DATA HANDLING AND RECORD KEEPING

Patients that are included in the study will be randomised by using the EDC. A code number will be randomly assigned to all patients entered in the EDC system.

On forms, digital or other documents submitted to the coordinating centre, sponsor or CI, patients will only be identified by the code number.
The correspondence between the code number and the patient identification will be safeguarded by the trial nurses.

9.1 Access to Data

Direct access to eCRF and eTMF will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

9.2 Archiving

The sponsor and investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be verified. The relevant (essential) documents are those documents which individually and collectively permit to assess the conduct of the trial, the quality of the data produced and the compliance with GCP standards and applicable regulatory requirements. Archiving will be authorised by the Sponsor following submission of the end of study report. All essential documents will be archived for a minimum of 20 years after completion of trial. The destruction of essential documents will require authorisation from the Sponsor.
If it becomes necessary for the sponsor or the appropriate Regulatory Authority to review any documentation relating to this trial, the investigator must permit access to such reports. The patient is granting access to his/her source data by signing the ICF.
Any difficulty in storing original documents must be discussed with the monitor prior to the initiation of the trial.

10 MONITORING & AUDIT

10.1 Monitoring

This Clinical Investigation will be monitored by sponsor representatives according to the current SOP for the monitoring of Clinical Investigations.

The monitor will perform on-site monitoring visits as frequently as necessary which will be documented on the monitoring log. Shortly before the Clinical Investigation starts, the monitor will meet with the Trial Nurse to review the Clinical Investigation specific procedures on Clinical Investigation conduct and recording the data in the eCRF. The first monitoring visit will take place as soon as possible after enrolment and the Trial Nurse shall permit the monitor to verify the progress of the study on a continuous basis. The Trial Nurse shall make the source documents available, provide missing or corrected data and sign the eCRFs. Key data transcribed onto the eCRFs, such as the patient's gender, date of birth, assessment dates, etc., will be reviewed against the available source documents. Personal information will be treated as strictly confidential and will not be made publicly available. Any inconsistency between source data and data recorded in the eCRF will be corrected. The sponsor will ensure that appropriate QC steps are included into the different Clinical Investigation processes to guarantee adequate protection of the patients and to guarantee the quality of the data.

The PI should ensure the accuracy, completeness, legibility, and timeliness of the data.

During monitoring visits, the monitor will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections and alterations are to be made by the responsible investigator or his/her designee. The monitor cannot enter data in the eCRFs. Once clinical data of the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the clinical study centre staff responsible for entering the clinical data into the eCRF will be determined in advance.

10.2 Audit

To ensure compliance with relevant regulations, an independent Quality Assurance (QA) representative, IECs may review this study. This implies that auditors will have the right to audit the site(s) at any time during and/or after completion of the study and will have access to the data generated during the Clinical Investigation, source documents, and patient's files. By participating in this Clinical Investigation, the PI agrees to this requirement.

11 ETHICAL AND REGULATORY CONSIDERATIONS

11.1 Ethics Committee

Before the start of the trial, approval will be sought from both central and local EC for the trial protocol, informed consent forms and other relevant documents.
Substantial amendments that require review by EC will not be implemented until the EC grants a favourable opinion for the study. Substantial amendments according to the law of May 7th 2004 will need to be reviewed and accepted by EC before they can be implemented in practice at sites.

The CI will notify the sponsor of the start of the study and the sponsor representative will notify the central EC of the start of the study. An annual progress report (APR) will be submitted to the central EC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. It is the Sponsor's responsibility to produce the annual reports as required. If the study is ended prematurely, the CI will notify the central EC, including the reasons for the premature termination. Within one year after the end of the study, the Sponsor will submit a final report with the results, including any publications/abstracts, to the Sponsor, which in turn submits it to the central EC. The CI will notify the central EC of the end of the study. All correspondence with the ECs will be retained in the Trial Master File/Investigator Site File.

11.2 Patient Informed Consent

The Trial Nurse must explain the Clinical Investigation to potential patients or their legally acceptable representatives prior to any Clinical Investigation-related activity.
The patient must be informed that participation is voluntary, that they can refuse participation and withdraw consent at any time from the Clinical Investigation without giving reasons and without prejudicing his/her further treatment. Patients must be provided with contact details where he/she may obtain further information about the Clinical Investigation.
Where a patient is required to re-consent or new information is required to be provided to a patient it is the responsibility of the PI at the site to ensure this is done in a timely way.

Where the patient population is likely to include a significant proportion of patients who cannot read or write, require translators or have cognitive impairment, appropriate alternative methods for supporting the informed consent process should be employed. This may include allowing a witness to sign on a patient's behalf (in the case of problems with reading or writing), designate a legal representative or providing Patient Information Sheets in other languages or in a format easily understood by the patient population (in the case of cognitive impairment) providing they are approved by the EC. The patient or legally acceptable representative will be given sufficient time to read the ICF and to ask additional questions. After this explanation and before entry to the Clinical Investigation, consent should be appropriately recorded by means of either the patient's or his/her legal representative's dated signature or the signature of an independent witness who certifies the patient's consent in writing. After having obtained the consent, a copy of the ICF must be given to the patient.

Patients who are unable to comprehend the information provided can only be enrolled after consent of a legally acceptable representative.
For all eligible patients with written informed consent, baseline data will be collected and checked before randomisation.

11.3 Public and Patient Involvement

Two patient or public representatives will be invited via the network of the CI and asked to be part of the Trial Steering Committee. They will be asked to review the informed consent document and to help disseminate the results and outcomes of the study.

11.4 Regulatory Compliance

This study will be conducted in accordance with the protocol, principles of current ICH-GCP guidelines and applicable law(s).

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting studies that involve the participation of human patients. Compliance with this standard provides public assurance that the rights, safety and well-being of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

11.5 Protocol compliance

Prospective, planned deviations or waivers to the protocol are not allowed. Accidental protocol deviations can happen at any time. Major deviations must be adequately documented and reported to the CI and Sponsor immediately.
Any deviation that potentially interferes with and/or affects the efficiency and/or quality conduct of the study, will be discussed during the study by Monitor with Trial Nurse/PI and will be documented on the protocol deviation log as well on the monitoring report including a proposed plan of action for resolution if applicable.
Critical issues that significantly affect patient safety, data integrity and/or study conduct will be communicated and discussed by the sponsor with the EC.

11.6 Notification of Serious Breaches to GCP and/or the protocol

A “serious breach” is a breach which is likely to effect to a significant degree:

- the safety or physical or mental integrity of the patients of the trial; or
- the scientific value of the trial

The Sponsor should immediately inform the central EC and applicable local EC when the non-compliance is a serious breach of the trial protocol or ICH-GCP. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

11.7 Data protection and patient confidentiality

All investigators and study site staff will comply with the requirements of the Belgian Privacy Act of 8 December 1992 on the protection of privacy in relation to the processing of personal data and by the Law of 22 August 2002 on patient rights.
A study number will be randomly assigned to participating patients.
In order to permit easy identification of the individual subject during and after the trial, the PI is responsible for keeping an updated Patient Identification Code List. The monitor will review this document for completeness. However, the PI must guarantee the patient’s anonymity will be maintained. Therefore, in order to ensure patient confidentiality, the Patient Identification Code List will remain at the clinical study centre and no copy will be made for filing in the eTMF.

11.8 Financial and other competing interests

- The CI has no financial or competing interests that might influence the design, conduct or reporting of the study. He has no ownership interest related to the device, no commercial ties with the companies, and no non-commercial potential conflicts to disclosure. The CI participated in one meeting of the scientific advisory board of Mölnlycke Health Care in 2014. Since the CI is active in pressure ulcer research since many years, Ghent University received multiple research grants to set- up investigator initiated studies to test the effectiveness of different interventions to prevent pressure ulcers. Research grants were received from following companies: Sage Products LLC (Carry, Illinois, US), 3M Healthcare Deutschland, Hill- Rom (Batesville, US), and Frontier Medical Group (UK). The research contracts were coordinated by UGent TechTransfer and the Legal Department and were in concordance with any ethical and legal requirements. No research has been performed using the device in this study.
- None of the protocol contributors has any financial or other competing interest to disclosure.

11.9 Indemnity

The sponsor will provide an insurance, even without fault, to cover its liability as the requesting party (as referred to in the Act of 7 May 2004 on clinical trials) in case of harm caused to the patient by participation in the study.
The sponsor will consider all loss or damage caused by one and the same event or sequence of events to be a single claim event.
The participating hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical study and they remain liable for clinical negligence and other negligent harm to patients under this duty of care.

11.10 Post-study care

In line with during trial care, after the study is completed or the patient has completed the protocol intervention, all patients will continue to receive standard care as determined by the attending clinical team.
This is not part of a protocol.

12 DISSEMINATION POLICY

This study will be fully reported and made publicly available both during conduct and after completion. The design of the study will be registered in the clinical studies register. The outcomes of the research will be reported in a research paper and will be submitted for publication in a suitable peer-reviewed open-access journal. The Consort Guidelines and checklist will be reviewed prior to generating any publication to ensure they meet the standards required for submission to a high-quality peer reviewed journal. If requested, anonymised participant level dataset, and statistical code for generating the results will be made available for the Journal. The data arising from this study are owned by the sponsor. Any appropriate funding or supporting body will be acknowledged within the publications. On completion of the study, the data will be analysed and tabulated and a final study report will be generated.

The International Committee of Medical Journal Editors (ICMJE) guidelines on authorship will be applied to determine eligibility of authorship for both the final report and any publications arising from this study. The ICMJE recommends that authorship be based on the following 4 criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

This trial uses a competitive recruitment scheme. Authorship of the publication of the main study results will be according to the usual scientific guidelines, as detailed above. The order of the authors representing the sites will be determined based on the number of patients randomised, managed and documented in accordance with the protocol and the study agreement. The overall recruitment period is expected to last 9 months but this period can be shorter or longer. Patient recruitment will be considered complete and no additional patients will be randomised when overall 1662 patients are randomised in this trial in accordance with the study protocol. Sites will be informed twice a month by DICE about the recruitment status in all sites.

13 REFERENCES

Beeckman, D., Matheï, C., Van Lancker, A., Van Houdt, S., Vanwalleghem, G., Gryson, L., . . . Van den Heede, K. (2013). *Een nationale richtlijn voor Decubituspreventie*: Federaal Kenniscentrum voor de Gezondheidszorg.

Beeckman, D., Matheï, C., Van Lancker, A., Vanwalleghem, G., Van Houdt, S., Gryson, L., . . . Stordeur, S. (2013). A national guideline for the treatment of pressure ulcers.

Bergstrom, N., Braden, B. J., Laguzza, A., & Holman, V. (1987). The Braden scale for predicting pressure sore risk. *Nursing research, 36*(4), 205-210.

Black, J., Clark, M., Dealey, C., Brindle, C. T., Alves, P., Santamaria, N., & Call, E. (2015). Dressings as an adjunct to pressure ulcer prevention: consensus panel recommendations. *International wound journal, 12*(4), 484-488.

Brindle, C. T., & Wegelin, J. A. (2012). Prophylactic dressing application to reduce pressure ulcer formation in cardiac surgery patients. *Journal of Wound Ostomy & Continence Nursing, 39*(2), 133-142.

Chaiken, N. (2012). Reduction of sacral pressure ulcers in the intensive care unit using a silicone border foam dressing. *Journal of Wound Ostomy & Continence Nursing, 39*(2), 143-145.

Clark, M., Black, J., Alves, P., Brindle, C., Call, E., Dealey, C., & Santamaria, N. (2014). Systematic review of the use of prophylactic dressings in the prevention of pressure ulcers. *Int Wound J, 11*(5), 460-471 412p. doi:10.1111/iwj.12212

Davies, P. (2016). Role of multi-layer foam dressings with Safetac in the prevention of pressure ulcers: a review of the clinical and scientific data. *Journal of wound care, 25*(1 Suppl), S1, S4-23.

Demarré, L., Beeckman, D., Vanderwee, K., Defloor, T., Grypdonck, M., & Verhaeghe, S. (2012). Multi-stage versus single-stage inflation and deflation cycle for alternating low pressure air mattresses to prevent pressure ulcers in hospitalised patients: a randomised-controlled clinical trial. *International journal of nursing studies, 49*(4), 416-426.

Demarré, L., Verhaeghe, S., Annemans, L., Van Hecke, A., Grypdonck, M., & Beeckman, D. (2015). The cost of pressure ulcer prevention and treatment in hospitals and nursing homes in Flanders: A cost-of-illness study. *Int J Nurs Stud, 52*(7), 1166-1179.

Gorecki, C., Brown, J. M., Nelson, E. A., Briggs, M., Schoonhoven, L., Dealey, C., . . . Nixon, J. (2009). Impact of pressure ulcers on quality of life in older patients: a systematic review. *Journal of the American geriatrics society, 57*(7), 1175-1183.

Hopkins, A., Dealey, C., Bale, S., Defloor, T., & Worboys, F. (2006). Patient stories of living with a pressure ulcer. *Journal of advanced nursing, 56*(4), 345-353.

Jing, H., Guizhi, L., Aimin, W., et al. (2011). Control study on pressure sore prevention for patients accepting posterior spinal surgery. *Chinese Nursing Research, 25*, 308-310.

Kalowes, P., Li, M., Carlson, C., Carr, L., Llantero, L., Lukaszka, D., . . . Messina, V. (2013). *USE OF A SOFT SILICONE, SELF-ADHERENT, BORDERED FOAM DRESSING TO REDUCE PRESSURE ULCER FORMATION IN HIGH-RISK PATIENTS: A RANDOMIZED CLINICAL TRIAL.* Paper presented at the JOURNAL OF WOUND OSTOMY AND CONTINENCE NURSING.

Levy, A., Frank, M. B.-O., & Gefen, A. (2015). The biomechanical efficacy of dressings in preventing heel ulcers. *Journal of tissue viability, 24*(1), 1-11.

Levy, A., & Gefen, A. (2016). Computer Modeling Studies to Assess Whether a Prophylactic Dressing Reduces the Risk for Deep Tissue Injury in the Heels of Supine Patients with Diabetes. *Ostomy/wound management, 62*(4), 42-52.

Moore, Z. E., & Webster, J. (2013). Dressings and topical agents for preventing pressure ulcers. *The Cochrane Library*.

National Pressure Ulcer Advisory Panel, E. P. U. A. P., Pan Pacific Pressure Injury Alliance. (2014). *Prevention and Treatment of Pressure Ulcers: Clinical Practice Guideline* (E. Haesler Ed.). Osborne Park, Western Australia: Cambridge Media.

Nixon, J., Cranny, G., Iglesias, C., Nelson, E. A., Hawkins, K., Phillips, A., . . . Cullum, N. (2006). Randomised, controlled trial of alternating pressure mattresses compared with alternating

pressure overlays for the prevention of pressure ulcers: PRESSURE (pressure relieving support surfaces) trial. *Bmj, 332*(7555), 1413.

Qiuli, B. a. J. Q. (2010). Observation on effect of Mepilex on the prevention and treatment of pressure sores. *Chinese Journal of Medical Nursing.*

Santamaria, N., Gerdtz, M., Liu, W., Rakis, S., Sage, S., Ng, A., . . . Morrow, F. (2015). Clinical effectiveness of a silicone foam dressing for the prevention of heel pressure ulcers in critically ill patients: Border II Trial. *Journal of wound care, 24*(8).

Santamaria, N., Gerdtz, M., Sage, S., McCann, J., Freeman, A., Vassiliou, T., . . . Liu, W. (2015). A randomised controlled trial of the effectiveness of soft silicone multi-layered foam dressings in the prevention of sacral and heel pressure ulcers in trauma and critically ill patients: the border trial. *International wound journal, 12*(3), 302-308.

Santamaria, N., Liu, W., Gerdtz, M., Sage, S., McCann, J., Freeman, A., . . . Manias, E. (2015). The cost-benefit of using soft silicone multilayered foam dressings to prevent sacral and heel pressure ulcers in trauma and critically ill patients: a within-trial analysis of the Border Trial. *International wound journal, 12*(3), 344-350.

Schoonhoven, L., Bousema, M. T. & Buskens, E. (on behalf of the prePURSE-study group) (2007). The prevalence and incidence of pressure ulcers in hospitalised patients in the Netherlands: a prospective inception cohort study. *International journal of nursing studies, 44*(6), 927-935.

Schuurman, J.-P., Schoonhoven, L., Defloor, T., van Engelshoven, I., van Ramshorst, B., & Buskens, E. (2009). Economic evaluation of pressure ulcer care: a cost minimization analysis of preventive strategies. *Nursing Economics, 27*(6), 390.

Severens, J. L., Habraken, J. M., Duivenvoorden, S., & Frederiks, C. M. A. (2002). The cost of illness of pressure ulcers in The Netherlands. *Advances in skin & wound care, 15*(2), 72-77.

Vanderwee, K., Defloor, T., Beeckman, D., Demarré, L., Verhaeghe, S., Van Durme, T., & Gobert, M. (2011). Assessing the adequacy of pressure ulcer prevention in hospitals: a nationwide prevalence survey. *BMJ quality & safety*, qshc. 2010.043125.

Walsh, N. S., Blanck, A. W., Smith, L., Cross, M., Andersson, L., & Polito, C. (2012). Use of a sacral silicone border foam dressing as one component of a pressure ulcer prevention program in an intensive care unit setting. *Journal of Wound Ostomy & Continence Nursing, 39*(2), 146-149.

WUWHS. (2016). *Consensus Document. Role of dressings in pressure ulcer prevention*. Retrieved from www.woundsinternational.com

APPENDIX 1: EQ-5D-5L INSTRUMENT

EQ-5D

Zet bij iedere hieronder vermelde groep een kruisje in één hokje achter de zin die het best uw gezondheidstoestand **van vandaag** weergeeft.

Mobiliteit

Ik heb geen problemen met lopen	❑
Ik heb een beetje problemen met lopen	❑
Ik heb matige problemen met lopen	❑
Ik heb ernstige problemen met lopen	❑
Ik ben niet in staat om te lopen	❑

Zelfzorg

Ik heb geen problemen met mijzelf wassen of aankleden	❑
Ik heb een beetje problemen met mijzelf wassen of aankleden	❑
Ik ben matige problemen met mijzelf wassen of aankleden	❑
Ik heb ernstige problemen met mijzelf wassen of aankleden	❑
Ik ben niet in staat mijzelf te wassen of aan te kleden	❑

Dagelijkse activiteiten *(bijv. werk, studie, huishouden, gezins- of vrijetijdsactiviteiten)*

Ik heb geen problemen met mijn dagelijkse activiteiten	❑
Ik heb een beetje problemen met mijn dagelijkse activiteiten	❑
Ik heb matige problemen met mijn dagelijkse activiteiten.	❑
Ik heb ernstige problemen met mijn dagelijkse activiteiten	❑
Ik ben niet in staat mijn dagelijkse activiteiten uit te voeren	❑

Pijn/ongemak

Ik heb geen pijn of ongemak	❑
Ik heb een beetje pijn of ongemak	❑
Ik heb matige pijn of ongemak	❑
Ik heb ernstige pijn of ongemak	❑
Ik heb extreme pijn of ongemak	❑

Angst/somberheid

Ik ben niet angstig of somber	❑
Ik ben een beetje angstig of somber	❑
Ik ben matig angstig of somber	❑
Ik ben erg angstig of somber	❑
Ik ben extreem angstig of somber	❑

Om mensen te helpen bij het aangeven hoe goed of hoe slecht een gezondheidstoestand is, hebben we een meetschaal (te vergelijken met een thermometer) gemaakt. Op de meetschaal hiernaast betekent "100" de beste gezondheidstoestand die u zich kunt voorstellen, en "0" de slechtste gezondheidstoestand die u zich kunt voorstellen.

We willen u vragen op deze meetschaal aan te geven hoe goed of hoe slecht volgens u uw eigen gezondheidstoestand vandaag is. Trek een lijn van het hokje hieronder "uw gezondheidstoestand vandaag" naar het punt op de meetschaal dat volgens u aangeeft hoe goed of hoe slecht uw gezondheidstoestand vandaag is.

Uw gezondheidstoestand vandaag