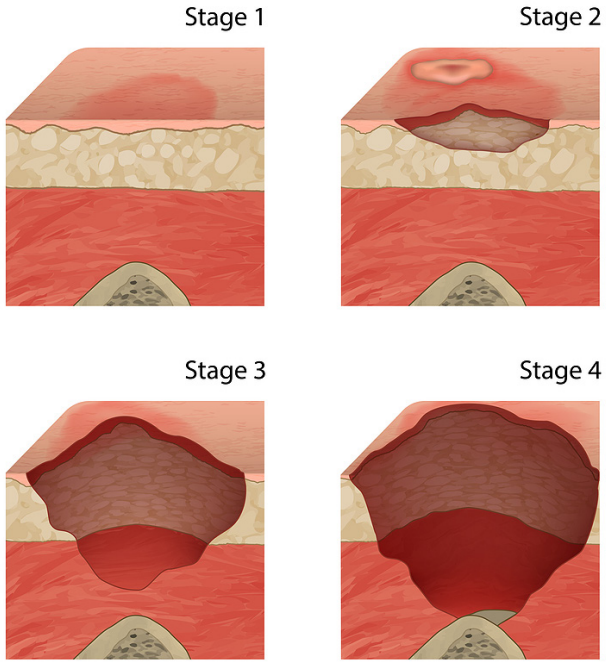
KCE REPORT 368

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

SILICONE ADHESIVE MULTILAYER FOAM DRESSINGS TO PREVENT HOSPITAL-ACQUIRED PRESSURE ULCERS: A BELGIAN RCT-BASED ECONOMIC EVALUATION



KCE REPORT 368
HEALTH TECHNOLOGY ASSESSMENT

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SILICONE ADHESIVE MULTILAYER FOAM DRESSINGS TO PREVENT HOSPITAL-ACQUIRED PRESSURE ULCERS: A BELGIAN RCT-BASED ECONOMIC EVALUATION

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COLOPHON

Title:	Silicone adhesive multilayer foam dressings to prevent hospital-acquired pressure ulcers: a Belgian RCT-based economic evaluation
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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ADE	Adverse Device Effect
AE	Adverse Event
AIC	Akaike Information Criterion
AR-DRG	Australian Refined Diagnostic Related Group
ARR	Absolute Risk Reduction
BIC	Bayesian Information Criterion
BMI	Body Mass Index
CBA	Cost-Benefit Analysis
CCA	Cost-Consequences Analysis
CEA	Cost-Effectiveness Analysis
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	Confidence Interval
CoI	Conflict of Interest
CRD	Centre for Reviews and Dissemination
CS	Company Submission
CSR	Clinical Study Report
DD	Device Deficiency
DTI	Deep Tissue Injury
EAC	External Assessment Centre
ED	Emergency Department
EED	Economic Evaluation Database
EUnetHTA	European Network for Health Technology Assessment
GDPR	General Data Protection Regulation

GLOBIAD	Ghent Global IAD Categorisation Tool
HAPU	Hospital-Acquired Pressure Ulcer
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
IAD	Incontinence-Associated Dermatitis
ICER	Incremental Cost-Effectiveness Ratio
ICU	Intensive Care Unit
IMA (IMA-AIM)	Intermutualistic Agency (InterMutualistisch Agentschap – Agence InterMutualiste)
INAHTA	International Network of Agencies for Health Technology Assessment
IQR	Interquartile Range
ITT	Intention-To-Treat
IVC	Information Security Committee (Informatieveiligheidscomité)
KCE	Belgian Health Care Knowledge Centre
LoS	Lenght of Stay
MTG	Medical Technologies Guidance
NA	Not Applicable
NH	Nursing Home
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHDI	National Institute for Health and Disability Insurance
NL	The Netherlands
NNT	Number Needed to Treat

NR	Not Reported
NUTH	Newcastle upon Tyne Hospitals
POP	Planned and Ongoing Projects
PrIs	Pressure Injuries
PRO	Patient-reported outcome
PU	Pressure Ulcer
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
RCT	Randomised Controlled Trial
RR	Risk Ratio
RRR	Relative Risk Reduction
SD	Standard Deviation
SNF	Skilled Nursing Facilities
SoC	Standard of Care
UK	United Kingdom
US	United States
VAS	Visual Analogue Scale
YHEC EAC	York Health Economics Consortium External Assessment Centre

SCIENTIFIC REPORT

1 INTRODUCTION

Disclaimer: The information in this chapter of the report is largely based on information from the clinical study report.[1]

1.1 What are pressure ulcers

A pressure ulcer (PU) is localised damage to the skin and/or underlying tissue, usually over a bony prominence (or associated with a medical or other device[a]), resulting from sustained pressure, or pressure in combination with shear. The damage may present as intact skin or as an open ulcer and may be painful. The International Classification System represents an international consensus (National Pressure Injury Advisory Panel, European Pressure Ulcer Advisory Panel, and Pan Pacific Pressure Injury Alliance) on the classification of pressure injuries/ulcers. It describes and classifies localized injuries to the skin and/or underlying tissues, as well as the categories of unstageable and suspected deep tissue injuries, which describe pressure injuries where the full extent of damage to the tissues and skin is still unknown. These stages include: 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) (See Figure 1). 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 or devices. The extent of skin and/or tissue damage depends on the duration and magnitude of the applied load (pressure and shear). International reviews and guidelines indicate that there is no single factor that can explain PU risk, but rather a complex interaction of factors that increase the likelihood of developing a PU. The risk factors most commonly found to be independent predictors of pressure ulcer development include mobility/activity, perfusion (including diabetes), and skin/pressure ulcer status.[2, 3] PUs remain a concerning and largely preventable health care-related harm.

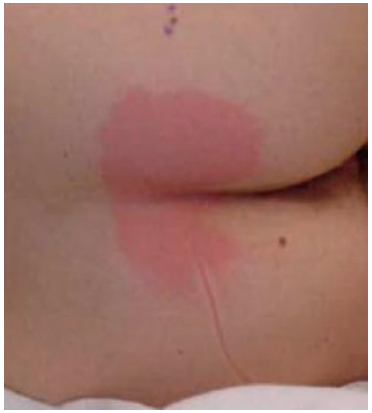
[a] A pressure ulcer caused by the presence of a medical device is referred to as a "medical device-related pressure ulcer".

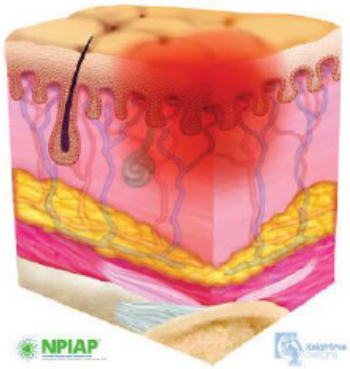
Figure 1 – Pressure ulcer categories

Category/Stage I pressure ulcer: Non- blanchable erythema

Intact skin with non-blanchable redness of localized area usually over a bony prominence. Darkly pigmented skin may not have visible blanching; its colour 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" persons (a heralding sign of risk).



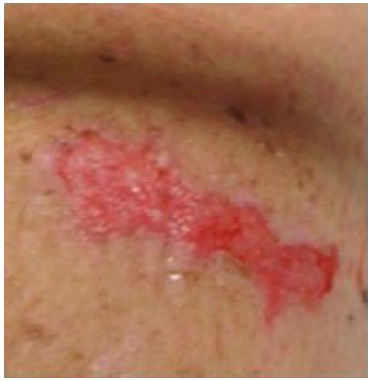


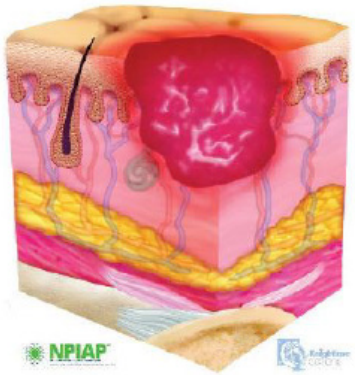
Category/Stage II pressure ulcer: Partial thickness skin loss

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.*

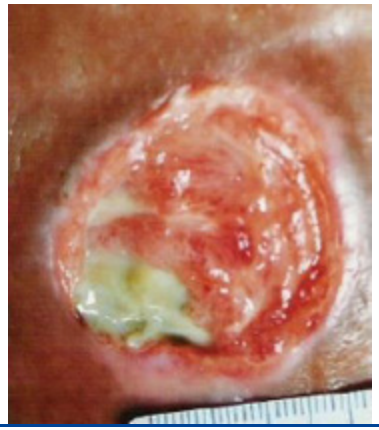




Category/Stage III pressure ulcer: Full-thickness skin loss

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 tunnelling.

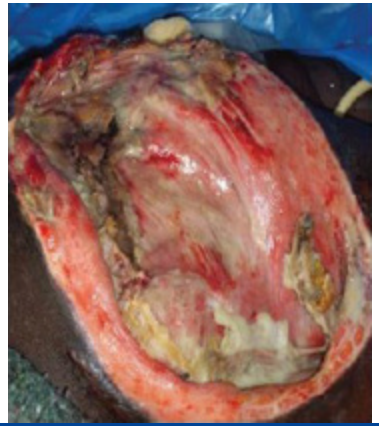
The depth of a Category/Stage III pressure ulcer varies by anatomical location. The bridge of the nose, ear, occiput and malleolus do not have subcutaneous tissue and Category/Stage III ulcers can be shallow. In contrast, areas of significant adiposity can develop extremely deep Category/Stage III pressure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

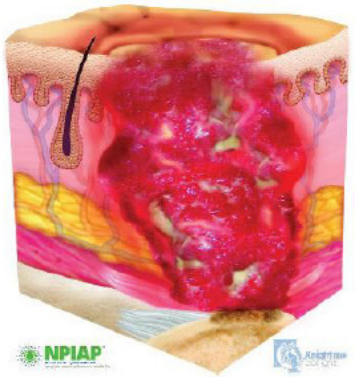


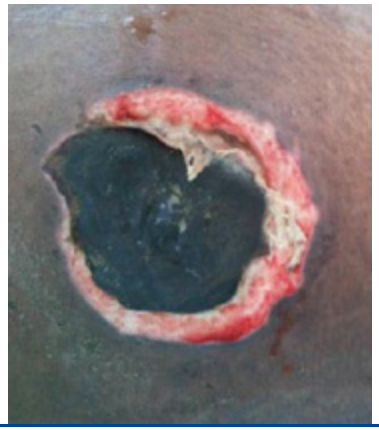
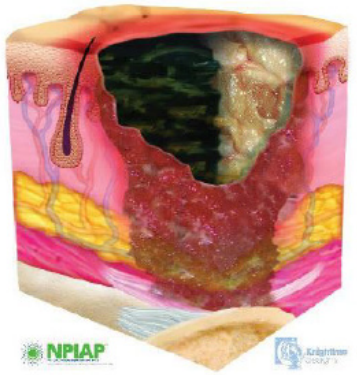
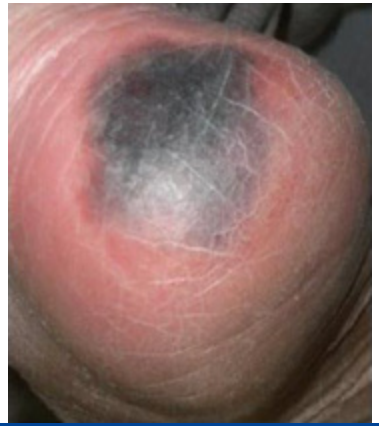
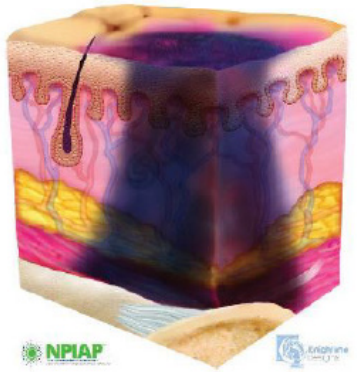
Category/Stage IV pressure ulcer: Full thickness tissue loss

Full thickness tissue loss with exposed bone, tendon or muscle. Slough or eschar may be present on some parts of the wound bed. Often include undermining and tunnelling.

The depth varies by anatomical location. The bridge of the nose, ear, occiput and malleolus do not have subcutaneous tissue and these ulcers can be shallow. Category/Stage IV ulcers can extend into muscle and/or supporting structures (e.g., fascia, tendon or joint capsule) making osteomyelitis possible. Exposed bone/tendon is visible or directly palpable.





Unstageable: Depth unknown Full thickness tissue loss in which the base of the ulcer is covered by slough (yellow, tan, grey, green or brown) and/or eschar (tan, brown or black) in the wound bed. Until enough slough and/or eschar is removed to expose the base of the wound, the true depth, and therefore Category/Stage, cannot be determined. Stable (dry, adherent, intact without erythema or fluctuance) eschar on the heels serves as 'the body's natural (biological) cover' and should not be removed.		
Deep tissue injury: Depth unknown Purple or maroon localised area of discoloured intact skin or blood-filled blister due to damage of underlying soft tissue from pressure and/or shear. The area may be preceded by tissue that is painful, firm, mushy, boggy, warmer or cooler as compared to adjacent tissue. Deep tissue injury may be difficult to detect in individuals with dark skin tones. Evolution may include a thin blister over a dark wound bed. The wound may evolve and become covered by thin eschar. Evolution may be rapid, exposing layers of tissue even with optimal treatment.		

Source: Clinical study report[1] and the European Pressure Ulcer Advisory Panel, National Pressure Injury Advisory Panel and Pan Pacific Pressure Injury Alliance, 2019.[4]

Pressure ulcers may affect all body locations covering a bony prominence. Two large studies, one in Belgium[5] (n=19 968), and one in the Netherlands[6] (n=1229), reported that PU prevalence varies between anatomical location. Both studies determined that most of the category II-IV PUs 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%).

1.2 Guidelines

Clinical practice guidelines recommend reducing the amount and duration of pressure and shear to prevent pressure ulcers. This includes the application of appropriate support surfaces combined with regular patient repositioning.

To prevent the development of pressure ulcers, the Belgian Health Care Knowledge Centre (KCE) clinical practice guideline recommends to reduce both the amount and the duration of pressure and shear.[7] This includes the use of appropriate support surfaces (such as mattresses or cushions), combined with correct patient repositioning on a continuous basis. Heels should always be free of all pressure. A general comment of the authors was the limited availability of randomized controlled trial (RCT) evidence for preventive measurements or the existing evidence was based on studies with methodological weaknesses.[7] Alternative approaches to achieving modification of applied mechanical loads (such as the use of multilayer foam dressings) were not considered in these practice guidelines. The more recent 2019 international guideline contains a weak positive recommendation for the use of a soft silicone multi-layered foam dressing to protect the skin for individuals at risk of pressure injuries. Moreover the use of a prophylactic dressing is weakly recommended as an adjunct to heel offloading and other strategies to prevent heel pressure injuries and beneath a medical device to reduce the risk of medical device-related pressure injuries.[3]

1.3 Silicone adhesive multilayer foam dressings

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 over a larger area, reducing the amount of pressure over the bony prominence (e.g. sacrum) and mitigate external shearing forces on the skin. In addition, it is suggested that the presence of multiple layers reduces shearing forces. 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).[8-10]

Softer **silicone-based adhesives**, which have lower surface tension than conventional adhesives, are incorporated into the multilayer foam dressings. The silicone adhesive adheres more quickly to the uneven skin surface, can be removed gently, and can be repositioned because the adhesive erodes few epidermal cells.[11, 12] This is of interest because it allows visualisation of the skin without the need to change the dressing after lifting.

2 SCOPE AND OBJECTIVES

KCE Trials is a programme of publicly funded, non-commercial, practice-oriented clinical trials. These studies address questions that are generally not studied by industry, despite their high social importance. KCE Trials is responsible for selecting the studies, provides funding for them and follows up on their progress. The studies themselves are carried out in the participating Belgian hospitals (https://kce.fgov.be/en/kce-trials).

One of the proposals submitted KCE Trials was related to the prevention of pressure ulcers. Based on a literature review, the study proposal mentioned there was limited and not generalizable evidence on prophylactic dressings for preventing pressure ulcers. The identified evidence on effectiveness and cost-effectiveness of prophylactic dressings was limited to individuals requiring critical care/intensive care, with dressings generally applied on first contact with health professionals (e.g. in the emergency department).[13]

By conducting a pragmatic clinical randomized controlled trial, the researchers aim to answer the following research question: Is a multilayer silicone foam dressing (cost-)effective as an adjuvant prophylactic therapy compared to standard pressure ulcer prevention to reduce pressure ulcer incidence in a high risk hospital population?

The trial was executed in different wards in both teaching hospitals and general hospitals in Belgium increasing the likelihood of an appropriate case mix and thus generalizability of the conclusions. The trial provided insights in the effectiveness of multilayer silicone foam dressings, as an adjuvant prophylactic therapy for pressure ulcer prevention in hospitalised patients at high risk of pressure ulcers. The hypothesis that the intervention is more effective than the comparator has been confirmed (see part 3). The cost-effectiveness of this intervention remains to be studied.

The study question in this report is as follows:

Is a multilayer silicone foam dressing cost-effective as an adjuvant prophylactic therapy compared to standard pressure ulcer prevention to reduce pressure ulcer incidence in a high risk hospital population?

The scope of this research question reflects the in- and exclusion criteria of the underlying trial.

3 CLINICAL EFFFECTIVENESS AND HARMS: THE BELGIAN MULTICENTRE RANDOMISED TRIAL

The Clinicaltrials.gov Identifier of this trial is NCT03442777. Disclaimer: The information in this chapter is copied from the clinical study report.[1]

3.1 Description of the trial

3.1.1 Purpose

The purpose of this trial was 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.

3.1.2 Study design

A multicentre, randomised controlled, open label, parallel group medical device trial was performed in 8 hospitals in Belgium. Patients were randomly allocated to three study arms based on a 1:1:1 allocation. The randomisation was stratified by hospital and intensive care unit (ICU) versus non-ICU ward and based on a permuted-block randomisation with varying block sizes used to reduce the probability to predict the next treatment assignment.

The participating study sites were the following: UZ Gent, AZ Groeninge, UZ Brussel, OLV Aalst, AZ Sint-Elisabeth, UZ Leuven, AZ Maria Middelares and OLV van Lourdes ziekenhuis Waregem.

3.1.3 Ethical considerations

Approval of the trial protocol was received from both central and local ethics committees. All participants or their legal representatives provided written informed consent before entry to the Clinical trial. For more information, we refer to the clinical study report.[1]

3.1.4 Population

The study population included hospitalised patients at risk for pressure ulcer development in university/teaching and general hospitals. Hospitals were eligible to participate if dressings were not used as standard of care to prevent pressure ulcers. The in- and exclusion criteria of the clinical study population are described in Table 1.

Table 1 – Clinical study population: in- and exclusion criteria

Inclusion criteria	Exclusion 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 from ICU wards.* 3. Skin at sacrum was assessable and there was no clinically relevant incontinence-associated dermatitis (IAD) or another skin condition that could have been a contra-indication for the application of the devices under study, and there was no pressure ulcer category II or worse present. Clinically relevant IAD was defined as any of the IV categories included in the Ghent Global IAD Categorisation Tool (GLOBIAD).[14] 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 had to be applicable: • A study dressing could have been applied as prevention of a pressure ulcer category II or worse at that skin site (there is no contra-indication) OR • There was already a pressure ulcer category II or worse at 3 of the 4 sites. 5. Written informed consent by the patient or his/her legal representative.	1. Aged < 18 years. 2. The presumed length of stay counting from first day of admission in one or (if the patient is transferred to another ward) more participating wards was < 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 trial. 6. Participation in another interventional clinical trial. 7. Patients who exceptionally received or were 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.

** This trial extends previous trial results obtained in the ICU setting. Therefore, a maximum of 25% of patients was intended to be recruited from ICU settings.*

3.1.5 Intervention

In the experimental groups, patients received silicone adhesive multilayer foam dressings. The devices were applied on dry intact skin on (1) sacrum, (2) right heel, (3) left heel, (4) greater trochanter right, and (5) greater trochanter left. The devices were applied in addition to the standard of care with a maximum treatment duration of 14 days.

Two silicone adhesive multilayer foam dressings were tested in this study:

- Silicone adhesive multilayer foam dressings by Smith & Nephew (AllevynR brand, type: AllevynR Life, AllevynR Life Sacrum and AllevynR Life Heel)
- Silicone adhesive multilayer foam dressings by Mölnlycke Healthcare (MepilexR brand, type: MepilexR Border, MepilexR Border Sacrum, MepilexR Border Heel)

Both dressings are available on the Belgian market in different shapes and sizes (see Figure 2). Both silicone adhesive multilayer foam dressing brands used during the study were procured by KCE and no sponsorships were received from the manufacturers.

Figure 2 – Silicone adhesive multilayer foam dressings included in the RCT

Allevyn® Life 12.9 x 12.9cm		**Mepilex® Border** 15 x 15cm	
Allevyn® Life Sacrum 21.6 x 23cm		**Mepilex® Border Sacrum** 22 x 25cm	
Allevyn® Life Heel 25 x 25.2cm		**Mepilex® Border Heel** 22 x 23cm	

3.1.6 Comparator

The practice in hospitals in Belgium during the trial period, reflected the KCE guidelines for prevention and treatment of pressure ulcers[7, 15] and the 2014 international guidelines.[16] While the trial was performed in 2018 (see 3.2.1), the practice is also in agreement with the 2019 guidelines[3] and thus not outdated. Patients in the control arm were cared for on the available support surfaces of the hospital and they received standard pressure ulcer preventative care as described by the hospital protocol. This care included: regular risk assessment, regular repositioning and skin care. No silicone adhesive multilayer foam dressing was applied on any skin sites to prevent pressure ulcer development. The maximum observation period was 14 days.

The standard practice during the trial period can be summarized as follows:

- 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.
- Continue **skin care** by cleansing, protecting and moisturising skin. Emollients and skin barrier products could be used if indicated.

3.1.7 Outcome

The **primary endpoint** of this trial was the incidence rate during the trial 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 compared between the pooled treatment groups and the standard of care group as per randomisation scheme.

Quality of life was measured at baseline, day 3 and day 14 or end of study with the EuroQol 5-Dimension 5-Level (EQ-5D-5L) questionnaire. This is a self-report survey that measures quality of life across 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. This generic utility instrument also contains a visual analogue scale (VAS) which records the patient's self-rated health. The quality of life (QOL) questionnaires planned for day 14 were completed as planned even if patients moved to non-participating wards or refused further dressing application.

Descriptive **safety** analyses were performed, based on reported adverse device effects.

For more information on exploratory analyses, we refer to the full clinical study report.[1]

3.2 Results

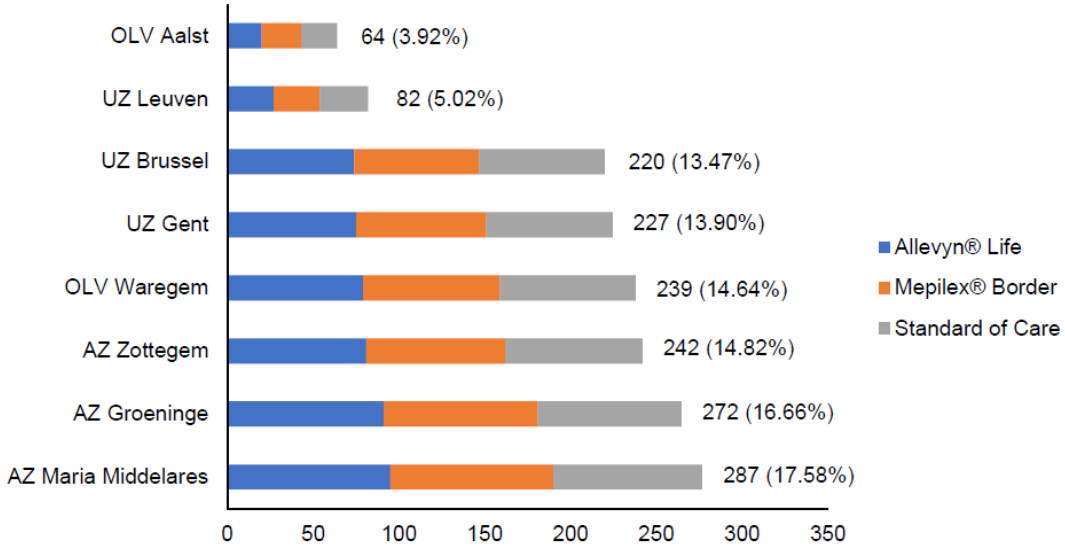
3.2.1 Patient population

From February 2018 until December 2018, 1680 patients were screened for eligibility and 1633 patients were randomised to one of the study arms:

- 542 (33.2%) to the Allevyn® Life group (experimental group 1),
- 545 (33.4%) to the Mepilex® Border group (experimental group 2) and
- 546 (33.4%) to the standard of care group (control group).

Patients were recruited in eight hospitals in Flanders (Belgium), of which three were university/teaching hospitals and five were general hospitals. The number of patients randomised per study site is shown in Figure 3.

Figure 3 – Recruitment rate per study site



Source: Beeckman et al. (2020)[1]

Baseline characteristics of the study population are presented in Table 2. Among the 1633 patients, the mean age was 80 years old (SD=12) and the majority (57.6%) were female. ICU patients counted for 12.4% and 39.1% of the patients had their consent signed by a legal representative. Patients being underweight (BMI <18.5) counted for 8.3% of the sample, versus 29.8% for overweight and 16.5% for obesity (BMI >30). Twenty-three percent of the patients had diabetes and 10.7% had a surgery since admission. Patient characteristics were equally distributed across the 3 study groups.

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Table 2 – Participant's baseline demographics, by randomised arm, ITT population

	Randomised arm							
	Allevyn® Life (N=542)		Mepilex® Border (N=545)		Standard of Care (N=546)		Total (N=1633)	
Consent signed by (n (%))								
Patient	318	(58.7)	336	(61.7)	340	(62.3)	994	(60.9)
Legal representative	224	(41.3)	209	(38.3)	206	(37.7)	639	(39.1)
Ward type at study start (n (%))								
ICU	65	(12.0)	67	(12.3)	71	(13.0)	203	(12.4)
Non-ICU	477	(88.0)	478	(87.7)	475	(87.0)	1430	(87.6)
Total Braden score* (mean (SD))	13.0	(2.3)	13.1	(2.5)	13.0	(2.3)	13.0	(2.4)
Total Braden score* (categories)								
≤11	129	(23.8)	142	(26.1)	126	(23.1)	397	(24.3)
12-16	392	(72.3)	376	(69.0)	403	(73.8)	1171	(71.7)
=17	21	(3.9)	27	(5.0)	17	(3.1)	65	(4.0)
* at baseline								
Age (years, mean (SD))	79.8	(12.3)	79.4	(12.5)	79.6	(11.7)	79.6	(12.2)
Age (years, n (%))								
<60	46	(8.5)	43	(7.9)	45	(8.2)	134	(8.2)
60-69	50	(9.2)	70	(12.8)	56	(10.3)	176	(10.8)
70-79	106	(19.6)	107	(19.6)	117	(21.4)	330	(20.2)
≥80	340	(62.7)	325	(59.6)	328	(60.1)	993	(60.8)
Gender (n (%))								
Female	320	(59.0)	302	(55.4)	319	(58.4)	941	(57.6)
Male	222	(41.0)	243	(44.6)	227	(41.6)	692	(42.4)

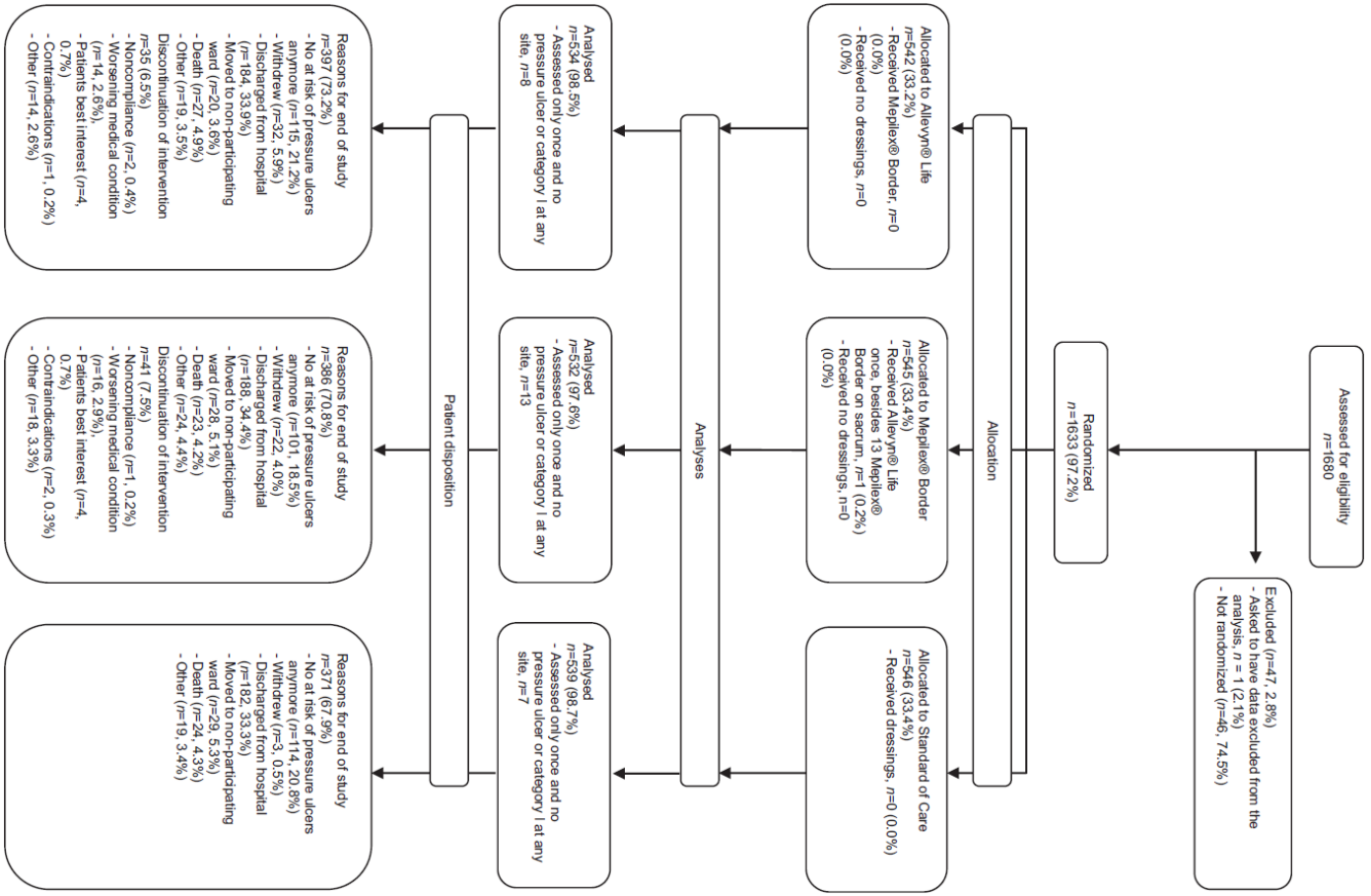
BMI (kg/m², mean (SD))	25.6	(5.8)	24.8	(5.3)	25.1	(5.1)	25.2	(5.4)
BMI (kg/m², n (%))								
Underweight (<18.5)	44	(8.1)	53	(9.7)	39	(7.1)	136	(8.3)
Normal weight (18.5 - 25.0)	234	(43.2)	249	(45.7)	258	(47.3)	741	(45.4)
Overweight (25.0 - 30.0)	161	(29.7)	163	(29.9)	162	(29.7)	486	(29.8)
Obesity (≥30.0)	103	(19.0)	80	(14.7)	87	(15.9)	270	(16.5)
Diabetes (n (%))								
No	419	(77.3)	427	(78.3)	412	(75.5)	1258	(77.0)
Yes	123	(22.7)	118	(21.7)	134	(24.5)	375	(23.0)
Surgery (n (%))								
No	484	(89.3)	486	(89.2)	489	(89.6)	1459	(89.3)
Yes	58	(10.7)	59	(10.8)	57	(10.4)	174	(10.7)

Source: Beeckman et al. (2020)[1]
BMI: Body Mass Index; ICU: intensive care unit; SD: standard deviation.
More details are available in de clinical study report: height and weight of patients; time (days) between surgery/hospital admission/informed consent/randomisation/discontinuation of intervention/discontinuation/end of study; median, range, interquartile range (IQR) and missing values for the continuous variables; details on the Braden subscales; and baseline skin condition (see tables 3-5 in the original clinical study report).[1]

Figure 4 gives an overview of the number of patients included in the study and analyses and reasons for discontinuation. Twenty-eight patients were excluded from the final intention-to-treat (ITT) population as they had no assessments of a site with the potential to develop a new PU (either no assessments at all, or patient/site only assessed once, or no assessment of a site with the potential to develop a new PU, i.e. the presence of a pre-existing PU), giving a sample of 1605 patients for the ITT population. In the ITT population, 12.4% of patients were in the ICU and 87.5% in non-ICUs.

The trial procedures were discontinued before day 14 in 1153 (70.6%) of the randomised patients. The main reasons for discontinuation were not being at risk of PU development (Braden score > 17) (n=330, 28.6%), and discharge from the hospital (n=554, 48.0%).

Figure 4 – Flow chart of participant inclusion, discontinuation, and analyses



Source: Beeckman et al. (2020)[1, 17]

Risk assessment:

- The majority of the participants had a 'moderate' Braden risk assessment score at Day 1 (12 – 16), with an even distribution between experimental group 1 (72.3%), experimental group 2 (68.9%) and control group (73.8%).
- The level of physical activity of most patients was either being bedridden/bedfast or chairfast (47.9% and 43.5% respectively) and 63.3% of patients required 'moderate to maximum assistance' with movement and a frequent need for repositioning. In total, 16.5% of participants were completely immobile and 60.6% could not change their body/extremity positions often (details: see table 4 in the original clinical study report).[1]

Baseline Skin Condition:

- In 87.3% of the cases (n=1427), the sacral area of the participants was 'mostly dry' vs. 12.6% 'wet' (Table 5). Most of the moisture exposure was related to sweating (6.1%), urine (5%) and diarrhoea (2.6%). At baseline, 4.1% of participants presented with a PU category I on the sacral area (details: see table 5 in the original clinical study report).[1]

3.2.2 Intervention – use of study material

The number of dressings applied by sites is described in Table 3. The total mean number of dressings applied to the patients during the study period was 13 (SD=7), with a mean of 3 (SD=2) for the sacrum and the heels and of 2 (SD=1) for the trochanters. There were no major differences across experimental arms.[1]

Table 3 – Number of dressings applied, by randomised arm, ITT population

		Randomised arm		
		Allevyn Life® (N=543)	Mepilex Border® (N=545)	Total (N=1088)
Any site				
Mean	(SD)	12.9 (6.5)	12.7 (6.8)	12.8 (6.7)
Median	(range)	12.0 (0.0 - 35.0)	12.0 (0.0 - 43.0)	12.0 (0.0 - 43.0)
IQR		8.0 - 16.0	8.0 - 16.0	8.0 - 16.0
Missing		0	0	0
Sacrum				
Mean	(SD)	3.0 (2.0)	3.0 (2.0)	3.0 (2.0)
Median	(range)	3.0 (0.0 - 10.0)	3.0 (0.0 - 11.0)	3.0 (0.0 - 11.0)
IQR		1.0 - 4.0	2.0 - 4.0	1.0 - 4.0
Missing		0	0	0
Heel right				
Mean	(SD)	3.1 (2.3)	2.8 (2.2)	3.0 (2.3)
Median	(range)	2.0 (0.0 - 12.0)	2.0 (0.0 - 16.0)	2.0 (0.0 - 16.0)
IQR		1.0 - 4.0	1.0 - 4.0	1.0 - 4.0
Missing		0	0	0
Heel left				
Mean	(SD)	3.0 (2.0)	2.7 (2.0)	2.9 (2.1)
Median	(range)	3.0 (0.0 - 12.0)	2.0 (0.0 - 12.0)	2.0 (0.0 - 12.0)
IQR		1.0 - 4.0	1.0 - 3.0	1.0 - 4.0
Missing		0	0	0
Trochanter right				
Mean	(SD)	1.9 (1.2)	2.0 (1.4)	1.9 (1.3)
Median	(range)	2.0 (0.0 - 7.0)	2.0 (0.0 - 10.0)	2.0 (0.0 - 10.0)
IQR		1.0 - 2.0	1.0 - 3.0	1.0 - 3.0
Missing		0	0	0
Trochanter left				
Mean	(SD)	1.9 (1.3)	2.1 (1.5)	2.0 (1.4)
Median	(range)	2.0 (0.0 - 8.0)	2.0 (0.0 - 11.0)	2.0 (0.0 - 11.0)
IQR		1.0 - 2.0	1.0 - 3.0	1.0 - 3.0
Missing		0	0	0

3.2.3 Primary endpoint

Of the 1605 participants in the intention-to-treat (ITT) population, 77 (4.8%) developed PU category II or worse (sacrum, trochanter, or heel); 4.0% in the treatment group and 6.3% in the control group receiving standard of care (SoC). The Cochran-Mantel-Haenszel test, controlling for type of ward (ICU/non-ICU), showed a statistically significant reduction in the risk of developing a PU in the treatment group group (Risk Ratio (RR)=0.64, 95% Confidence Interval (CI) 0.41-0.99, p=0.04), meaning that patients in the treatment group had a 36% reduced risk of developing a new PU compared with those in the SoC group. This result was confirmed by a logistic regression model adjusted for hospital, age, gender, type of ward, and Braden score at baseline (p=0.01).

Of the 77 patients who developed PU category II or worse, 14 (18.2%) already had a baseline PU, where 8 were sacrum PU of category I (see Table 4).

Table 4 – Patients with presence of baseline PU and who developed PU within the trial follow-up

	Treatment		Standard of Care	
	n/N	%	n/N	%
Overall	12/77*	15.6	2/77	2.6
Body site				
Sacrum	7	9.1	1	1.3
Any heel	8	10.4	1	1.3
Any trochanter	0	0	0	0

3.2.4 Exploratory and subgroup analyses

We note that all exploratory analyses presented were pre-planned in the statistical analysis plan. In the clinical study report,[1] the authors remark that any apparent (lack of) effect should be regarded with caution as the trial was not specifically powered with interactions in mind.

Exploratory analyses

Table 5 presents the results per anatomic site. The findings are as follows:

- PUs on the sacrum were observed in 2.8% and 4.8% of the patients in the treatment group and the SoC group, respectively. The risk to develop a new PU on the sacrum was statistically significantly reduced by 41% in the treatment group (RR=0.59, 95% CI 0.35-0.98, p=0.04).
- PUs on the heels occurred in 1.4% and 1.9% of patients in the treatment and SoC group, respectively, and no statistical difference was identified (p=0.49).
- Only one patient (0.1%) developed a PU on the trochanter.

Table 5 – Estimated RR (and 95% CI) for PUs category II or worse, in the treatment group compared to the SoC group, ITT population

	Intervention group					
	Treatment		Standard of Care			
	n/N	%	n/N	%	RR (95% CI)*	p-value
Overall	43/1066	4.0	34/539	6.3	0.64 (0.41-0.99)	0.04
Body site						
Sacrum	30/1062	2.8	26/539	4.8	0.59 (0.35-0.98)	0.04
Any heel	15/1063	1.4	10/538	1.9	0.76 (0.34-1.68)	0.49
Any trochanter	1/1065	0.1	0/539	0.0	NA	NA

** Reference is the Standard of care group.*
NA: not applicable

While the incidence of PUs was similar in ICU and non-ICU wards, the difference between the treatment group and the SoC group incidences was higher in the non-ICU wards (3.9% and 6.6% respectively in non-ICU wards vs. 4.8% and 5.6% in ICU wards). However, the association between the incidence of PUs and the intervention groups were not statistically different according to the type of ward (Breslow test for homogeneity: p=0.36).

Exploratory data analyses did not demonstrate any major differences in effectiveness between the 2 brands, considering that the study was not powered to detect such differences.

Subgroup analyses

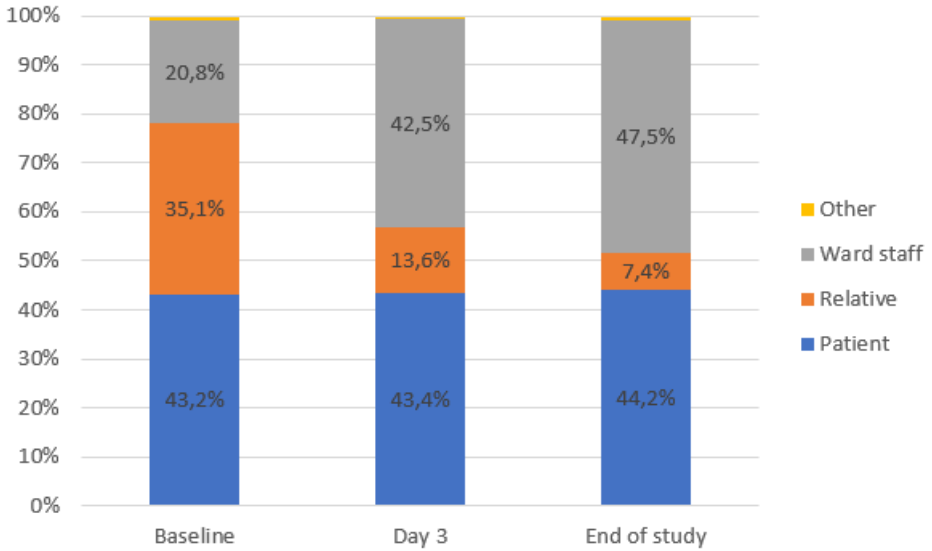
The incidence of PUs increased with age (from 0.8% for <60 years old to 5.9% for ≥80 years old) and was higher among women (5.1% vs 4.4% among males). While the incidence of PUs was similar in ICU and non-ICU wards, the difference between the treatment group and the SoC incidences was higher in non-ICU wards (3.9% and 6.6% respectively in non-ICU vs. 4.8% and 5.6% in ICU wards). The incidence of PU decreased across Braden score categories, from 6.7% (Braden score ≤11) to 4.3% (Braden score 12-16) and 1.6% (Braden score ≥17).

More details on these and other subgroups analyses, sensitivity analyses and per-protocol population (instead of ITT) analyses are available in the clinical study report.[1]

3.2.5 Quality of life

Quality of life data was reported at baseline, day 3 and day 14 or end of study. At baseline, 1539 EQ-5D-5L questionnaires were completed (94.2%). Of the questionnaires 43.2% were completed by the patients themselves (Figure 5). In 35.1% of the cases a relative completed the questionnaire and in 21.5% by the ward staff or someone else. On day 3 and at the end of the study, 1336 (84.6%) and 1319 (80.8%) questionnaires were completed, respectively. Compared with baseline, similar percentages of questionnaires were completed by the patients themselves. However, at day 3 and at the end of the study, fewer relatives filled out the questionnaires and a higher percentage were completed by the ward staff (see Figure 5).

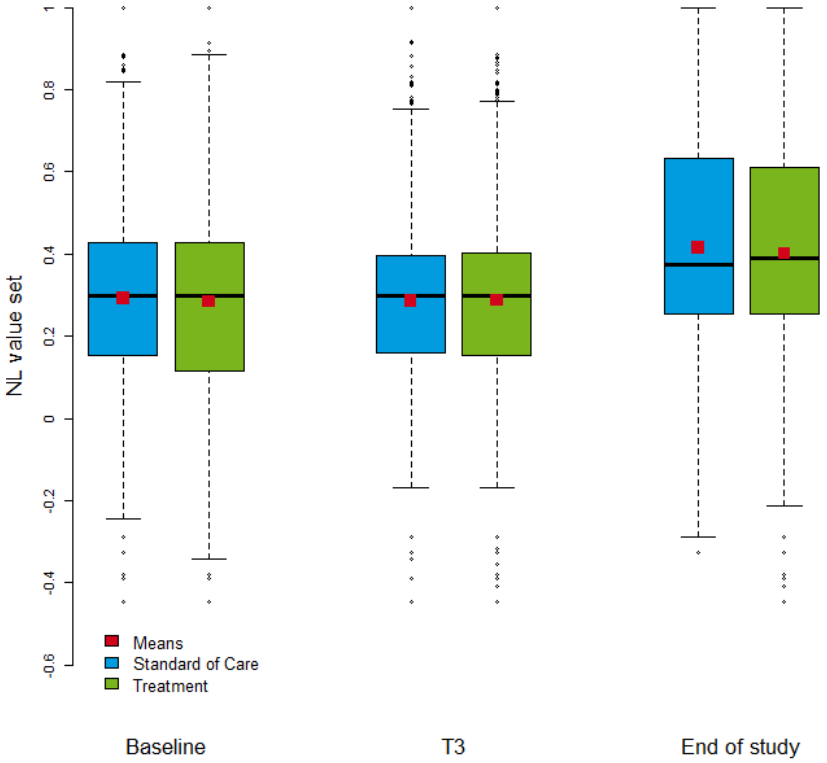
Figure 5 – Individuals who completed the QoL questionnaire at baseline, day 3 and at the end of study



Source: based on information retrieved from clinical study report.[1]

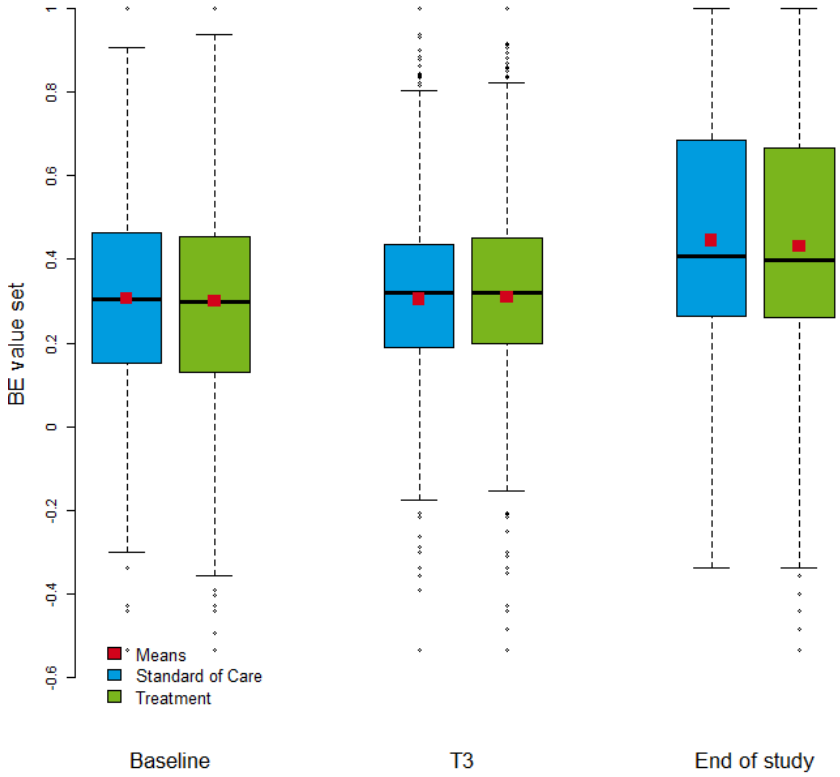
Figure 6 presents the utility measures for the treatment group and the standard of care group at baseline, day 3 and at the end of the study. Results were originally reported using the standard EQ-5D-5L value set of the Netherlands because a Belgian value set was not available at that moment. Descriptive analysis showed similar results between the groups. The mean utilities were as follows: 1) baseline: 0.28 (SD 0.28) and 0.29 (SD 0.28); 2) day 3: 0.29 (SD 0.25) and 0.29 (SD 0.25); 3) end of study: 0.40 (0.28) and 0.42 (SD 0.27) in the treatment and standard of care group, respectively. In 2021, KCE published an EQ-5D-5L value set for Belgium.[18] Figure 7 presents the results applying the Belgian utility values: 1) baseline: 0.28 (SD 0.28) and 0.29 (SD 0.28); 2) day 3: 0.29 (SD 0.25) and 0.29 (SD 0.25); 3) end of study: 0.40 (SD 0.28) and 0.42 (SD 0.27) in the treatment and standard of care group, respectively.

Figure 6 – Utility measures at baseline, day 3 and at the end of the study (Dutch value set)



*The lower whisker of the box plot is equal to the 25th percentile-1.5*interquartile range (IQR) and the upper whisker is equal to 75th percentile+1.5*IQR.*

Figure 7 – Utility measures at baseline, day 3 and at the end of the study (Belgian value set)



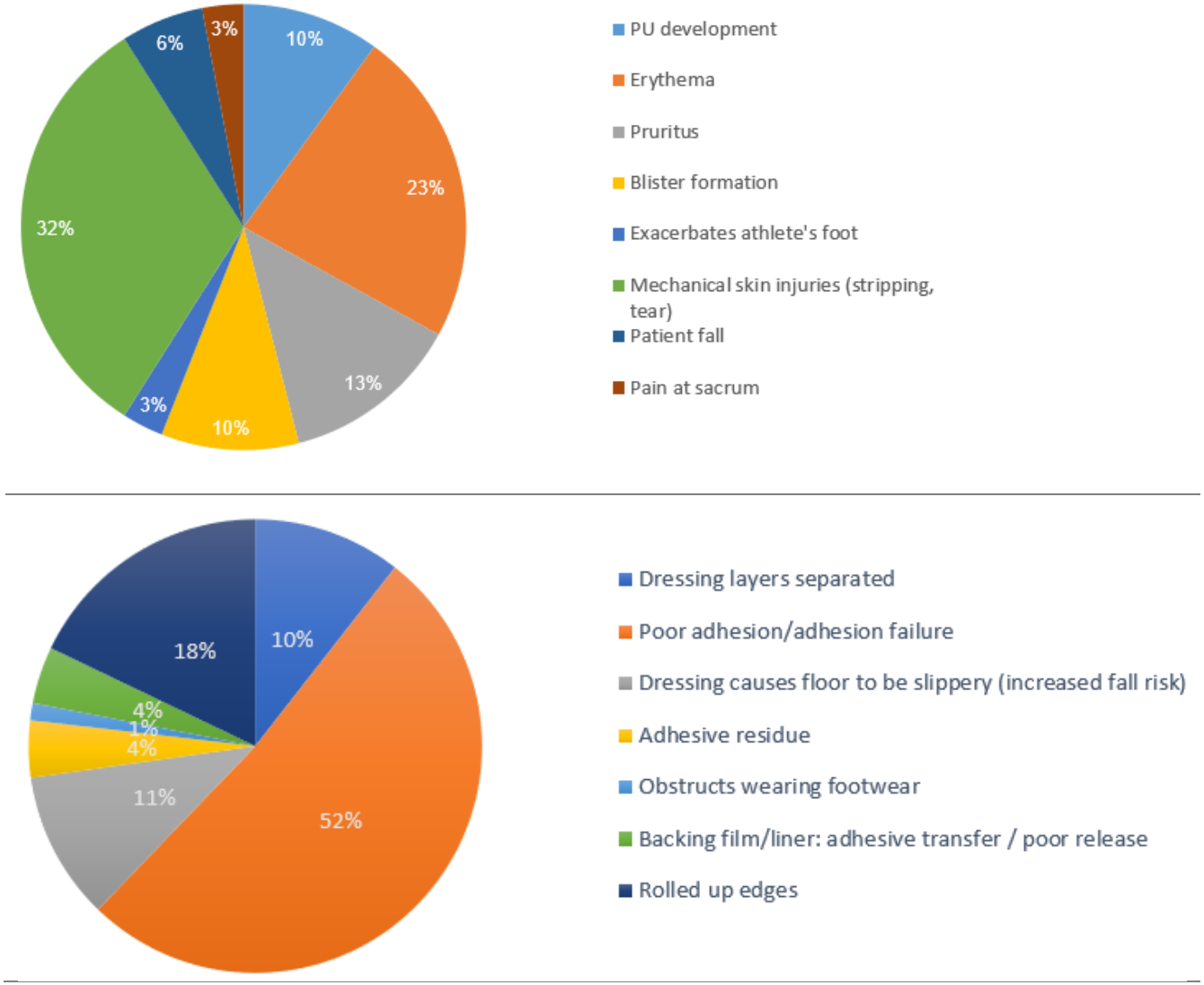
*The whiskers of the box plot are equal to the 25th percentile-1.5*interquartile range (IQR) and 75th percentile+1.5*IQR.*

3.2.6 Safety

The safety population (n=1077) was calculated after exclusion of participants in the ITT population who wanted their data excluded (n=1), who were not randomised (n=46), where no information was available on the number of dressings (n=10) or who received standard of care (n=546). For this study, only adverse effects or serious adverse effects related to the study intervention i.e. the study dressings and their application, have been reported. Categories had to be described as either a) adverse device effects, b) serious adverse device effects or c) device deficiencies - classified according to the seriousness of the event.

While no serious adverse device effects were reported during the study, 33 adverse device effects (ADEs) were reported from 28 patients of the safety population (n=1077). Most common ADEs reported were classified as “mechanical skin injury’ (n=11), ‘erythema’ (n=8), ‘pruritus’ (n=4) or ‘PU development’ (n=3). Also, 246 device deficiencies (DDs) were reported in 97 patients. Most DDs were related to poor adhesion/adhesion failure, rolled-up edges, dressing layers separation, dressing causing the floor to be slippery and increased risk of falling. Heel dressings (of both brands) caused a couple of falls (n=2) when the dressing was in direct contact with the floor. In some cases, it was reported (n=26) that heel dressings made the floor slippery for others, and in 1 case this resulted in a fall without significant harm.

Figure 8 – Adverse device effects (upper panel, n = 33) and device deficiencies (lower panel, n = 246) in the safety population (n = 1077)



3.2.7 Conclusion

The main findings of this multicentre randomised controlled trial were as follows:

- The use of multilayer dressings for prevention at sacrum, heels and trochanters significantly decreased the incidence of pressure ulcers (PU) category II or worse from 6.3% to 4.0% in hospitalized at-risk patients.
- While this effect was clearly seen for sacrum (from 4.8% to 2.8%), no clear effect was seen for heels (from 1.9% to 1.4%), and the incidence for trochanter was too low (only a single patient developed a pressure ulcer).

In conclusion, this large multicentre trial showed no clear protective effect of multilayer dressings for pressure ulcers at heels or trochanter sites when applied in hospitalised at risk patients. This randomised trial confirmed previous reports that multilayer dressings reduce the incidence of sacral pressure ulcers in hospitalised patients in conjunction with standard of care, both on ICU as well as on other wards. With a number needed to treat to prevent one new PU of 50, a health-economic analysis could be informative before such intervention is routinely implemented in hospitals.

Key points

- **A large RCT was conducted in 8 Belgian hospitals to investigate the (cost-)effectiveness of using multilayer silicone foam dressings as adjuvant prophylactic therapy for pressure ulcer prevention.[1, 17] It was concluded that the use of multilayer foam dressings for PU prevention significantly reduces the incidence of PUs. Of the 1605 participants in the ITT population, 77 (4.8%) developed a PU category II or worse (sacrum, trochanter, or heel); 4.0% in the treatment group and 6.3% in the control group receiving SoC.**
  - **The use of multilayer dressings on the sacrum for PU prevention clearly reduced the incidence of sacral PUs. PUs on the sacrum were observed in 2.8% and 4.8% of the patients in the treatment group and the SoC group, respectively.**
  - **No significant effect was seen on the heels. PUs on the heels occurred in 1.4% and 1.9% of patients in the treatment and SoC group respectively.**
  - **The incidence of PU on the trochanter was too low to show any effect. Only one patient developed a PU on the trochanter.**
- **The reported QoL was similar in both treatment groups.**
- **No serious adverse device effects were reported. Some less serious adverse device effects and defice deficiencies were documented during the trial. The heel dressings caused some falls.**

4 COST-EFFECTIVENESS: REVIEW OF ECONOMIC LITERATURE

Before conducting an economic evaluation for the Belgian situation, we give an overview of the findings in other economic evaluations. The aim of the literature review is not to identify whether or not PU prevention with silicone adhesive multilayer foam dressing is cost-effective or not for the studied population since the scope of the included economic evaluations differs substantially, especially regarding the included population. We are also not performing a critical assessment looking at potential sources of bias and confidence in conclusions of published studies. The aim of this review is to provide us with insights on e.g. the structure of the models, the most important variables, missing information, etc. This knowledge can be used to develop the context-specific evaluation.

4.1 Search strategy

A systematic search for economic literature about the cost-effectiveness of silicone adhesive multilayer foam dressings for the prevention of pressure ulcers was performed by consulting various databases. In November 2021, we checked in the EUnetHTA (European Network for Health Technology Assessment) Planned and Ongoing Projects (POP) database whether other agencies were doing/planning research on this topic. This non-public database is only accessible to EUnetHTA partners. Only our own study could be identified. Next, the international HTA database of INAHTA (International Network of Agencies for Health Technology Assessment) and the CRD (Centre for Reviews and Dissemination) HTA and NHS EED (National Health Service Economic Evaluation Database) databases were consulted. In January 2022, the websites of HTA institutes which are members of the INAHTA network were searched. Finally, also in January 2022, Medline (OVID) and EMBASE databases were searched to retrieve both full economic evaluations and reviews of full economic evaluations of silicone adhesive multilayer foam dressings for the prevention of pressure ulcers. A search filter for economic studies was complemented with search terms for dressings and pressure ulcers. Only articles in English, Dutch or French were selected. An overview of this search strategy and results is provided in Appendix 1.

4.2 Selection criteria

All retrieved references were assessed against pre-defined selection criteria, in terms of population, intervention, comparator, and design (Table 6). The aim of this project is to assess the cost-effectiveness of silicone adhesive multilayer foam dressings for the prevention of pressure ulcers in hospitalised patients at risk for pressure ulcer development in university/teaching and general hospitals. The population in this research question reflects the population of the underlying RCT.

We selected the economic evaluations to find out more about how cost-effectiveness was calculated in other studies, which were the most important variables, what were specific points of attention, etc. Therefore, we selected a broad population of hospitalized patients, no matter which type of hospital or ward they were hospitalized. The intervention was limited to the use of silicone adhesive multilayer foam dressings for the prevention of pressure ulcers. The comparator consisted of interventions reflecting the local standard of care. The design is restricted to full economic evaluations, i.e. studies comparing at least two alternative treatments in terms of costs and outcomes. Cost-minimization, cost-effectiveness, cost-utility, cost-benefit and cost-consequence analyses were eligible.

Table 6 – Economic evaluation selection criteria

	Inclusion criteria	Exclusion criteria
Population	Hospitalized patients	No specific restrictions
Intervention	Silicone adhesive multilayer foam dressings for the prevention of pressure ulcers	Treatment of pressure ulcers
Comparator	Standard of care (without use of multilayer foam dressings)	Interventions not reflecting standard of care
Outcome/Design	Full economic evaluations without restrictions on the used outcome (i.e. both QALYs and disease-specific outcomes were eligible)	Other designs such as cost calculations

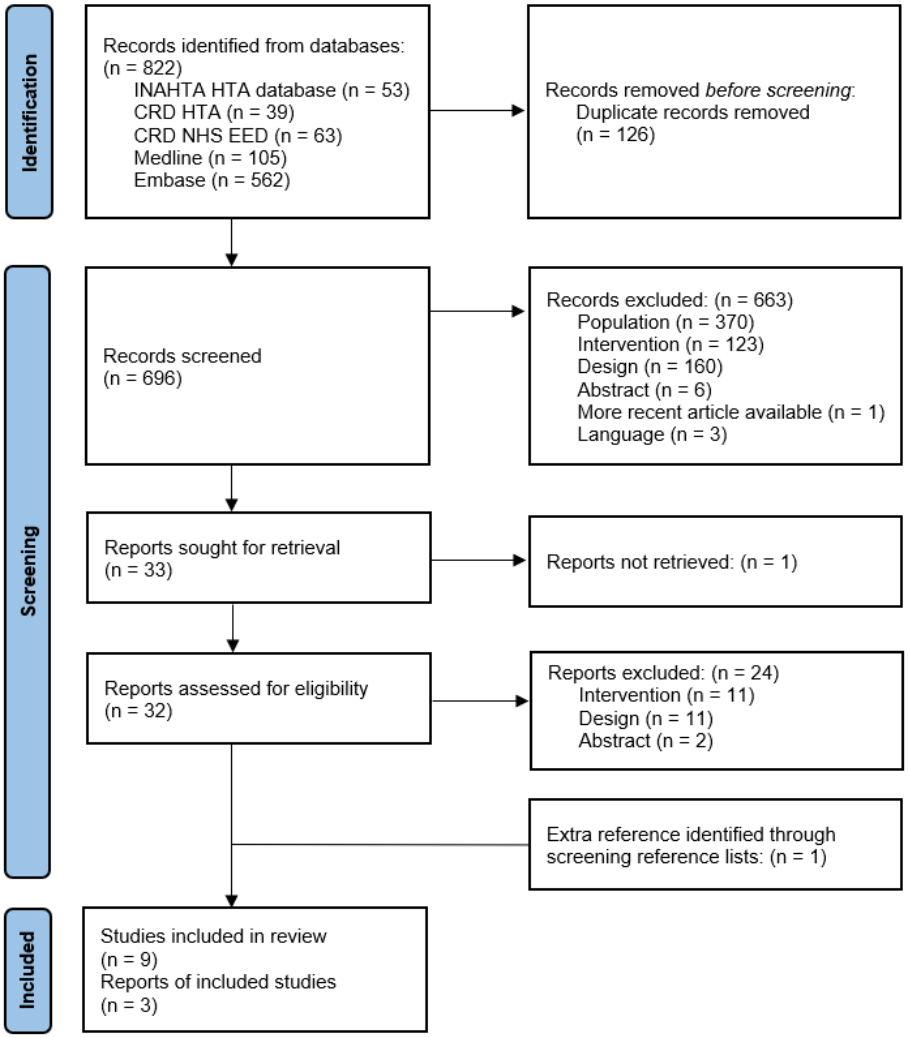
QALY: quality-adjusted life year

The selection of relevant articles was performed in a two-step procedure: initial assessment of the title, abstract, and keywords, followed by a full-text assessment of the selected references. When no abstract was available and the citation was unclear or ambiguous, consideration of the citation was directly made on the basis of a full-text assessment. Reference lists of the selected studies were checked for additional relevant citations. The primary full economic evaluations were summarized in an in-house data extraction sheet (see Appendix 2). This in-house document is used as a reporting checklist to gather all relevant information. The data extraction sheets of all identified studies are working documents that provide the basis for the summary tables and a critical assessment of identified economic evaluations.

4.3 Results of the economic search strategy

Figure 9 provides the PRISMA flow chart of the selection process. Eight articles were identified in the electronic databases.[19-26] An extra reference was identified through searching the reference lists.[27] Three reports[28-30] linked to the publication of Marshall et al.[24] were identified. The findings in these reports are considered simultaneously. Finally, Santamaria and colleagues published two studies based on the same underlying trial. The budget impact analysis is excluded[23] and only the cost-benefit analysis[22] that provides more details relevant for an economic evaluation is included in our overview. The list of selected economic evaluations is provided in Table 7. The list of excluded references and reason for exclusion is provided in Appendix 1.2.

Figure 9 – PRISMA flow diagram: identification of studies via databases



CRD HTA: Centre for Reviews and Dissemination Health Technology Assessment database; CRD NHS EED: NHS Economic Evaluation Database; INAHTA: International Network of Agencies for Health Technology Assessment.

Table 7 – Selected references

	References identified in databases
1	El Genedy M, Hahnel E, Tomova-Simitchieva T, Padula WV, Haus A, Löber N, Blume-Peytavi U,Kottner J. Cost-effectiveness of multi-layered silicone foam dressings for prevention of sacral and heel pressure ulcers in high-risk intensive care unit patients: An economic analysis of a randomised controlled trial. International Wound Journal. 2020;17(5):1291-9.[19]
2	Forni C, Searle R. A multilayer polyurethane foam dressing for pressure ulcer prevention in older hip fracture patients: an economic evaluation. Journal of Wound Care. 2020;29(2):120-7.[20]
3	Johnson C, Renwick C, Parkinson J, Burn K, Colledge D. Prophylactic dressing use to prevent heel ulceration in post-epidural orthopaedic patients. Wounds UK. 2018;14(1):84-9.[25]
4	Kalowes P, Messina V, Li M. Five-Layered Soft Silicone Foam Dressing to Prevent Pressure Ulcers in the Intensive Care Unit. American journal of critical care : an official publication, American Association of Critical-Care Nurses. 2016;25(6):e108-e19.[26]
5	Marshall C, Shore J, Arber M, Cikalo M, Oladapo T, Peel A, McCool R, Jenks M. Mepilex Border Sacrum and Heel Dressings for the Prevention of Pressure Ulcers: A NICE Medical Technology Guidance. Applied Health Economics and Health Policy. 2019;17(4):453-65.[24] The following three reports are linked to the above article. This assessment is performed by the NUTH and YHEC EAC. The findings in these reports are considered simultaneously. In first instance, the most elaborated report of Marshall et al.[28] is considered. If information was missing/unclear, the other reports were consulted. • Marshall C, Shore J, Arber M, Cikalo M, Peel A, McCool R, Jenks M, Taylor M. Mepilex Border Heel and Sacrum dressings for preventing pressure ulcers. Newcastle upon Tyne Hospitals (NUTH) and York Health Economics Consortium (YHEC) External Assessment Centre (EAC). May 2018.[28] • National Institute for Health and Care Excellence (NICE). May 2018. Mepilex Border Heel and Sacrum dressings for preventing pressure ulcers. Medical technology guidance – Assessment report overview.[29] This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the External Assessment Centre (EAC) report. • National Institute for Health and Care Excellence (NICE). January 2019. Mepilex Border Heel and Sacrum dressings for preventing pressure ulcers. Medical technologies guidance (MTG40).[30] www.nice.org.uk/guidance/mtg40
6	Padula WV, Chen YH, Santamaria N. Five-layer border dressings as part of a quality improvement bundle to prevent pressure injuries in US skilled nursing facilities and Australian nursing homes: A cost-effectiveness analysis. International Wound Journal. 2019;16(6):1263-72.[21]
7	Santamaria N, Liu W, Gerdtz M, Sage S, McCann J, Freeman A, Vassiliou T, DeVincentis S, Ng AW, Manias E, Knott J, Liew D. 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. 2015;12(3):344-50.[22] The following study is a budget impact analysis based on the same underlying trial. In our overview, we only discuss the cost-benefit analysis. • Santamaria N, Santamaria H. An estimate of the potential budget impact of using prophylactic dressings to prevent hospital-acquired PUs in Australia. Journal of Wound Care. 2014;23(11):583-4, 6, 8-9.[23]
	Reference identified in reference list
8	Johnstone A, McGown K. Innovations in the reduction of pressure ulceration and pain in critical care. Wounds UK 2013; 9: 3, 76–80.[27]

4.4 Overview of identified economic evaluations

4.4.1 General information

The eight included studies carried out evaluations for the UK (3), US (3), Australia (2), Germany (1) and Italy (1) (Table 8). A conflict of interest (CoI) is noticed in most papers, with an exception for the NICE assessment performed by Marshall et al..[24, 28] In this assessment, there is a CoI for the underlying company submission (CS), but not for the independent assessment of the External Assessment Centre (EAC). The declared conflict of interest consists of receiving financial support to perform the study or being an employee, paid consultant and member of the scientific advisory board of a company selling the dressings under investigation. We notice common authorship on the papers of El Genedy et al.,[19] Padula et al.[21] and Santamaria et al..[22] Three of the eight identified studies do not transparently report all information related to a full economic evaluation. Instead of excluding these studies, we preferred to keep them in the overview tables and refer to these studies where relevant.

One study[21] set up a Markov model, in which patients who developed a pressure injury simulated advancement through stages 1 to 4, to calculate the incremental costs per quality-adjusted life year (QALYs) gained. The other studies used a decision tree or bottom-up approach to perform a cost-benefit analysis (CBA) or cost-effectiveness analysis (CEA). In the CEA, a disease-specific outcome was used when better outcomes were accompanied with extra costs. In such cases, an incremental cost-effectiveness ratio (ICER) was calculated expressing the results in terms of cost per PU avoided.[19, 20] The approach of the bottom-up calculations and decision trees are comparable, i.e. in both cases the costs for preventive dressings in the intervention group and costs for treatment of pressure ulcers in both the intervention and comparator group are measured.

Mainly short-term horizons were modelled, in some cases restricted to the hospital stay period.[19, 22] Marshall et al.[24, 28] considered a time horizon of less than 1 year appropriate given that even stage IV pressure ulcers are expected to heal within 155 days.[31] The longest time horizon was 18 months,[21] reflecting the follow-up duration of the underlying trial. Only in this trial, a 3% discount rate was applied for both costs and effects. In all other studies, due to a time horizon of less than one year, discounting of future costs and effects was not required.

The majority of studies is performed from a hospital perspective. Padula et al.[21] state to perform the study from a societal perspective, but when looking at the included costs in their analysis, only prevention and treatment costs are included (see part 4.4.3). Therefore, this study also rather reflects the hospital perspective. Santamaria et al.[22] refers to a health care sector's perspective. Also this study only considers the within-trial cost, including the hospital resources and time used to provide PU care by hospital health professionals. This approach is comparable across the identified studies.

Table 8 – General information on the identified economic evaluations

Reference	Country	CoI	Analytic technique	Design	Time horizon	Discount rate	Perspective
El Genedy et al. (2020)	Germany	Yes	CEA (dis. spec.)	Bottom-up	average duration on ICU	NA	Hospital
Forni et al. (2020)	Italy & US	Yes	CEA (dis. spec.)	Decision tree	180 days	NA	Hospital
Marshall et al. (2019) & NICE (2018) CS/EAC	UK	Yes/No*	Cost-benefit analysis	Decision tree	<1 year	NA	NHS and Personal Social Services
Padula et al. (2019)	US and Australia	Yes	Cost-utility analysis	Markov model	18 months	3% for costs and effects	~~Societal~~ Hospital
Santamaria et al. (2015)	Australia	Yes	Cost-benefit analysis	Bottom-up	Hospital stay	NA	Hospital
Less detailed analyses							
Johnson et al. (2018)	UK	NR	NR	NR	NR	NA	NR
Johnstone et al. (2013)	UK	NR	Cost-benefit analysis	NR (bottom-up)	3 months	NA	NR
Kalowes et al. (2016)	US	NR	NR	NR	6 months	NA	NR

** While there is a CoI for the CS, there is no CoI for the EAC analysis.*
CEA: cost-effectiveness analysis; CoI: conflict of interest; CS: company submission; dis. spec.: disease specific; EAC: External Assessment Centre; NA: not applicable; NR: not reported

4.4.2 Population, intervention and comparator(s)

The populations in the identified economic evaluations differ from each other. They rely on different underlying RCTs or non-randomized studies with differences in mean age, gender ratio, and type of included patients (Table 9). For example, the underlying RCT in the economic evaluation of Santamaria et al.[22] included patients admitted to the emergency department (ED) and subsequently transferred to the intensive care unit (ICU) for critical illness and/or major trauma. These patients were mainly male (60%) with a mean age of 55 years. In contrast, the study of Padula et al.[21] refers to the Border III trial including patients in certain nursing home (NH) units where only 30% male patients were included and the mean age was about 85 years. The Italian RCT used in the economic evaluation of Forni et al.[20] included older patients (≥65 years) with fragility hip fracture where 81% were male. Also the risk assessment tool used in the selection criteria might differ between studies. For example, in Johnstone et al.,[27] patients could only be included in the underlying study if the Waterlow score >15, while Kalowes et al.[26] refer to a Braden score ≤13.

We refer to Table 9 for further information on all identified economic evaluations. The underlying characteristics of the selected patients impact the baseline risk for PUs and thus also the absolute benefit (see part 4.4.5.1) and the intervention's cost-effectiveness.

The intervention in all studies was standard prevention in combination with multi-layered silicone foam dressings applied to the sacrum and/or heels. Where specified, the intervention were five-layer dressings applied to the sacrum and/or heels. In the study of Marshall et al.,[24, 28] the External Assessment Centre (EAC) excluded the Mepilex three-layer dressings as

these were deemed to be out of scope given that they are a separate device utilising different technology.

The combination of standard prevention and multi-layered silicone foam dressings was compared with standard prevention. In several studies,[19, 21, 22, 24, 25, 28] a description of standard prevention was given, including a combination of patient information, nursing care and education, daily skin inspection and PU risk assessment, frequent repositioning, best support surfaces/pressure redistribution devices such as high-specification foam mattresses, other dressings or skin applications, nutrition, managing moisture and incontinence, etc. However, it is not clear in how far standard prevention in practice reflects this description and is comparable across countries. Differences in standard prevention might exist between countries and facilities. For example, in the study of Padula et al.,[21] support surface costs (e.g., beds and mattress toppers) were different between US and Australian models, applying Group II hospital beds and chair cushions at US skilled nursing facilities (SNFs), while air mattresses and air chairs were used at Australian nursing homes (NHs).

Table 9 – Population, intervention and comparator of the identified economic evaluations

Reference	Population (year inclusion patients) Mean age/% male in underlying trial	Underlying trial	Intervention	Comparator
El Genedy et al. (2020)	High- or very high-risk intensive care units patients (2015-2018) Mean age: 63.5y Male: 65.4%	RCT Germany (Berlin, Hahnel et al., 2020[32])	Standard prevention + multi-layered silicone foam dressings (sacral and heel)	Standard prevention
Forni et al. (2020)	Older patients with hip fractures (2016) Mean age: 83.7y Male: 80.5%	RCT Italy (Bologna, Forni et al., 2018[33])	Standard prevention + multi-layered silicone foam dressings (sacral)	Standard prevention
Marshall et al. (2019) & NICE (2018) CS/EAC	High-risk patients No details available for the pooled RCTs	Three RCTs: Aloweni et al., 2017;[34] Kalowes et al., 2016;[26] Walker et al., 2017[35]	Standard care + Mepilex Border Sacrum and Heel dressings	Standard prevention
Padula et al. (2019)	Residents with a high risk of developing PrIs at nursing homes (2016-2017) Mean age: 85y Male: 29.9%	RCT Australia (Melbourne, Santamaria et al., 2018) – the Border III trial[36]	Standard prevention + multi-layered silicone foam dressings (sacrum and heel)	Standard prevention
Santamaria et al. (2015)	Critically ill patients in the emergency department (ED) and intensive care unit (ICU) (2011-2012) Mean age: 55y Male: 60.1%	RCT Australia (Melbourne, Santamaria et al., 2013*) – the Border trial[37]	Standard prevention care + prophylactic silicone multilayered foam dressings (sacrum and heels)	Standard prevention

Less detailed analyses				
Johnson et al. (2018)	Patients undergoing hip repair under spinal/epidural anaesthesia (NA) Mean age: / (range 49-86y) Male: 47.1%	Non-randomized small quality assurance study on an orthopaedic ward in the UK	Standard prevention + 5-layer soft silicone dressing on the heel	Standard prevention
Johnstone et al. (2013)	High-risk patients admitted to the critical care units in two large teaching hospitals (2012) Mean age: / (>65y) Male: /	Non-randomized study in two large teaching hospitals in the UK	3-month period with five-layer silicone foam dressing (sacrum)	3-month period with standard care
Kalowes et al. (2016)	Critically ill patients admitted to the cardiac, medical, surgical, and trauma ICUs. (2011-2012) Mean age: 65.9y Male: 55.5%	RCT, US (Kalowes et al. 2016[26]).	Standard pressure ulcer prevention + 5-layered soft silicone foam dressing (sacrum)	Standard prevention

** the study refers to a publication of Santamaria et al in 2013. This article was finally published in 2015.[37] CS: Company Submission; EAC: External Assessment Centre; PrIs: Pressure injuries*

4.4.3 Costs

An overview of the cost items and their valuation included in the identified economic evaluations is provided in Table 10. The costs include direct costs for the preventive dressings (intervention group) and PU treatment costs. We remark that the studies of Johnson et al.[25] and Kalowes et al.[26] do not provide a detailed cost analysis. In the study of Johnstone et al.,[27] the cost calculations were also not clear: the costs of standard PU treatment per day were compared with the costs of PU prevention per day. However, not all patients have PU and it is not clear whether and how this was taken into account.[27]

Costs for the standard PU prevention are not presented separately because the dressings are used in addition to standard care protocols for pressure ulcer prevention. Therefore, it is assumed that standard PU prevention is provided in both groups equally, and thus the related costs are assumed to be similar in both groups.[19, 22, 24, 28] Any implementation or training costs associated with the introduction of the dressings are also not included. This was judged to be appropriate by the EAC because free training is provided by the company and staff time associated with this was considered to be negligible on a per patient basis.[28] In contrast to all other studies, Padula et al.[21] applied a micro-costing method to calculate the full costs of prevention, including nursing time costs, time spent conducting assessment and repositioning, cost of skin care management related to moisture and incontinence, costs of nutritional supplements, costs of support surfaces and an extra 25% of total standard care cost to account for any costs overlooked in the calculation. However, in the end, it's the incremental costs that impact the result of the economic evaluation, thus solely focusing on the differences between the intervention and comparator group is appropriate.

The direct costs for preventive dressings in the intervention group were measured using a bottom-up approach, combining the number and cost of dressings used per patient and the time needed per dressing application.[19]

- The unit cost of the dressing was context-specific with relatively lower costs for sacrum versus heel dressings (see Table 10). This cost is multiplied with the number of dressings used per patient, which varies widely from an average of 1.25 sacrum and 2.12 heel dressings (Santamaria et al.[22]) to respectively 4.95 and 10.66 sacrum and heel dressings (El Genedy et al.[19]). In the UK analysis,[24, 28] the number of dressing in the company's model was based on Santamaria et al.,[37] an RCT conducted in Australia. This was amended by the EAC using data from a single arm observational study conducted in the UK because this was judged to be more reflective of resource use in the NHS. Minor amendments were also made to other resource use parameters, including staff costs and dressing costs.[28]
- In general, if mentioned, authors indicate dressings are changed every 3 days and additionally in case of becoming soiled or dislodged.[19, 22] The time per dressing application or change takes about 2 minutes.[19] This time is limited since the dressing application or change was performed when the patient was turned over and held by nurses as part of regular repositioning, skin inspections or other medical examinations.[19] In the study of Forni et al.,[20] the time taken to change the dressing was estimated at 15 minutes. However, the authors mention this is a very conservative estimate and in practice the actual time is likely to be much shorter than this. The time needed to apply or change the dressing is multiplied with the nursing time cost, varying between €18/hour (Italy[20]) and £37.2/hour (UK[28]).

The highest additional cost for PU prevention of €150.81 per patient was calculated in the study of El Genedy et al.[19] due to the relatively high number of applied dressings.

While the extra cost of PU prevention is only relevant for the intervention group, costs for the treatment of incident pressure ulcers applies in both groups. We provide an overview of included costs in the identified economic evaluations in Table 10. Where information was available, treatment costs are expressed according to the category of PUs.

- In the study of El Genedy et al.,[19] PU treatment costs were categorised into material costs (dressings, gloves and further medical consumables) and labour costs (external wound consultations, wound assessment and documentation, wound care). The total costs for PU treatment in the intervention group (n = 6 PUs) were €134.88 (€106.77 material; €28.11 labour costs) with an average cost of €22.48 per patient. In the control group (n = 22 PUs) the total costs for treatment were €569.49 (€445.96 material; €123.53 labour costs) with an average of €25.89 per patient.[19] No impact of a potential prolonged stay in hospital was included in this study.

This relatively low cost contrasts with the PU treatment costs in other studies:

- In the Italian analysis of Forni et al.,[20] The cost of treating a PU from the hospital perspective was derived from an analysis of patients with PUs in Italy.[38] The majority of these patients were >65 years of age. The mean cost per patient episode of PU of €5500 was adjusted to 2017 prices using health-care inflation indices for Italy,[39] to give a unit cost per episode of €6878.

  In their US analysis, the cost of treating a PU from the hospital perspective was derived from a retrospective analysis of a large US hospital database. In a matched sample of 110 808 patients, after adjustment, hospitalisation costs for the patients with hospital-acquired PUs (HAPU) cost an average of $8014 more compared with control patients.[40]
- In the study of Marshall et al.,[24, 28] the EAC did not identify any robust cost sources reporting the cost of pressure ulcers (by stage) at specific locations. The source used for the cost of PU treatment in the company's model, although UK-specific, was considered to be outdated. The EAC used a UK-specific source[41] with high event numbers to weight the costs by stage. The staging of pressure ulcers was assumed to be equal in both treatment arms and PU treatment was estimated to cost £4823.

- In the US model of Padula et al.,[21] the authors assumed an average length of stay (LoS) for stages 1 and 2 of 8 days per cycle (the model simulated outcomes in 1-month cycles) and 4 days per cycle for stages 3 and 4 and unstageable PrIs. The average total treatment cost of stages 1 and 2 was $8454 per cycle and $22 852 per cycle for stages 3 and 4 and unstageable PrIs. Surgery costs were $142 633, which comprised hospital accommodation, operating room services, pathology, etc.[42] In the Australian model, relatively lower costs were calculated with a treatment cost per cycle (excluding accommodation costs) of $76.17 (stage I), $337.97 (stage II), $553.77 (stage III), $1716.38 (stage IV), and $500.05 (unstageable PU). The cost of surgery for full-thickness PUs, based on Australian Refined Diagnostic Related Group (AR-DRG), totalled $48 654.[21]
- Santamaria et al.[22] included the material and labour costs to calculate the within-trial PU treatment cost. The costs per episode (20 days) varied between $864.4 (stage I sacral ulcer) and $1469 (stage IV heel ulcer).
- In the study of Johnson et al.,[25] not much detail was provided and the individual dressing cost of about £7 was compared with a potential cost of £6000 for the management of one category II pressure ulcer.

El Genedy et al.[19] and Santamaria et al.[22] remark that costs of PU treatment might be underestimated since costs associated with the PUs after the patients had been discharged from the hospital were not included in the analysis.

Table 10 – Costs in the identified economic evaluations

Reference	Currency and year of costs	Resource use PU prevention	Monetary value	
			PU prevention	PU treatment
El Genedy et al. (2020)	€, 2015-2018	Dressings/ptn: - sacrum: 4.95 - heel: 10.66 Nursing time/dressing: 2 min.	Unit cost dressing: - sacrum: €5.81-7.84 - heel: €9.86 Nurse time: €0.53/min. (€31.83/hour) Total costs: €150.81/ptn	Material and labour costs: - Int. group (6 PUs): €22.48/ptn - Control group (22 PUs): €25.89/ptn
Forni et al. (2020)	€ (Italy) & $ (US), 2017	Dressings/ptn: 1.8 Nursing time/dressing: 15 min.	Dressing and other materials: - Italy: €5 - US: $10 Nurse time: - Italy: €0.3/min. (€18/hour) - US: $0.59/min. ($35.36/hour)	- Italy: €6878 - US: $8014
Marshall et al. (2019) & NICE (2018) CS/EAC	£, 2016-2017	CS – Dressing/ptn: - sacrum: 2 - heel: 4	CS – Unit costs dressing: - sacrum: £4.44 - heel: £7.21	CS: - Int. group: £3111 - Control group: £3858

		EAC – Dressing/ptn: - sacrum: 4 - heel: 6 Nursing time/dressing: 2 min.	EAC – Unit costs dressing: - sacrum: £4.63 - heel: £6.50 Nurse time: - CS: £0.51/min. - EAC: £0.62/min.	EAC: - Int. group: £4823 - Control group: £4823
Padula et al. (2019)	$, 2017	No detail on number of dressings (3 days per dressing) Nursing time/dressing: 2 min.	Unit cost dressing: - US: $18 - Australia: $12 Nurse time: $0.52/min. Total cost prevention: US - standard care: $109/day - intervention: $115/day Total cost prevention: Australia - standard care: $64/day - intervention: $68/day	Average total treatment cost: US - stage I&II (8 days): $8454/cycle (1 month) - stage III&IV and unstageable (4 days): $22 852/cycle (1 month) - surgery: $142 633 Average total treatment cost: Australia - stage I: $76.17 - stage II: $337.97 - stage III: $553.77 - stage IV: $1716.38 - unstageable: $500.05 - surgery: $48 654.10
Santamaria et al. (2015)	AU$, 2013	Dressings/ptn: - sacrum: 1.25 (274 for 219 ptns) - heel: 2.12 (465 for 219 patients) Nursing time/dressing: 2 min.	Unit cost dressing: - sacrum: AU$11 - heel: AU$9 Nurse time: AU$0.49/min. (AU$29.2/hour) Average marginal cost PU prevention: AU$36.61	Treatment cost of PUs (AU$): Stage I: sacrum & heel - 43.22/day; 864.4/episode* Stage II: sacrum - 57.14/day; 1142.8/episode Stage II: heel - 58.85/day; 1177/episode Stage IV: heel - 73.45/day; 1469/episode * episode of 20 days
Less detailed analyses				
Johnson et al. (2018)	£, NR	NR	Dressing cost: £7	Cat. II PU: £6000
Johnstone et al. (2013)	£, 2012	Dressings/ptn: 4	Unit cost dressing: £4.5 (or £1.5/day)	PU treatment cost: £31.06/day
Kalowes et al. (2016)	$, NR	NR	NR	NR

/day: per day; /episode: per episode; /ptn: per patient; AU$: Australian dollars; CS: company submission; EAC: External Assessment Centre; Int. Group: intervention group; min.: minutes; ptns: patients; PU: pressure ulcer.

4.4.4 Adverse events

Concerning the adverse events, not much information is retrieved form the identified economic evaluations. Kalowes et al.[26] mention no adverse events related to the experimental (Mepilex Border Sacrum) foam dressing were noted. In the UK analysis, the reviewer group noted adverse events were excluded from the company's model. This was considered appropriate by the reviewers since very little evidence of adverse events was identified, and where these were identified, they were associated with very little or no cost.[24, 28]

4.4.5 Treatment effect

4.4.5.1 Pressure ulcers

In Table 11, we provide an overview of the modelled treatment effect, based on information from the underlying trial. The information shows important differences in both the description of PUs, baseline risk and relative/absolute treatment effect.

We remark that the description of the outcome might be different between studies, making comparisons more complicated. In the study of El Genedy et al.,[19] the primary outcome was the cumulative incidence of PUs of category II, III, IV, unstageable and deep tissue injury (DTI) at heels or sacrum developed in the ICU. This is the only study that explicitly limits the outcomes to ≥category II PUs (see Table 11). In Forni et al.,[20] the base case includes any grade of PUs and excludes category I PUs only in a scenario. In the latter study, the absolute benefit is smaller when category I PUs are excluded (absolute risk reduction (ARR) of 5.9% instead of 10.9%).

The UK analysis[28] shows the importance of taking into account the baseline risk of developing PUs in the relevant patient population. The company's submission included data from Santamaria et al.,[22] however the pressure ulcer incidence from this trial appeared to be much higher than would be expected in the UK. Instead, the reviewer group used data from a meta-analysis of three trials.[26, 34, 35] The EAC deemed it more appropriate to identify a baseline incidence of PUs from a UK-specific source for use in the standard-care arm.[b] This was then combined with a relative risk from the meta-analysis to derive a risk of pressure ulcers in the standard care plus Mepilex Border dressings arm.[28] The absolute gain was very different comparing the company submission versus the reviewer's re-analysis: 10% versus 1.9%.

The information provided in the study of Padula et al.[21] is somewhat confusing. The included treatment effect does not reflect the evidence from the underlying trial (see Table 11). In contradiction with the other identified economic evaluations, an impact on mortality is also modelled, not being supported by reliable evidence.

In the study of Santamaria et al.,[22] the primary outcome measured in the underlying RCT was the incidence rates of PUs in the ICU developed in both groups. The results of this trial showed that 13.1% of patients (n =20) in the control group developed a PU on the sacrum or heel compared with 3.1% of patients (n =5) in the intervention group (P=0.001).[22]

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[b] The approach to estimating the baseline risk also involved uncertainty and was described as follows: "*A targeted literature search was conducted by the EAC to identify a UK-specific incidence of pressure ulcers in a population at risk or at high risk of pressure ulcer. The NHS safety thermometer was deemed to be the most useful source by the EAC because, although a voluntary scheme, most NHS trusts submit data every month on the prevalence of pressure ulcers, along with other safety measures.[43] Prevalence of new pressure ulcers is reported (whereby data are recorded on one day each month only and new pressure ulcers are those that have occurred since the last month). The EAC used this value as a proxy for incidence of pressure ulcers. Due to limitations associated with the data , the EAC adjusted the value from the NHS safety thermometer to account for known under-reporting and the fact that only stage II or higher pressure ulcers were reported.[44, 45] The value was further adjusted to include only pressure ulcers on the heel and sacrum.[44]*"[24]

There were also two non-randomized studies. In the small quality assurance study undertaken on an orthopaedic ward by Johnson et al.,[25] no tissue damage occurred in the study group (n=87) during the wear time or whilst in hospital. In the comparator group, 12 patients (18.75%) developed category II heel pressure ulcers during the same period. In the non-randomized study of Johnstone et al.,[27] over a 3-month period with standard care (intensive nursing care, use of dynamic therapy surfaces and proactive pressure ulcer prevention strategies), 33% (20/60) patients had sacral cleft ulcers. In the 3-month period that a five-layer silicone foam dressing was applied to the sacrum, the incidence of pressure ulceration development in the sacral cleft was 0% (0/75).[27]

Finally, also the study of Kalowes et al.[26] revealed a significant treatment effect (hazard ratio (HR) = 0.12, 95%CI 0.02 – 0.98, p = 0.048). The incidence rate of hospital-acquired PUs was significantly less in patients treated with the foam dressing than in the control group (0.7% vs 5.9%, p = 0.01) or an absolute difference of 5.2%.

Table 11 – The underlying trial and treatment effect in the identified economic evaluations

Reference	Population (year inclusion patients) Mean age/% male in underlying trial	Underlying trial	Treatment effect
El Genedy et al. (2020)	High- or very high-risk intensive care units patients (2015-2018) Mean age: 63.5y Male: 65.4%	RCT Germany (Berlin, Hahnel et al., 2020[32])	PU ≥cat. II (sacral and heel) - Intervention: 2.8% - Comparator: 10.5% Relative risk: 0.26 (95%CI 0.11 – 0.62) Absolute risk reduction: 0.08 (95%CI 0.03 – 0.13) NNT: 12.3 (95% CI 29.9 – 7.8)
Forni et al. (2020)	Older patients with hip fractures (2016) Mean age: 83.7y Male: 80.5%	RCT Italy (Bologna, Forni et al., 2018[33])	PU sacrum (any grade): - Intervention: 4.5% - Comparator: 15.4% Relative Risk: 0.29 (95%CI 0.14 – 0.61) NNT: 9 (95%CI 6 – 21) PU sacrum (scenario excl. cat. I PU): - Intervention: 3.4% - Comparator: 9.3%
Marshall et al. (2019) & NICE (2018) CS/EAC	High-risk patients No details available for the pooled RCTs	Three RCTs: Aloweni et al., 2017;[34] Kalowes et al., 2016;[26] Walker et al., 2017[35]	Company submission (based on Santamaria et al.[22]): PU ≥cat. I: - Intervention: 3.1% - Comparator: 13.1% Changed values by EAC: PU ≥cat. I (sacrum): - Intervention: 1.9% - Comparator: 3.8%

			RR = 0.51 (95% CI 0.22.1.18)
Padula et al. (2019)	Residents with a high risk of developing PIs at nursing homes (2016-2017) Mean age: 85y Male: 29.9%	RCT Australia (Melbourne, Santamaria et al., 2018) – the Border III trial[36] *Information from the underlying trial: PU (sacrum and heels):* - *Intervention: 2.1%* - *Comparator: 10.6%* *Relative risk reduction (RRR): 80%* *absolute risk reduction (ARR): 8.5%* *number needed to treat (NNT): 12*	Baseline risk: unclear US model: - 67% less stage I & II PUs - 47% less full-thickness PUs Australian model: - 64% less stage I PUs - 69% less stage II PUs - 46% less full-thickness PUs
Santamaria et al. (2015)	Critically ill patients in the emergency department (ED) and intensive care unit (ICU) (2011-2012) Mean age: 55y Male: 60.1%	RCT Australia (Melbourne, Santamaria et al., 2013*) – the Border trial[37]	PU (any grade): - Intervention: 3.1% - Comparator: 13.1% Hazard ratio: 0.198 (95%CI 0.065 – 0.555) ARR: 10% NNT: 10
Less detailed analyses			
Johnson et al. (2018)	Patients undergoing hip repair under spinal/epidural anaesthesia (NA) Mean age: / (range 49-86y) Male: 47.1%	Non-randomized small quality assurance study on an orthopaedic ward in the UK	PU (cat. II heel): - Intervention (n=87): 0% - Comparator (n=64): 18.75%
Johnstone et al. (2013)	High-risk patients admitted to the critical care units in two large teaching hospitals (2012) Mean age: / (>65y) Male: /	Non-randomized study in two large teaching hospitals in the UK	Rate of recorded sacral cleft ulcers: - 3-month prior period: 33% (20/60) - 3-month evaluation period: 0% (0/75)
Kalowes et al. (2016)	Critically ill patients admitted to the cardiac, medical, surgical, and trauma ICUs. (2011-2012) Mean age: 65.9y Male: 55.5%	RCT, US (Kalowes et al. 2016[26]).	PU (sacrum): - Intervention: 0.7% (1/184) - Comparator: 5.9% (7/182) Hazard ratio: 0.12 (95%CI 0.02 – 0.98)

** the study refers to a publication of Santamaria et al in 2013. This article was finally published in 2015.[37]*

4.4.5.2 Quality of life

In the analysis by NICE,[28] it is explicitly stated that QoL was not considered as an outcome within the analysis. Only the study of Padula et al.[21] calculated QALYs. In their US model, the mean utility of Americans >55 years was 0.764 QALYs.[46] In the Australian model, this was 0.703 for Australians >71 years.[47] The authors assumed that, compared with people without PUs, the utility of people with stage I or II PUs was 6% lower. A further reduction of 22% was assumed if patients had higher-stage PUs.[48] Patients who recovered were assumed to return to the same utility without PUs. Rather strange, a utility reward was given to patients who received a proper prevention bundle, including a dressing. Furthermore, a disutility of -0.155 was modelled for surgery.[48] The underlying evidence refers to a modelling exercise[48] based on a large number of assumptions and other resources and is unfortunately rather weak.

4.4.6 Results

Most studies provide results that indicate costs savings when using multi-layered silicone foam dressings.[20, 22, 24-28] In two studies, a separate analysis is presented for the sacrum and provided more favourable results in comparison with the heel.[19, 28] The results of the included studies are presented in Table 12 and are as follows:

- El Genedy et al.:[19]

  In the base case, the ICER for additional preventive dressings compared with hospital PU standard care alone was €1945.30 per PU avoided. The analysis of the ICERs for preventive dressings separated by heels and sacrum shows more favourable results in the sacrum group, i.e. €8144.72 per heel and €701.54 per sacrum PU avoided.

- Forni et al.:[20]

  Switching to foam dressing and standard prevention would result in an expected cost saving of €733 per patient in Italy and $840 per patient in the US, and an expected reduction in PU incidence of 10.9%. An analysis excluding category I PUs demonstrated that the dressing intervention continued to dominate standard prevention alone.

- Marshall et al.:[24, 28]

  In the company's model, base-case results estimated dressings generated cost savings of £177 per patient.

  In the reviewer's group reanalysis, on average, the dressings were also dominant, with cost savings being somewhat lower than in the company's model. In the probabilistic model, most simulations showed cost savings. Results for the sacrum were more favourable in comparison with the heel and sacrum together.

- Padula et al.:[21]

  Dressing use yielded greater QALYs with an ICER of $36 652/QALY for the US model and $15 898/QALY for Australia. However, we note the uncertainty around the QoL assumptions made in this analysis (see part 4.4.5.2) and refer to the original studies for further details on incremental costs and effects.

- Santamaria et al.:[22]

  The intervention cost was estimated to be AU$36.61 per person, which was offset by lower downstream costs associated with PU treatment (AU$1103.52). Therefore, the average net cost of the intervention was lower than that of the control (AU$70.82 versus AU$144.56).

- Johnson et al.:[25]

  In this study, the cost of treating the 12 category II ulcers (£72,000) in the comparator group was compared with the individual dressing cost of about £7.00 in the intervention group.

- Johnstone et al.:[27]

  If the five-layer silicone foam dressing were to be included as a prophylactic dressing into a package of care, based on the mean treatment duration of 9 days per patient, there would be an average cost saving of £266.04 per patient.

- Kalowes et al.:[26]

  This analysis did not conduct a comprehensive cost analysis.

  More general results indicate the health system's annual cost for the prophylactic dressings is $130 000, while organizational estimates demonstrate that savings of more than $1 million has been amortized in the past 2 years, after dressing purchase.

Not surprisingly, the most determining variables were the incidence of PUs[19, 20, 24, 28] and the cost of prevention/dressing costs.[19, 21, 22] As mentioned in the NICE report, cost-savings are increased where the baseline incidence of pressure ulcers with standard care increases.[29] In individual studies, also the number of used dressings,[19] the cost of treating PUs,[20] and the frequency and time required for dressing changes[22] were identified as the most influential variables.

Table 12 – The results of the identified economic evaluations

Reference	Result
El Genedy et al. (2020)	Base case: €1945.30 per PU avoided - heels: €8144.72 per heel PU avoided - sacrum: €701.54 per sacrum PU avoided
Forni et al. (2020)	Cost saving (both inclusive and exclusive cat. I PUs)
Marshall et al. (2019) & NICE (2018) CS/EAC	Company's base case: cost savings of £177 per patient Mepilex: Dressings £38; Staffing costs £73; PU treatment costs £120 Standard care: Dressings £0; Staffing costs £0; PU treatment costs £408 EAC analysis: - Sacrum & heel: Cost savings of £19/ptn (57% cost saving). - Sacrum: Cost savings of £27/ptn (81% cost saving)
Padula et al. (2019)	ICER: - US: $36 652/QALY - Australia: $15 898/QALY
Santamaria et al. (2015)	Average marginal cost intervention: AU$36.61 Average treatment cost per ulcer: AU$1103.52 Weighted average treatment cost: - Intervention: AU$34.21 - Control group: AU$144.56 Total average cost: (cost savings) - Intervention: AU$70.82 - Control group: AU$144.56
Johnson et al. (2018)	Comparator group: cost of treating the 12 cat. II ulcers: ~£72 000 Intervention group: individual dressing cost: ~£7
Johnstone et al. (2013)	With mean treatment duration of 9 days: average cost saving of £266.04 per patient (or cost saving of £29.56 per patient per day)
Kalowes et al. (2016)	Cost saving

/ptn: per patient; ~: approximately.

4.4.7 Authors' conclusions

In Table 13 we provide an overview of the authors' conclusions. In general, all are in favour of using multi-layered silicone foam dressings. It is of importance to mention the setting in which these dressings are used (see part 4.4.2 for the underlying population). For example, in the NICE dossier,[24] the key points mention that "Mepilex Border Heel and Sacrum dressings show promise for preventing pressure ulcers in people who are considered to be at risk in acute-care settings. However, there is currently insufficient evidence to support the case for routine adoption in the NHS." Research is recommended to explore issues such as "the incidence of heel and sacrum pressure ulcers in NHS acute-care settings and criteria for patient selection to reduce pressure ulcer incidence with Mepilex Border Heel and Sacrum dressings in addition to standard care."[24] This is related to the baseline PU risk that determines the intervention's cost-effectiveness. We elaborate on this in the discussion (see part 7.2.3).

Table 13 – The authors' conclusions of the identified economic evaluations

Reference	Authors' conclusions
El Genedy et al. (2020)	We conclude that application of preventive dressings is cost-effective for the sacral area, but only marginal on heels for critically ill patients.
Forni et al. (2020)	The foam dressing intervention is likely to be a cost-effective strategy compared with standard prevention alone.
Marshall et al. (2019) & NICE (2018) CS/EAC	The EAC concluded that, despite a relatively large body of clinical evidence, there remains uncertainty in the treatment effect of Mepilex Border dressings. In particular, there are limited data for Mepilex Heel and Mepilex Border general (applied to the heel or sacrum) dressings, patients 'at risk' but not 'at high risk' of pressure ulcers, and paediatric patients. Further, many of the outcomes of interest to the decision problem are not addressed by the evidence.
Padula et al. (2019)	A quality improvement bundle, including prophylactic five-layer dressings, is a cost-effective approach for pressure injury prevention in all US and Australia long-term care residents.
Santamaria et al. (2015)	We conclude that the use of soft silicone multilayered foam dressings to prevent sacral and heel PUs among critically ill patients results in cost savings in the acute care hospital.
Johnson et al. (2018)	As a result of this study, the 5-layer soft silicone foam dressing is used prophylactically on patients undergoing spinal anaesthesia and has proven to be an invaluable addition to the organisation's pressure injury prevention strategy. No avoidable pressure injuries have been seen in our organisation in the past 12 months.
Johnstone et al. (2013)	Introducing a prophylactic dressing within critical care as a prevention strategy was demonstrated to be effective in reducing the incidence of ulceration to the sacrum. Auditing and comparing data collected over the 6 months in both units has been useful to demonstrate how practice can be changed and patient's outcomes improved. This evaluation highlights that nurses have embraced the challenge of improving quality and outcomes for their group of patients in critical care.
Kalowes et al. (2016)	Use of a soft silicone foam dressing combined with preventive care yielded a statistically and clinically significant benefit in reducing the incidence rate and severity of HAPUs in intensive care patients. This novel, cost-effective method can reduce HAPU incidence in critically ill patients.

HAPUs: hospital-acquired pressure ulcers.

Key points

- **Based on the economic literature identified, the additional costs for the preventive treatment (dressings and time investment) appear to be relatively small. In contrast, the costs associated with pressure ulcer treatment are estimated to be quite high in most studies.**
- **The underlying trials show a positive treatment effect, but large differences exist in terms of population, description of the outcome, baseline risk, and absolute and relative risk reduction.**
- **The majority of authors conclude that the multilayer foam dressing is (likely) cost-effective or cost-saving as an additional measure to prevent PUs.**

5 DATA ANALYSIS: BELGIAN DATA

In order to perform an economic evaluation for Belgium (chapter 6), we first collect relevant Belgian data. We use information from the Belgian multicentre randomized trial described in chapter 3. We also link data from the participants in this trial to reimbursement data from the Intermutualistic Agency (IMA, InterMutualistisch Agentschap – Agence InterMutualiste (IMA – AIM)) to identify the total duration of the hospitalization and see whether we can identify relevant information on specific (incremental) PU related costs.

5.1 Methods

5.1.1 Study population

The study population was drawn from the multicentre, randomised controlled, open label, parallel group medical device trial, that was performed in 8 hospitals in Belgium (UZ Gent, AZ Groeninge, UZ Brussel, OLV Aalst, AZ Sint-Elisabeth, UZ Leuven, AZ Maria Middelares and OLV van Lourdes ziekenhuis Waregem). Patients were randomly allocated to three study arms based on a 1:1:1 allocation (see 3.1).

For this HTA report, a request was sent to the participating hospitals to have their agreement to participate in the present study. A coupling of data of the clinical trial and healthcare reimbursement data via the e-health platform was authorised by the Information Security Committee (IVC – Informatieveiligheidscomité) in deliberation 20/190 on the 1st of September 2020. The participating hospitals received instructions to submit a file with the participants' study number and the corresponding patients' unique social security identification number to the eHealth platform, that performed the linkage of the clinical study data and the IMA data.

All but one of the hospitals participating in the underlying RCT accepted to contribute to this study. Patients without Belgian health insurance and thus no healthcare reimbursement data were excluded from the analysis. As such, 88.7% of the trial participants (ITT population) were included in this

follow-up study (see Table 14). Following the IVC deliberation, KCE received the final pseudonimised database on 17 October 2022.

Table 14 – Participating (ITT) patients in the RCT and in the data analysis

Site ID	Patients in the RCT	Patients in the data analysis	% patients included in the data analysis
UZ Gent	227 (13.90%)	183 (12.64%)	80.6*
AZ Groeninge	272 (16.66%)	266 (18.37%)	97.8
UZ Brussel	220 (13.47%)	212 (14.64%)	96.4
OLV Aalst	64 (3.92%)	64 (4.42%)	100
AZ Zottegem	242 (14.82%)	234 (16.16%)	96.7
AZ Maria Middelares	287 (17.58%)	273 (18.85%)	95.1
OLV Waregem	239 (14.64%)	216 (14.92%)	90.4
UZ Leuven	82 (5.02%)	0 (0%)	0
Total	**1 633**	**1 448**	**88.7**

** Remark: the underlying reason why data was missing was not tracked. It was indicated that a large number of foreign patients were being treated in the hospital, but exact figures were not available.*

5.1.2 Selection of data

Information from the following two sources was linked:

- **Clinical study report KCE-16012 data**: For the present study, data from the clinical study KCE-16012 were used.
- **IMA data**: Cost information was retrieved from the IMA database. In Belgium, residents must, in principle, have a compulsory health insurance provided through one of the seven national sickness funds. Healthcare reimbursement data are available at IMA. IMA is a non-profit organisation that manages and analyses information on all reimbursements related to the compulsory health insurance, collected by the Belgian sickness funds. These data cover all reimbursed services, both ambulatory and in-hospital (consultations, pharmaceuticals, diagnostic and therapeutic procedures), and some patient socio-demographic and socio-economic characteristics.
- For the present study, the data were retrieved for all reimbursed healthcare services from the first day of the index hospitalisation (i.e. the hospital stay in the clinical study) to one year (365 days) after the first day of the index hospitalisation. All the actual dates were coded as relative dates, where the day of inclusion in the RCT was the reference point in time (day 1).

5.1.3 Study groups

The two groups of patients that were studied are the standard of care (SoC) group and the treatment group that received the multilayer foam dressings (Allevyn® or Mepilex®) as an adjuvant prophylactic therapy.

5.2 Study sample and RCT population

5.2.1 Baseline characteristics

Comparison of the baseline characteristics between the study groups can be found in Table 15. As for the RCT, patient characteristics were equally distributed in the standard of care group and the multilayer foam dressings group.

Table 15 – Baseline characteristics

Variable	Standard of care (n=483)	Multilayer foam dressings (n=965)
Age (years)	80.2 ± 11.4	80.1 ± 12.0
<60 years	33 (6.8%)	71 (7.3%)
60-69 years	47 (9.7%)	99 (10.3%)
70-79 years	102 (21.1%)	191 (19.8%)
≥80 years	301 (62.3%)	604 (62.6%)
BMI	25.1 ± 5.0	25.3 ± 5.6
Male gender (n, %)	200 (41.4%)	404 (41.9%)
Diabetes (n, %)	118 (24.4%)	209 (21.7%)
Surgery (n, %)	51 (10.6%)	94 (9.7%)

5.2.2 Risk assessment

The average Braden risk assessment score at baseline was about 13.0 (see Table 16). Most patients (74.3% in the SoC group and 69.7% in the multilayer foam dressings group) had a Braden score at the beginning of the RCT between 12-16. Less than 5% of patients (2.7% in the SoC group and 4.6% in the multilayer foam dressings group) had a Braden score above 16.

At baseline, 62 patients presented with a PU category I on the sacrum, of which 17 (3.5%) were in the SoC group and 45 (4.7%) in the multilayer foam dressings group. On the other sites, 41 PUs category I and 30 PUs in other categories were observed at baseline, equally distributed between the two groups.

Table 16 – Risk assessment, per group

Variable	Standard of care (n=483)	multilayer foam dressings (n=965)
Braden score	12.9 ± 2.3	13.0 ± 2.4
Braden Cat. I (n, %)	111 (23.0%)	248 (25.7%)
Braden Cat. II (n, %)	359 (74.3%)	673 (69.7%)
Braden Cat. III (n, %)	13 (2.7%)	44 (4.6%)
Baseline PU – Location Sacrum	17 (3.5%)	45 (4.7%)
1 – Non-blanchable Erythema	17 (3.5%)	45 (4.7%)
Baseline PU – Location Heel right	9 (2.0%)	22 (2.4%)
1 – Non-blanchable Erythema	6 (1.2%)	14 (1.5%)
2 – Partial Thickness Skin Loss	0 (0%)	1 (0.1%)
3 – Full Thickness Skin Loss	1 (0.2%)	2 (0.2%)
Suspected Deep Tissue Injury: Depth Unknown	2 (0.4%)	4 (0.4%)
Unstageable: Depth Unknown	0 (0%)	1 (0.1%)
Baseline PU – Location Heel left	14 (3.0%)	23 (2.4%)
1 – Non-blanchable Erythema	8 (1.7%)	12 (1.2%)
2 – Partial Thickness Skin Loss	2 (0.4%)	3 (0.3%)
3 – Full Thickness Skin Loss	2 (0.4%)	1 (0.1%)
4 – Full Thickness Tissue Loss	0 (0%)	1 (0.1%)
Suspected Deep Tissue Injury: Depth Unknown	2 (0.4%)	4 (0.4%)
Unstageable: Depth Unknown	0 (0%)	2 (0.2%)
Baseline PU – Location trochanter right	0 (0.0%)	2 (0.2%)
3 – Full Thickness Skin Loss	0 (0%)	1 (0.1%)
4 – Full Thickness Tissue Loss	0 (0%)	1 (0.1%)
Baseline PU – Location trochanter left	1 (0.2%)	0 (0.0%)
1 – Non-blanchable Erythema	1 (0.2%)	0 (0%)

Braden Cat. I= braden score risk ≤11; Braden Cat. II= braden score risk [12-16]; Braden Cat. III= braden score risk ≥17.

5.2.3 Number of multilayer foam dressings per patient

The number of multilayer foam dressings applied by sites is described in Table 17. A total mean number of about 13 multilayer foam dressings (SD=7) were applied per patient during the study period, with a mean of about 3 (SD=2) for the sacrum and the heels and of 2 (SD=1) for the trochanters.

Table 17 – Number of multilayer foam dressings applied per patient

	Multilayer foam dressings group (n=957)	
	Mean ± SD	Median [min-max]
Any sites	12.93 ± 6.58	12 [1-43]
Sacrum	3.06 ± 2.01	3 [0-11]
Heel right	2.96 ± 2.24	2 [0-16]
Heel left	2.89 ± 2.08	2 [0-12]
Trochanter right	1.97 ± 1.29	2 [0-10]
Trochanter left	2.03 ± 1.39	2 [0-11]

5.2.4 Outcome: presence of pressure ulcer

Of the study population (n=1448), 67 patients developed a total of 70 PUs category II or worse during the study, of which 31 (6.4%) were in the SoC group and 39 (4.0%) in the multilayer foam dressings group (Table 18). Three patients (two in the SoC group and one in the multilayer foam dressings group) presented two different pressure ulcers, both on the sacrum and the left heel. As in the RCT, the difference in the incidence of PU in favour of the treatment group was only statistically significant for PUs on the sacrum. For PUs on the heels, no statistical difference was identified. No patients developed a PU on the trochanter.

Table 18 – Number of pressure ulcer developed, per group

Variable	Standard of care (n=483)	multilayer foam dressings (n=965)	P-value
Location sacrum	23 (4.8%)	26 (2.8%)	0.047
Location heel right	5 (1.1%)	5 (0.5%)	0.31
Location heel left	3 (0.7%)	8 (0.9%)	0.76
Location trochanter right	0 (0.0%)	0 (0.0%)	-
Location trochanter left	0 (0.0%)	0 (0.0%)	-

The information in this section shows that in the subgroup of the patients included in the RCT for which information could be linked to the IMA data, similar results were observed in the description of the study population, the risk assessment and outcomes.

5.3 Quality of life

The Belgian guidelines for economic evaluations in health care explicitly encourage the use of the EQ-5D instrument to describe patients' health states.[49] The EQ-5D, developed by the EuroQol Group, is a generic health-related quality of life (HRQoL) instrument commonly used for indirect utility measurement. It encompasses five dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), combined with a visual analogue scale ranging from "worst imaginable health state" to "best imaginable health state". Depending on the version of the instrument, each health dimension has either 3 levels of severity (EQ-5D-3L; 3L: no problems, some/moderate problems, extreme problems/unable to) or 5 levels of severity (EQ-5D-5L; 5L: no problems, slight problems, moderate problems, severe problems, extreme problems/unable to).

For the KCE-16012 clinical trial, the EQ-5D-5L was planned to be collected at baseline, day 3 and at the day 14 or end of the study. The end of the study was ≤3 days for 230 patients (14.1%), 4-7 days for 428 patients (26.2%), 8-11 days for 329 patients (20.1%), 12-13 days for 611 patients

(37.4%) and ≥14 days for 35 patients. The collection planned for day 14 was completed as planned, even if patients moved to non-participating wards or refused further dressing application.

At the time of writing the CSR, no Belgian value set was available to transfer the EQ-5D-5L health states to utilities and the Dutch[50] and UK[51] value sets were suggested. In the meantime, a Belgian[18] value set also became available and was applied in the present study.

5.3.1 Utilities at baseline, day 3 and end of study

The frequencies and proportions are reported by dimension and level of the EQ-5D-5L questionnaire in Appendix 3 (at baseline, day 3 and end of study).

The average utilities at baseline, and at the end of the study, for all the patients with an available value of QoL, are presented in Table 19 for the Belgian value set. As described in the development of the Belgian value set,[18] a single value was proposed for unconscious patients and taken into account in this analysis.

For the 77 patients who developed a PU during the RCT, the date first reported has been taken into account. As the QoL data was available for the baseline, the day 3 of hospitalization and the last day of hospitalization, it was determined whether the PU was developed before or after day 3. Of the 77 patients, 24 patients developed a PU before day 3, and 53 after day 3.

Table 20 presents the utilities for all patients who have all the measurements available, at day 1, day 3 and last day of the study (also represented in the Figure 10).

In both analysis (all patients included and only patients with all three measurements), the mean utility is higher at the end of study compared with the baseline, for both patients with or without development of pressure ulcer.

Table 19 – Quality of life EQ-5D Belgian data set for patients with and without development of PU (RCT population)

Belgian value set	First day of the study (1624 available values)	Day 3 of the study (1400 available values)	Last day of the study or day 14 (1356 available values)	Difference D1-D3 (1396 available values)	Difference D1-Last day (1348 available values)
Patients without PU development (n=1633)	0.27 ± 0.35	0.28 ± 0.30	0.42 ± 0.31	0.01 ± 0.35	0.14 ± 0.36
Patients without PU development and with no baseline PU (n=1458)	0.27 ± 0.34	0.28 ± 0.30	0.42 ± 0.32	0.01 ± 0.35	0.14 ± 0.36
Patients with PU development before day 3 (n=24)	0.23 ± 0.28	0.21 ± 0.18	0.30 ± 0.31	-0.03 ± 0.26	0.09 ± 0.34
Patients with PU development after day 3 (n=53)	0.13 ± 0.32	0.14 ± 0.35	0.25 ± 0.35	0.02 ± 0.29	0.13 ± 0.40
Patients with sacrum PU development before day 3 (n=16)	0.23 ± 0.29	0.23 ± 0.17	0.32 ± 0.26	0.00 ± 0.25	0.09 ± 0.34
Patients with sacrum PU development after day 3 (n=40)	0.15 ± 0.33	0.15 ± 0.37	0.27 ± 0.37	0.01 ± 0.31	0.13 ± 0.42

Table 20 – Quality of life EQ-5D Belgian data set for patients with and without development of PU (Patients with all measurements at day 1, day 3 and last day of the study available)

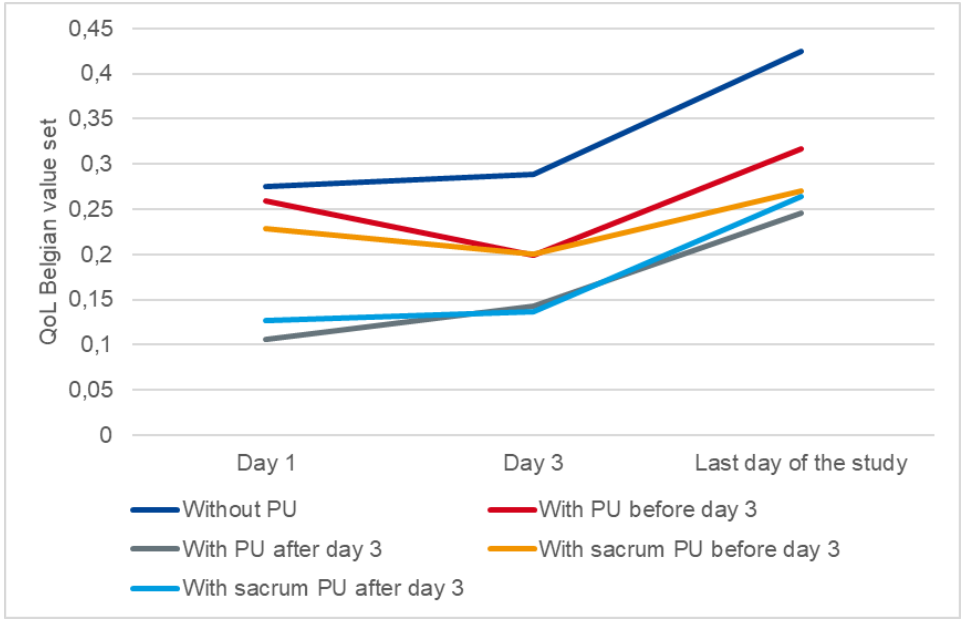
Belgian data set	First day of the study	Day 3 of the study	Last day of the study (or day 14)	Difference D1-D3	Difference D1-Last day
All patients (n=1187)	0.27 ± 0.34	0.28 ± 0.30	0.42 ± 0.31	0.01 ± 0.35	0.15 ± 0.36
Patients without PU development (n=1132)	0.28 ± 0.33	0.29 ± 0.29	0.42 ± 0.31	0.01 ± 0.35	0.15 ± 0.35
Patients without PU development and with no baseline PU (n=1065)	0.28 ± 0.34	0.29 ± 0.30	0.43 ± 0.31	0.01 ± 0.36	0.15 ± 0.36
Patients with PU development before day 3 (n=16)	0.26 ± 0.31	0.20 ± 0.19	0.32 ± 0.25	-0.06 ± 0.29	0.06 ± 0.32
Patients with PU development after day 3 (n=39)	0.11 ± 0.33	0.14 ± 0.36	0.25 ± 0.35	0.04 ± 0.28	0.14 ± 0.39

Patients with sacrum PU development before day 3 (n=10)	0.23 ± 0.34	0.20 ± 0.19	0.27 ± 0.25	-0.03 ± 0.28	0.04 ± 0.30
Patients with sacrum PU development after day 3 (n=31)	0.13 ± 0.35	0.14 ± 0.38	0.26 ± 0.37	0.01 ± 0.29	0.14 ± 0.42

The QoL utility is higher at day 1, day 3 and the last day of the study for patients without PU than for patients who developed a PU during the study. Regarding the difference of the QoL utilities between the first and the third day of the study, it is negative for the patient who developed a PU (including a sacrum PU) before day 3, otherwise, it is on average 0.01 for patients without PU or for patients who developed a PU (including a sacrum PU) after day 3.

The difference between the first day and the last day of the study is also higher for patients without a PU or for patients who developed a PU (including a sacrum PU) after day 3, compared with the patient who developed a PU (including sacrum PU) before day 3.

Figure 10 – Evolution of quality of life during the RCT (Patients with all measurements at day 1, day 3 and last day of the study available)



PU: pressure ulcer; QoL: quality of life

5.4 Length of stay

The length of stay (LoS) of the hospitalisation included in the clinical study is given by the number of days between the first and the last day invoiced. For the SoC group, the LoS was higher than for the multilayer foam dressings group (Table 21, 22.1 days ± 20.9 days vs 19.2 days ± 15.7 days).

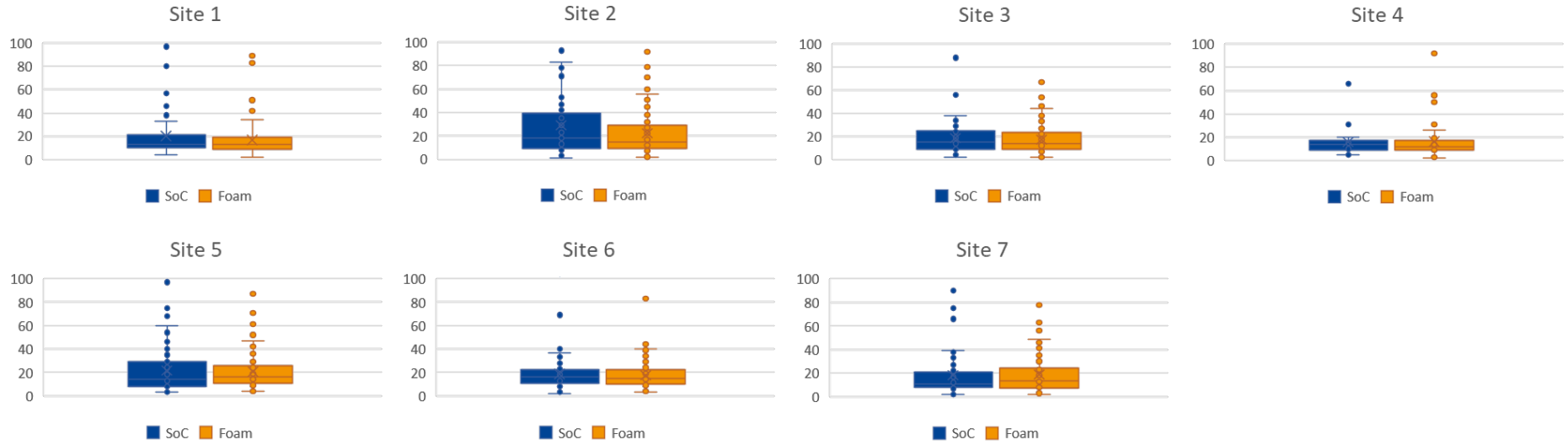
Table 21 – Length of stay according to the treatment group

Length of stay (days)	Standard of care (n=483)	Multilayer foam dressings group (n=965)
Mean ± Std	22.1 ± 20.9	19.2 ± 15.7
Median [IQR]	16 [10-26]	15 [9-24]

Multilevel regression model

A multilevel regression model was built, with the use of the log(LoS) as dependant variable. The randomization of the population was stratified by the different centers and, inside each center the way of entrance of the patient: from ICU ward or not. The value of LoS by treatment arm for the different centers is presented in Figure 11 where a difference is seen across the centers (Intraclass coefficient correlation= 0.020, p=0.046). The value of LoS by treatment arm for the ICU ward or not is presented in Table 22.

Figure 11 – Box plot of length of stay by treatment arm for the different centers



Note: The distribution has been limited at 100 days for better visibility.

Table 22 – Length of stay according to ICU ward or not, by treatment arms

	SoC	Mulltilayer foam dressings
ICU ward	31.52 ± 30.33	23.24 ± 23.23
Non-ICU ward	20.92 ± 18.95	18.76 ± 14.46

ICU: Intensive care unit, SoC: Standard of care

Centre and ICU ward were treated as random factors in a multilevel regression model. The multilevel model shows that even with the inclusion of random effect, the residual variation is large and suggests the model lacks important determinants of length of stay (R^2 of 0.016). The model and its construction is presented in Appendix 5.

5.5 Other PU-related costs after trial follow-up

5.5.1 Surgical interventions possibly related to the treatment of PUs

During the follow-up of a PU, it is always possible that the PU does not heal completely and requires a surgical intervention. The aim of this analysis is to assess how many surgical interventions for PU were done during and after the index hospitalization.

The surgical interventions taken into account and their costs are listed in Appendix 4.1.

For fourteen patients, one of these surgical interventions was found.

Six of them were performed during the same hospitalisation as the clinical study. Of those, four were done at the beginning of the hospitalization (three patients at day 1 and one patient at day 4), and two later on during the hospitalization. The surgery were two pedicle or fascio-cutaneous flap, two Musculo-cutaneous flap, one Muscle flap and one pedicle flap plastic surgery. All six patients were in the multilayer foam dressings group, and none of them had a development of PU during the RCT.

Eight patients underwent one of these interventions during another hospitalization, principally one-day surgery (five surgical interventions for deep phlegmon, one curettage with or without biopsy, one pedicle or fascio-cutaneous flap, and one pedicle flap plastic surgery).

Of the eight patients, one was in the SoC group and 7 in the multilayer foam dressings group, and none of them had a development of PU during the RCT. We have no information about the development of PUs before and after the follow-up period of the pragmatic RCT.

No link could thus be identified between the selected surgical interventions and the PU development in the RCT. Therefore, no further analysis was performed.

5.5.2 Complicated dermatological dressings

The complications we could identify in the nomenclature are the so-called complicated dermatological dressing for extensive lesions (NIHDI nomenclature code 145305 and 145272, see description in Appendix 4.2).

During the index hospitalization, 52 patients had one complicated dermatological dressing, of which 21 were in the SoC group (4.35%) and 31 in the multilayer foam dressings group (3.21%). Of these patients, five developed a PU during the study (three sacrum PU), of which four were in the SoC group and one in the multilayer foam dressings group.

And outside the index hospitalization, 57 patients had one complicated dermatological dressing, of which 14 were in the SoC group (2.90%) and 43 were in the multilayer foam dressings group (4.46%). Of these patients, only one patient in the intervention group developed a PU during the study. No further analysis was performed. Regarding the number of complicated dressings per patient, there is no significant difference between the two groups (Table 23).

In total, six patients out of the 67 patients (9.0%) who developed a PU had a complicated dermatological dressing.

Table 23 – Number of 'complicated dermatological dressing' per patient

Number of 'complicated dermatological dressing'	during the index hospitalisation			outside the index hospitalisation		
	Number of patients	SoC Group (n=483)	Multilayer foam dressings group (n=965)	Number of patients	SoC Group (n=483)	Multilayer foam dressings group (n=965)
1	29	11 (2.3%)	18 (1.9%)	26	7 (1.4%)	19 (2.0%)
2	8	3 (0.6%)	5 (0.5%)	10	3 (0.6%)	7 (0.7%)
3	4	1 (0.2%)	3 (0.3%)	6	1 (0.2%)	5 (0.5%)
4	4	1 (0.2%)	3 (0.3%)	5	1 (0.2%)	4 (0.4%)
5	0	0 (0.0%)	0 (0.0%)	3	1 (0.2%)	2 (0.2%)
>6	7	5 (1.0%)	2 (0.2%)	7	1 (0.2%)	6 (0.6%)

5.6 Hospitalisation costs

A difference in LoS was observed. However, as mentioned in part 5.4, only very little variation in the LoS could be explained with the variables we had at our disposal. Therefore, it was decided not to conduct further analysis of costs linked to hospitalisations.

Key points

- **For a large subgroup of patients (88.7%) in the Belgian RCT, the study data could be linked to a set of reimbursement data from the IMA database. The RCT results in terms of study population description, risk assessment and outcomes were still valid in this subgroup.**
- **PU development may cause a temporary decrease in QoL.**
- **Although the mean length of stay was 3 days shorter for patients in the treatment group, only very little variation could be explained with the available variables, so no further analysis of hospitalisation costs was performed.**
- **Information on surgical interventions possibly related to PU treatment was extracted from the IMA data, but no link with PU development within the trial could be identified. About 9% of patients that developed a PU during the trial received a complicated dermatological dressing with no significant difference between both groups.**

6 COST-EFFECTIVENESS: BELGIAN RCT-BASED ECONOMIC EVALUATION

In this section, we provide details on the economic evaluation of silicone adhesive multilayer foam dressings used as adjuvant therapy to prevent hospital-acquired pressure ulcers. Information is presented following the Consolidated Health Economic Evaluation Reporting Standards (CHEERS, see Appendix 6).[52, 53]

6.1 Methods

6.1.1 Population, intervention and comparator

The economic evaluation of silicone adhesive multilayer foam dressings is carried out in the Belgian context. The population, intervention and comparator of this economic evaluation reflect the characteristics of the underlying Belgian trial presented in part 3.1 of this report. We refer to parts 3.1.4, 3.1.5 and 3.1.6, respectively, for a detailed description of the eligible adult hospitalized patients in ICUs and non-ICU wards at risk for PU development, the tested silicone adhesive multilayer foam dressings, and the standard pressure ulcer preventative care.

In the Belgian trial, the silicone foam dressings were applied to the sacrum, heels and greater trochanters. The results of the pragmatic trial show that it is beneficial to use silicone adhesive multilayer foam dressings on the sacrum, in addition to standard of care, to help prevent hospital-acquired PUs.[17] No statistical differences were noticed for the heel and trochanter areas (see part 3.2.4). Therefore, this economic evaluation is limited to the use of silicone adhesive multilayer foam dressings on the sacrum.

6.1.2 Perspective

According to the Belgian guidelines for economic evaluations,[49] the reference case analysis should only include direct health care costs from the perspective of the health care payers, including both government and patients. Other perspectives are allowed, but should be distinguished from the reference case. For this report, in line with the identified economic evaluations in our literature review (see Table 8 in part 4.4.1), a hospital perspective is added.

6.1.3 Time horizon and discount rate

The appropriate time horizon for the economic evaluation depends on the duration of the impact of the study intervention on relevant costs and outcomes as compared to the comparator intervention.[49] A one-year time horizon is originally considered to include potential surgical reoperations occurring within this time horizon. If no incremental impact is considered to be appropriate, this time horizon will be reduced to the initial hospitalisation period. Due to this short-term time horizon, discounting of future costs and effects is not required.

6.1.4 Outcomes

The primary endpoint of the Belgian pragmatic RCT was the incidence of a new PU of category II or worse at the studied body sites (see part 3.1.7).[17] Given the significant decrease of PUs for the sacrum, this outcome is retained for the economic evaluation. Since there is no impact of using the sacrum multilayer foam dressings on (severe) adverse events with a relevant impact on costs or effects, adverse events can be left out of consideration in the economic evaluation.

Where possible, inputs for costs and effects reflecting the Belgian context will be used. For impact on effects, quality of life measured via the EQ-5D-5L in the Belgian pragmatic RCT is converted to utilities via the Belgian value set.[18] The impact on costs will be expressed in price units for the year 2022/2023, depending on available information.

No modelling is applied. Given the results on QoL in this prevention trial (see part 5.3.1), we decided not to present results in quality-adjusted life-years (QALYs). The impact on costs and effects are presented through a cost-consequences analysis (CCA).

6.2 Results

6.2.1 Incremental effects

6.2.1.1 PU occurrence

As mentioned in the conclusion of the clinical part of this report (part 3.2.7), the Belgian large multicentre RCT showed that multilayer dressings reduce the incidence of sacral pressure ulcers in hospitalised patients in conjunction with standard of care, both on ICU as well as on other wards. PUs on the sacrum were observed in 2.8% (30/1062, 95% CI 1.8-3.8%) and 4.8% (26/539, 95% CI 3.0-6.6%) of the patients in the treatment group and the SoC group, respectively. The risk of developing a new PU on the sacrum was statistically significantly reduced by 41% in the treatment group (RR=0.59, 95% CI 0.35-0.98, p=0.04). The absolute risk reduction of 2.0% (95% CI -0.1-4.1%) coincides with a number needed to treat to prevent one new PU of category II or worse on the sacrum of 50.0 (95% CI 24.6-1429).[3]

Table 24 lists the type of sacrum PUs identified in the treatment and SoC group. In both groups, the largest part of PUs are category II PUs. The main difference between the two groups lies in the number of unstageable PUs. In the intervention group, 77% of the sacrum PUs are category II PUs and none are unstageable. In the SoC group, this is 65% and 12%, respectively.

In this economic evaluation, we make a conservative assumption that the distribution of type of PUs is similar in both groups.

Table 24 – Category of sacrum PUs in the treatment and SoC group

	Treatment group (n=30)	SoC group (n=26)
Category II	23 (76.7%)	17 (65.4%)
Category III	1 (3.3%)	1 (3.8%)
Category IV	/	/
Unstageable	/	3 (11.5%)
Deep Tissue Injury: Depth Unknown	6 (20.0%)	5 (19.2%)

See Figure 1 in part 1.1 for a description of these categories. SoC: standard of care.

The safety analysis (part 3.2.6) shows that there are no specific AEs related to the application of silicone adhesive multilayer foam dressings applied to the sacrum which might be correlated with a substantial impact on costs or effects. Similarly, the analysis of surgical interventions possibly related to the treatment of PUs occurring withing one year after the initial hospitalization did not provide evidence for an incremental impact (part 5.5.1). Therefore, these elements are further excluded from the cost-consequences analysis.

[3] Absolute risk reduction is calculated with the Newcombe Score method and show that for the sacrum PU, the absolute risk is 0.048 [0.030-0.066] for the SoC group, and 0.028 [0.018-0.038] for the treatment group. An absolute RR is calculated as 0.020 [-0.0007-0.0406], which gives a NNT of 50.0 [24.6-1429].

6.2.1.2 Quality of life

QoL analysis showed that no differences were observed between the utilities in the treatment and SoC group measured with the EQ-5D-5L on day 1, 3 and end-of-study. This is not surprising given that most patients of both groups have no PUs at all.

To look at the potential impact of PUs, we distinguished between patients with and without PUs in the data analysis (see previous chapter). Clearly, these populations are not comparable at baseline. The QoL of patients who developed PUs was already much lower at baseline than the QoL of patients who did not develop PUs (see part 5.3.1). Hence, it is better to look at the evolution in QoL. The results of this analysis show that in the Belgian pragmatic RCT, mean QoL did not improve or even worsened between the first and third day of the study in patients who developed PUs within this time period, while this was not the case for the other patients (see part 5.3). Over the entire study period, there was a mean improvement in QoL of 0.04 for patients with a sacrum PU development before day 3.

In patients who developed a PU between day 3 and the end of the study, the impact on QoL was less clear. These patients had a mean improvement in QoL of 0.14 over the entire study period. In patients without PU development, this was on average 0.15.

Given the small sample of patients with sacrum PUs, it is difficult to make firm conclusions about the evolution of QoL. But the available data suggest that the presence of PUs may be linked to a potentially smaller average improvement in QoL over the study period in comparison with patients without PUs.

6.2.2 Incremental costs

6.2.2.1 Cost PU prevention

In the treatment group, we have the incremental cost of the silicone adhesive multilayer foam dressings applied to the sacrum. In the pragmatic RCT, a mean of 3.0 (SD=2) dressings was used in the treatment group (see part 3.2.2). This number is multiplied by the cost of these dressings. Table 25 provides an overview of the list prices for the dressings used in the Belgian pragmatic RCT, which are the silicone adhesive multilayer foam dressings from Smith & Nephew (AllevynR brand, type: AllevynR Life, AllevynR Life Sacrum and AllevynR Life Heel) and Mölnlycke Healthcare (MepilexR brand, type: MepilexR Border, MepilexR Border Sacrum, MepilexR Border Heel) (see Figure 2 in part 3.1.5). Only the cost of the sacrum dressing is relevant for this economic evaluation. For the Allevyn Life Sacrum dressing, a cost of €8.90 per dressing is used in the analysis. This is €10.96 for the Mepilex Border Sacrum dressing. In our cost-consequences analysis, we apply an average cost of €10 per dressing and also perform a scenario analysis with a price of €9 (close to the price of the cheapest alternative). No adjustments were made for potential discounts.

Table 25 – List prices of silicone adhesive multilayer foam dressings included in the RCT

	Smith & Nephew	Price/piece (company*)	*Price/piece (RIZIV/INAMI**)*
Sacrum	Allevyn Life Sacrum Large 21.6x23cm	€8.90	*€8.91*
Heel (right and left)	Allevyn Life Heel 25x25.2cm	€13.14	*€13.02*
Greater trochanter (right and left)	Allevyn Life M 12.9x12.9cm	€4.72	*€4.61*
	Mölnlycke Healthcare	**Price/piece***	
Sacrum	Mepilex Border Sacrum 22x25cm	€10.96	*€13.12*
Heel (right and left)	Mepilex Border Heel 22x23cm	€10.08	*€11.94*
Greater trochanter (right and left)	Mepilex Border Flex 15x15cm	€5.61	*€7.23*

Remark: prices are inclusive 6% VAT.
** Source: personal communication with Smith & Nephew (5 January 2023) and Mölnlycke Healthcare (2 January 2023).*
*** Source: https://www.inami.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/geneesmiddel-gezondheidsproduct/terugbetalen/Paginas/terugbetaling-actieve-verbandmiddelen-chronische-wonden.aspx. If you suffer from chronic wounds, compulsory health care insurance intervenes in the price of active dressings for patients with chronic wounds, upon prescription and authorisation from the health insurance fund (www.riziv.fgov.be). The compulsory health care insurance refunds 20% of the public price of a box of bandages registered on this list of reimbursable active dressings. The prices mentioned in the last column of the above table are based on the information from the list available on the NIHDI website (after adding 6% VAT).*
The difference between the prices mentioned on the NIHDI website and those received from the company are in line with each other for the Allevyn dressings. The differences are larger for the Mepilex dressings. The personal communication with Mölnlycke Healthcare mentioned these are the standard prices for the hospitals in 2023. Therefore, we opted to use the information received from the companies.

There is no need to list the remaining costs for standard PU prevention. This is because these are not incremental elements, as they are present in both the SoC group and the treatment group. In line with the previous economic evaluations,[19, 22, 24, 28] it is thus assumed that standard PU prevention is provided in both groups equally, and thus the related costs are assumed to be similar in both groups. The only difference is that besides the cost of the silicone adhesive multilayer foam dressings, there is also the time required to apply the dressings. In the economic evaluation of El Genedy et al.,[19] it is assumed the time per dressing application or change takes about 2 minutes. The authors argued this time is limited since the dressing application or change was performed when the patient was turned over and held by nurses as part of the regular repositioning, skin inspections or other medical examinations.[19] In the study of Forni et al.,[20] an estimate of 15 minutes was taken into account. However, the authors mention the actual time is likely to be much shorter, and also a Belgian consulted expert indicated 15 minutes is not realistic and extremely long. Therefore, we keep it to three times the 2 minutes extra time that is taken to apply the silicone adhesive multilayer foam dressings at the sacrum. According to the Belgian manual for cost-based pricing of hospital interventions, in March 2012, the cost per hour was €36.30 for a nurse. Adjusting this to 2022 values applying the Health index, this becomes €45.16 per hour (March 2012=100; 2022=124.40; https://statbel.fgov.be/nl/themas/consumptieprijsindex/index-search), or €4.52 for three times the two minutes.

The cost impact of the above elements depends on the perspective taken. We contacted the eight centres that participated in the pragmatic RCT to find out how the costs of silicone adhesive multilayer foam dressings to prevent PUs are funded. It was indicated that this cost is part of the hospital stay price. This means it is borne by the hospital and not charged to the patient. In that case, there is a cost from the hospital's perspective, but not from the healthcare payer's perspective if this would only include government and patients. One of the centres indicated that there was currently no systematic use of these dressings, but there are plans to do so based on the results of the Belgian pragmatic trial. The expert indicated it is possible that the cost of these dressings will be passed on to the patient because the additional cost to the hospital could be too high. In that case, the cost from the hospital's perspective would be transferred to the healthcare payer's perspective.

Similarly, the (limited) time needed to apply the dressings are only relevant to the hospital perspective. It does not have an impact on the healthcare payer's perspective since this (limited) time investment does not generate additional costs for government or patients.

6.2.2.2 Cost PU treatment

Belgian cost-of-illness study

Since there is a difference in occurrence of PUs, we try to estimate what impact this may have on costs from a healthcare payer and hospital perspective. For the treatment cost of PUs, a distinction can be made between two periods. On the one hand, you have the extra PU-related treatment cost during the period when the patient would also have been hospitalized if they had no PU. On the other hand, you have the extra cost related to an extended hospital stay due to the presence of a PU.

Based on our trial and linked IMA data, we cannot estimate PU-related costs. Indeed, there is no exhaustive list of PU-specific nomenclature codes to select all relevant costs and total hospitalization costs are largely influenced by other factors independent from the presence of PUs. Hence, for the inclusion of PU treatment costs in our study, we prefer to rely on a Belgian study that examined the cost of PU prevention and treatment in an adult population in hospitals and nursing homes in Flanders, a region of Belgium:[d]

- Demarré L, Verhaeghe S, Annemans L, Van Hecke A, Grypdonck M, Beeckman D. The cost of pressure ulcer prevention and treatment in hospitals and nursing homes in Flanders: A cost-of-illness study. International Journal of Nursing Studies 52 (2015) 1166–1179.[54]

Hereafter, we provide further details about this study.[54] Only the section on PU treatment costs in hospitals is relevant for our economic evaluation.

To calculate the treatment cost, 78 treatments were observed in a random sample of 10 hospitals in Flanders. Data were collected between November 2012 and April 2013. This cost-of-illness study used a bottom-up approach. Only direct medical costs were included, i.e. labour costs and cost of materials. Medical resource use for PU treatment was examined through direct observation by one of the researchers. Resources used for the treatment of pressure ulcers included cleaning solvents, disinfectants, topical agents, dressings, antibiotics, medication, nutritional support, and contact isolation measures in case of wound infection with multi-resistant bacteria. The costs of medical resources used for treatment were provided by the pharmacies and logistics departments of participating hospitals. These costs were adjusted to account for discounts provided to the participating hospitals. Data collection on the cost of nursing labour in hospitals was adopted from a manual for cost-based pricing of hospital interventions of the Belgian Health Care Knowledge Centre.[55] All costs were adjusted to 2013 values applying the health index.[54]

[d] We note that this Belgian cost-of-illness study also makes calculations for PU prevention costs. We did not use this information in part '6.2.2.1 – cost PU prevention' since the SoC in the comparator group also includes costs for prevention and only the incremental costs should be taken into account.

The mean cost of treatment was calculated per pressure ulcer severity category. No extra length of stay due to a pressure ulcer category I was assumed. For PUs category II-IV, based on the results of the multivariate study of Graves et al.,[56] an extra length of stay of 4.31 days was assumed. The formula to calculate the treatment cost of category II-IV PUs was as follows:[54]

- PU treatment cost category II–IV = Cost/patient/day per PU category x (7.57 (average length of stay) + (4.31 (extra length of stay due to pressure ulcer x €366.85 (hospitalisation cost/day)

The mean (SD) cost of treatment per patient per day for category I-IV PUs was as follows: €2.34 (1.14), €10.81 (4.25), €17.15 (7.33), and €77.36 (35.95), respectively. Applying the above formula, the mean cost for the local treatment of a PUs category I was €17.71 per hospitalization. This cost was not relevant for our study since only PU ≥2 were included in the Belgian pragmatic RCT. The average cost to treat a PU category II, III, and IV, respectively, was €1709.54, €1784.86, and €2500.16[e] per hospitalization (not including the cost of secondary prevention).

Adjustments to 2022/2023 values

To adjust the values of this Belgian cost-of-illness study to current values (2022/2023), two adjustments were made. First, the mean cost of treatment per patient per day for 2013 were adjusted to 2022 values by applying the Health index (2013=100; 2022=122.59; https://statbel.fgov.be/nl/themas/consumptieprijsindex/index-search). This first adjustment results in a mean cost of treatment per patient per day for category I-IV PUs of: €2.87, €13.25, €21.02 and €94.84, respectively. Second, the most up-to-date (January 2023) hospital stay price is applied based on the information available from the NIHDI (https://www.riziv.fgov.be/nl/themas/kost-terugbetaling/door-ziekenfonds/verzorging-ziekenhuizen/Paginas/verpleegdagprijzen-ziekenhuizen.aspx). Different approaches are possible: 1) The unweighted average price of the eight participating centres, resulting in a hospital stay price of €753.81; 2) A weighted average price of the eight participating centres. The weight is based on the number of patients participating in the Belgian pragmatic trial (see Figure 3), which results in a hospital stay price of €735.06; 3) The unweighted average price of the 99 acute hospitals, resulting in a hospital stay price of €690.14. For this economic evaluation based on the Belgian pragmatic RCT, we opted for the middle value reflecting the weighted average price of the eight participating centres.

These 2022/2023 adjustments result in the following treatment costs:[f]

- Category II PU: €3325.52
- Category III PU: €3417.83
- Category IV PU: €4294.81

Adjustments for (PU-attributable) length of stay

A limitation mentioned in the Belgian cost-of-illness study is the lack of data about the extra length of stay related to PU treatment. They rely on the study of Graves et al..[56] This Australian cross-sectional observational study applied quantile median robust regression on data from 2 000 hospitalized patients (≥18 years) in a prospective survey conducted between October 2002 and January 2003 in a single Australian hospital. After exclusion of 253 patients, data were analysed. Forty-three (4.5%) of the 966 males and 38 (4.9%) of the 781 females developed a PU. Their model could explain 18.7% of the variation in excess length of stay. According to their results, the presence of PUs prolongs the length of stay by a median of 4.31 days (95% CI 1.85-6.78). An important limitation is that this study could not make a distinction between different stages of PUs and reports results for any stage of PU (category I-IV). This would mean the impact on excess length of stay would increase if stage I PUs would be excluded.

[e] €1709.54 = €10.81 x (7.57 + 4.31) + €366.85 x 4.31; €1784.86 = €17.15 x (7.57 + 4.31) + €366.85 x 4.31; €2500.16 = €77.36 x (7.57 + 4.31) + €366.85 x 4.31.

[f] €3325.52 = €13.25x (7.57 + 4.31) + €735.06x 4.31; €3417.83 = €21.02 x (7.57 + 4.31) + €735.06x 4.31; €4294.81 = €94.84x (7.57 + 4.31) + €735.06x 4.31.

There are other studies that analyse the impact of PUs on length of stay, but which all have their limitations. In a non-systematic search, we identified several studies trying to estimate the impact of PUs on length of stay.

In the study of Goudie et al. (US)[57] a propensity score matching method was applied to adjust for case-mix at the patient level, then estimating differences in length of stay for comparable pediatric patients with and without PUs. The study identified 504 094 pediatric inpatient stays at risk for PUs. The incidence rate per 10 000 at-risk patient discharges was 2.9 for PUs. The study identified a relatively small number of PUs (n=120) that could be included in there case-control estimates for length of stay. The average difference in length of stay in children aged 1-17 years was 4.9 days (95% CI -1.0-10.8).[57]

In the study of Wang et al. (US)[58] differences in length of stay for comparable hospitalizations of patients with spina bifida (SB) with and without pressure injuries were estimated. This retrospective study used data over a five-year period (from 2010 through 2014) from the National Inpatient Sample (NIS) database. Hospitalizations among patients with SB and pressure injuries (n=3888) were matched to hospitalizations among patients with SB but without pressure injuries (n=3888). After matching by propensity scores, mean/median difference in length of stay associated with pressure injuries was 1.5/1 days (mean: 7.4 vs. 5.9 days, $p < 0.0001$; median: 5 vs. 4 days, $p < 0.0001$). In multivariate models, hospitalizations among patients with SB and pressure injuries had on average, an increased length of stay of 1.2 days.[58]

In the study of Han et al. (Korea)[59] 1000 patients with pressure injuries (≥ stage II) were compared to 4000 patients who acted as controls. Based on multiple linear regression analysis, pressure injuries were significantly associated with an extended length of hospitalization ($\beta = 20.84$; $p < 0.001$) and length of intensive care unit (ICU) stay ($\beta = 8.16$; $p < 0.001$).[59]

Finally, the study of Dealey et al. (UK)[41] refers to a study performed by employers of a company selling dressings mentioning an average 5-8 days additional length of stay per PU.[38] Unfortunately, the underlying study does not refer to such an impact. It only states that “a severe ulcer (EPUAP grade 3 or 4) is likely to result in a longer hospital stay.”[38]

The methodology applied in the above studies is associated with high uncertainty because of the inability to include many (un)known variables that have a potential impact on length of stay. If reported, only a very small part of the variation in length of stay could be explained by the model. It is possible that there are variables that have an impact on the presence of PUs as well as on the length of stay and for which no correction could be made in the above studies resulting in an overoptimistic estimate of the extension in LoS due to the presence of a PU. Based on the high uncertainty regarding the impact on hospital length of stay, we added a scenario where this extension varies from no extension up to five days.

We also include an adjustment for the length of stay based on the observations in the Belgian pragmatic RCT. In the 67 patients who developed a PU in the Belgian pragmatic RCT, the total length of stay was on average 22.1 days (median 17). The part before and after the development of the PU was on average 6.2 days (median 6) and 15.9 days (median 10), respectively. In our calculations, we apply the average length of stay of about 16 days after the development of a PU to calculate the PU-related treatment cost, of which 0-5 days are interpreted as a PU-related extension of this hospital stay. The results are presented in Table 26.

Table 26 – PU treatment cost category II–IV (2022/2023 values)

Extension in LoS (days)	0	1	2	3	4	5
PU category II	€212	€934	€1656	€2377	€3099	€3821
PU category III	€336	€1050	€1764*	€2478	€3192	€3907
PU category IV	€1517	€2158	€2798	€3438	€4078	€4719

*LoS: length of stay; PU: pressure ulcer. * example: €1764 = (16-2 days) x €21.02 + 2 days x €735.06.*

6.2.3 Cost-consequences analysis

In this section, we bring together all the relevant information discussed above. First we have the investment cost. From a healthcare payer perspective only including government and patients, this would cost nothing as it is a cost borne by the hospital. However, assuming a cost of €0 does not seem justified, hence we prefer to include the cost for the hospital. As such, we use a healthcare payer perspective including costs for both government, patients and hospitals. If we consider an NNT of 50, we obtain a total cost of about €1700 for avoiding one PU. If we take into account the lowest price of the sacrum dressings used in the pragmatic RCT with a price of about €9 per dressing, this becomes about €1600.

In calculating benefits, we use the distribution of PUs as in the SoC group, where about two-thirds were category II PUs. The remaining PUs were mainly unstageable and DTIs, which experts have indicated is definitely not comparable to a category II PU and rather in line with a category III/IV PU. Hence, we assume that these are category III & IV PUs. One of the variables for which there is little reliable evidence is the impact of a PU on extending the length of stay. In the Belgian cost-of-illness study, an extension of 4.31 days was applied to both category II, III and IV PUs. As this assumption is unlikely for a category II PU, we did not adopt this assumption. For a category II PU, we assume no prolongation of the length of stay. In our cost-consequences analysis, we work out the scenario where for category III and IV PUs we assume a 5-day extension. In that case, we save on average €1631 per PU avoided. The benefits of a potential better improvement in QoL when avoiding PUs are not quantified and are listed as a consequence in Table 27.

If these assumptions are plausible, this means that sacrum PU prevention with silicone adhesive multilayer foam dressings can already reach a break-even point using a number of conservative assumptions. Given the results of this simple conservative CCA, we chose not to perform an extensive sensitivity analysis. If costs for treating PUs outside the hospital, possible discounts on the dressings, etc. would also be taken into account, then the results of this cost-consequences analysis would only improve.

Table 27 – Overview of costs and consequences sacrum PU prevention with silicone adhesive multilayer foam dressings

Variable	Value	More information in part
Cost prevention: - Dressings (average use: 3) - Time (3 times 2 minutes)	€30 (~€27**) €4.52	6.2.2.1
ARR PU (NNT)	2% (50)	6.2.1.1
Total investment cost per PU avoided: €1726* (~€1576)**		
Distribution PUs	Cat. II: 65.4% Cat. III/IV: 34.6%	6.2.1.1
QoL	Potentially smaller improvement in QoL in patients with PUs	5.3.1
Cost PU treatment under assumption of no increase in LoS for PU cat. II.	€212	6.2.2.2
Cost PU treatment under assumption of an increase in LoS of 5 days for PU cat. III/IV.	€4313***	6.2.2.2
Total savings under the applied assumptions: €1631**		

ARR: absolute risk reduction; Cat.: category; NNT: number needed to treat; PU: pressure ulcer; QoL: quality of life.
** (€30 + €4.52) x 50 (NNT) = €1726.*
*** This is the result if a cost of about €9 per dressing is applied.*
**** (€3907 + €4719)/2 = €4313.*
***** (65.4% x €212) + (34.6% x €4313) = €1631.*

Key points

- **Based on the results of the pragmatic Belgian RCT described in chapter 3, a cost-consequence analysis (CCA) was performed on the use of multilayer foam dressings in conjunction with SoC to reduce the incidence of sacral PUs in hospitalised patients at risk for PU development.**
- **The incremental costs of the PU prevention with multilayer foam dressings consist of the price of the dressings and the time to apply them. The cost for the dressings is paid by the hospitals and is included in the hospital stay price. The CCA is performed from the healthcare payer's perspective, including these costs born by the hospitals.**
- **A reliable CCA could be performed due to the availability of reliable data for most variables:**
  - **The Belgian RCT provides reliable data on the baseline risk for PUs, the relative/absolute treatment effect and thus the NNT, the proportion of different categories of PUs in the intervention and comparator group, the number of multilayer silicone foam dressings used on the sacrum, and the impact on QoL.**
  - **Through linkage with IMA data, total length of stay and the remaining length of stay after the development of a PU could also be determined.**
  - **PU treatment costs for hospitalized patients relevant for the Belgian context could be derived from a Belgian cost-of-ilness study. Costs were adjusted to 2022/2023 values.**
  - **There is only uncertainty about the extra length of stay related to PU treatment. A conservative assumption including no prolongation for category II PUs is included in our base case scenario.**
- **In a conservative scenario we obtain a break-even situation. If we would also include larger discounts, costs for PU treatment after hospitalization, or an impact on the length of stay for category II PUs, this would only have a positive effect on the results and lead to further savings.**

7 DISCUSSION

Limited and not generalizable evidence on prophylactic dressings for preventing pressure ulcers has led to the public funding of a large RCT in Belgium by the KCE Trials programme. In this pragmatic RCT, researchers aimed to determine whether multilayer silicone foam dressings are effective as an adjuvant prophylactic therapy compared to standard pressure ulcer prevention to reduce the incidence of pressure ulcers in a hospitalized population at risk for PU development.

Two key characteristics of the selected population were 1) at risk for PU development based on Braden risk assessment (Braden score ≤17), and 2) a presumed length of stay (LoS) of more than seven days. The pressure ulcer trial (KCE-16012) compared two multilayer foam dressings as an adjuvant prophylactic therapy for pressure ulcers to the standard of care. The silicone adhesive multilayer foam dressings were applied to dry, intact skin on the sacrum, heels and greater trochanters for a maximum treatment duration of 14 days.

The trial randomized 1633 patients in 8 Belgian hospitals. The mean age of the population was 80 years and the majority of patients were non-ICU patients (88%) and had a Braden score of 12-16 (72%). The trial procedures were discontinued before day 14 in 71% of the randomised patients, mainly because they were no longer at risk of PU development (Braden score >17) or because they were discharged from the hospital.

In the intention-to-treat (ITT) population, 4.0% (43/1066) of patients in the treatment group and 6.3% (34/539) in the SoC group (p=0.04) developed a PU category II or worse (sacrum, trochanter, or heel).

This result is obtained because of the impact on sacrum PUs observed in 2.8% and 4.8% of patients (p=0.04) in the treatment group and the SoC group, respectively. PUs on the heels occurred in 1.4% and 1.9% of patients (p=0.49) in the treatment and SoC group, respectively, and only one patient (0.1%) developed a PU on the trochanter.

7.1 Strengths and limitations

Overall, we have very reliable information for most variables due to the availability of the Belgian pragmatic RCT (part 7.1.1), the linking of this trial to reimbursement data (part 7.1.2), and the presence of a Belgian cost study (part 7.1.3). Only for the impact of a PU on length of stay, no reliable data was identified. We address this with a conservative approach (part 7.2.1) and reach a break-even point in this approach in our cost-consequences analysis (part 7.2.2).

7.1.1 Availability of Belgian pragmatic RCT

The trial showed (partially) positive results, which prompted the idea to conduct a cost-effectiveness analysis. Since significant results occur only in the prevention of sacrum PUs, we conducted the economic evaluation only for this group. We will return further in this discussion to the prevention of PUs on the heels and trochanter (see part 7.2.3).

Conducting a credible economic evaluation starts with the availability of good reliable data. Since we can rely on the pragmatic RCT, we have data applicable to the Belgian context for the following inputs:

- Population: patients were recruited in eight hospitals in Flanders (Belgium), of which three were university/teaching hospitals and five were general hospitals. Since this is a pragmatic trial in both university/teaching and general hospitals, it reflects the current Belgian practice in the SoC group, and the results are transferable to the current Belgian situation.
- Intervention: the applied dressings are available on the Belgian market
- Comparator: the SoC group reflected the KCE guidelines for the prevention and treatment of pressure ulcers[7, 15] and the 2014 international guidelines,[16] which are also in agreement with the 2019 guidelines.[3]
- Outcomes: Information on the development of PUs, QoL (measured with the EQ-5D-5L) and safety were gathered in the underlying trial.

Meanwhile, a Belgian value set has become available for the EQ-5D-5L QoL data.[18] In this prevention trial, there is no noticeable difference in QoL between the intervention and SoC groups. This is not surprising given that only a small proportion of the population developed PUs. In the subgroup of patients who developed a PU before day 3, we observed a temporary deterioration in QoL on day 3, whereas an improvement in QoL was observed in patients who did not develop a PU before day 3. However, given the small sample, the results of this analysis should be interpreted with caution. For patients who developed a PU after day 3, the evolution in QoL between day 3 and the end of the study was similar to this evolution in the other patients. Several explanations are possible: the impact on QoL is temporary and the measurement is done only when this impact is over, the end of the study is not on the same day for all patients, or QoL is mainly influenced by all kinds of other underlying co-morbidities that are not affected by the presence/treatment of a PU. It is not possible to make further statements about this with the available data.

A generic questionnaire provides information about the patient's overall quality of life. Such an instrument does not provide information about specific details, such as the patient's comfort when applying the intervention. For such specific information, the complementary use of a disease-specific instrument is more appropriate. We remark there also exists a patient-reported outcome (PRO) instrument for interventions aimed at preventing PUs, the PU-QOL-P instrument.[60] This instrument provides a standardised method for assessing PU-specific symptoms and functional outcomes for quantifying the benefits of associated interventions from the patient's perspective. It can be used in research with adults at risk of PU development. However, the evaluation of the psychometric properties of this instrument where published in December 2018 after the inclusion of patients in the Belgian pragmatic RCT was finalized. This instrument was thus not applied in this trial.

7.1.2 Possibility to link information from the Belgian pragmatic RCT to IMA data

Some data were not collected in the underlying pragmatic RCT. For example, follow-up was limited to 14 days. This follow-up was sufficient to demonstrate a significant impact on the development of PUs. This follow-up was not sufficiently long to correctly estimate the average length of stay or to check whether there were possibly fewer surgical procedures that could be linked to treating a PU. A longer follow-up would have resulted in a more expensive trial anyway. Alternatively, we chose to link data from the trial participants with data from the IMA database (see part 7.4).

In this way, it was possible to determine the total length of stay for each patient, as well as the remaining length of stay after the occurrence of a PU. In the pragmatic RCT, the average length of stay after the occurrence of a PU was approximately 16 days (median 10).

The linkage also allowed an analysis of the use of specific nomenclature codes potentially linked to the treatment of PUs. Initially, a link was made to the nomenclature code for the so-called complicated dermatological dressing for extensive lesions. In 6 patients (9%) with PUs, this code was used, with no significant difference observed between the intervention and SoC groups. Therefore, no further analyses were performed for this variable.

Also for the selected surgical interventions, it was determined that there were no interventions within a time horizon of one year that could be linked to the occurrence of a PU in the pragmatic RCT. Again, therefore, it was not useful to conduct further cost analyses on this variable.

Linking the trial data to the IMA data allowed us to perform the analyses in an efficient way without increasing the cost of the pragmatic RCT.

7.1.3 Belgian PU treatment costs and impact on the length of stay

Belgian cost-of-illness study

Unfortunately, there are no PU-specific nomenclature codes to identify PU-treatment related costs. Fortunately, a Belgian cost-of-illness study[54] was identified that also examined the cost of PU treatment in an adult population in hospitals and nursing homes in Flanders, a region of Belgium. Information was available separately for hospitalized patients. Costs from this study were adjusted to 2022/2023 values via the health index and by including the most up-to-date hospital stay price of January 2023. Also, the length of stay from the pragmatic RCT was applied to the daily PU treatment cost, differentiating according to whether it was a category II, III or IV PU.

Impact on length of stay

In the PU treatment cost, the most determining factor is the impact on the length of stay. According to the Belgian cost-of-illness study, the additional cost for PU treatment is less than €100, even for a category IV PU, if the patient is already hospitalized for another reason. The weighted average hospital stay price of the eight participating centres already amounts to €735. In the Belgian cost-of-illness study, the authors indicate that it is a limitation that they have no data about the extra length of stay related to PU treatment. Based on an Australian study,[56] it is hypothesized that there is an additional LoS of about 4.3 days for category II, III and IV PUs. A problem with this study is that only 19% of the variation in excess length of stay could be explained by their model. The reliability of the results based on regression analysis can be strongly questioned. To assume an identical lengthening in LoS for category II versus III and IV pressure ulcers is also unrealistic.

In the pragmatic RCT, we also looked at the LoS. A difference is observed between the intervention and comparator group of about 3 days (22.1 versus 19.2 days). It is immediately clear that this cannot be explained by an absolute risk reduction in PUs of 2%. A multilevel regression model was realized, but the model with the variables at our disposal explained very little variation (R^2<2%). This means that the current study has insufficient data to examine in detail the determinants of LoS. The specific underlying reasons for hospitalization varied among patients but were not available in the database. The diversity in possible underlying reasons for hospital admission may explain the large variation in the LoS.

If so little variation can be explained by the variables present, it does not make much sense to apply regression-analyses or propensity adjustments to try to find out what impact PUs have on the LoS. An analysis of the cost impact also makes no sense in this case and would not yield reliable or interpretable results.

A non-systematic search for studies examining the effect of PUs on LoS yields disappointing results. The identified studies apply propensity score matching methods or multiple linear regression analysis. PUs are associated with an extended length of hospitalization. However, correlation should not be confused with causality. It is possible that there are variables that have an impact on the presence of PUs as well as on the length of stay and for which no correction could be made in the identified studies resulting in an overoptimistic estimate of the extension in LoS due to the presence of a PU. Caution should be exercised in concluding a causal relationship between the presence of one or more PUs and the prolongation of hospital stay. Because of this uncertain impact on LoS, we preferred to vary this impact from zero to five days when presenting the PU treatment costs for category II, III and IV PUs.

7.2 Results of the Belgian cost-consequences analysis

Despite this one uncertain point about the impact on the LoS, we can state that we were able to perform a simple but reliable cost-consequences analysis with inputs applicable to the current Belgian context. The Belgian RCT provides reliable data on the baseline risk for PUs, the relative/absolute treatment effect and thus the NNT, the proportion of different categories of PUs in the intervention and comparator group, the number of multilayer silicone foam dressings used on the sacrum, and the impact on QoL. Through linkage with the reimbursement data, we also have a perfect view on the total length of stay of all patients and the remaining length of stay after the development of a PU in the pragmatic RCT. In combination with the Belgian cost-of-illness study, a reliable cost-consequences analysis could be performed.

7.2.1 A conservative approach

Our cost-consequences analysis is a conservative approach. First, there is the cost of the intervention. In the pragmatic RCT, an average of three silicone adhesive multilayer foam dressings on the sacrum were used per patient. At an average price of about €10 per piece, this is about €30 per patient. This price does not take into account possible discounts and is thus a conservative estimate.

In addition, we make the assumption that the distribution of type of sacrum PUs is similar in both groups. In the SoC group, about two-thirds (17/26) were category II PUs. The others were category III (1/26), unstageable (3/26) or deep tissue injury (DTI) with unknown depth (5/26). In the intervention group, approximately 77% of PUs were category II injuries. Thus, the assumption of an equal distribution is also a conservative estimate.

It is also important to note that no treatment costs were considered after the patient left the hospital, such as potential costs in home care. However, PU treatment does not stop when the patient leaves the hospital. Dealey et al.[41] refer to a mean expected time to heal of 28, 94, 127, and 155 days for a PU category I, II, III and IV, respectively. In a retrospective cohort analysis of the records of 209 UK patients who developed a PU in the community (excluding hospital-acquired PUs), the average time to healing per patient was 1.1 months (category I), 5.0 months (category II), 7.7 months (category III/IV) and 10.0 months (unstageable).[61] Including the extra cost in treatment after leaving the hospital would only positively affect outcomes.

7.2.2 Potential to break even by avoiding category III-IV, non-stageable and DTI sacrum PUs

As mentioned above, there is no good evidence regarding the impact on LoS by developing a PU. However, the lack of reliable evidence is not the same as evidence of no impact on LoS. One of the Belgian experts in the field shared the following consideration:

- The presence of non-complicated PUs that do not require treatment of a local/systemic infection, planned reconstructive surgery, complicated local treatment requiring special skills, etc., is not a reason for (prolonged) hospitalisation of the patient. Only in the case of complicated PUs that require special treatment of infections or reconstruction and require specially trained nursing staff, the patient must stay longer in the hospital.
- In practice, however, we see that patients with PUs stay in the hospital longer than patients without PUs. The reason is not the wound, but other underlying factors (sometimes associated with PU risk and sometimes not). We are thinking of immobility that requires special care and monitoring in home care or placement in a nursing home or rehabilitation centre. Preparing for such a discharge and waiting for the availability of a place in a facility for specialised assistance often affects the length of hospital stay (long waiting times). This means that patients with PUs do indeed often stay longer in hospital, but that the PU itself is not always the reason.

Experts indicate the probability of wound complications is higher for category III-IV PUs,[41] which is associated with longer and more intensive treatment, extended hospital stays, readmission and specialist medical or surgical intervention. Posnett et al.[38] indicate a severe ulcer (category III-IV) is likely to result in a longer hospital stay. In a scenario analysis, we assumed no increase in LoS for category II PUs, and an increase of 5 days in LoS for category III-IV PUs. In this scenario, a break-even point was achieved taking into account all conservative assumptions. This shows the economic potential of sacrum PU prevention in the hospitalised patients at risk for PU development in university/teaching and general hospitals. This result is mainly driven by the potential to avoid category III-IV, non-stageable and DTI, as proven by the underlying pragmatic RCT.

The cost-consequences analysis was performed from a healthcare payer's perspective, including the costs for the hospitals. If we would only include costs paid by government and patients, the hospital's initial investment would not be included because it is funded through the hospital stay price. The cost of the initial purchase of the dressings, as well as PU treatment costs during a stay were included in the CCA. In addition, we considered a reduction in length of stay as something positive and have valued it from the healthcare payer's perspective by applying the hospital stay price. This choice was made because it is not possible to ascertain exactly the impact of a reduced length of stay on a hospital's use of resources and revenues. Including the reduced length of stay as a positive element also ensures that the analysis does not lead to perverse results.

7.2.3 Results not transferable to PU prevention on heels and trochanter

The results of the cost-consequences analysis apply only to the prevention of sacrum PUs. As was shown in the pragmatic RCT, the incidence for trochanter was too low with only one patient (0.1%) developing a PU. Thus, for this group, prevention would only generate costs and no effects. In the case of heels, the initial cost for the patches is twice as high since an average of six patches were used for both heels together in the pragmatic RCT. Heel PUs occurred in 1.4% and 1.9% of patients in the treatment and SoC groups, respectively (p=0.49). In the pragmatic RCT, heel dressings also caused a couple of falls (n=2) when the dressing was in direct contact with the floor. In some cases, it was reported (n=26) that heel dressings made the floor slippery for others and in one case, this resulted in a fall without significant harm. Therefore, the balance between extra costs and benefits cannot be compared with the results for sacrum PU prevention.

7.3 Comparison with other economic evaluations

No economic evaluation was performed for the selected population in a Belgian context before. Besides differences in costs in the studies identified, it is important to point out some important differences in the clinical part of the evaluation.

First, there is the selected population. The pragmatic RCT included hospitalised patients at risk for pressure ulcer development (Braden score ≤17) in university/teaching and general hospitals with a presumed LoS ≥7 days. This contrasts with the populations included in the identified economic evaluations: high- or very high-risk intensive care units (ICU) patients,[19] older patients with hip fractures,[20] residents with a high risk of developing PUs at nursing homes,[21] critically ill patients in the emergency department (ED) and ICU,[22] patients undergoing hip repair under spinal/epidural anaesthesia,[25] high-risk patients admitted to critical care units,[27] or critically ill patients admitted to the cardiac, medical, surgical, and trauma ICUs.[26] This is also reflected in noncomparable risks of development of PUs in the comparator group, as well as the absolute risk reduction. For example, in the study of Forni et al.,[20] excluding category I PUs, there is an absolute risk reduction of about 6% (9.3% versus 3.4% in the comparator and intervention group, respectively). In addition, several studies also include category I PUs in their baseline scenario.[20-22, 28, 29] The combination of the above elements leads to a reported NNT of about 9,[20] 10[22] and 12,[19] which contrasts with a NNT of 50 in our pragmatic RCT.

The majority of authors conclude that the multilayer foam dressing is (likely) cost-effective or cost-saving as an additional measure to prevent PUs in their studied population. However, given the large differences in the selected population, description and baseline risk of outcomes, and relative/absolute risk reductions, a meaningful comparison of our results with the identified economic evaluations is difficult.

7.4 From clinical trial design to HTA report: a journey

The tables and graphs in this HTA report hide an elaborate journey between their rows and lines. The current section provides an overview of the efforts and time dedicated by patients and the many people in hospitals and other organisations over the course of six and a half years that ultimately led to this report.

A summary of key events is shown in Figure 12. The key events are briefly described below the figure in Table 28.

Figure 12 – From clinical trial design to HTA report: a timeline

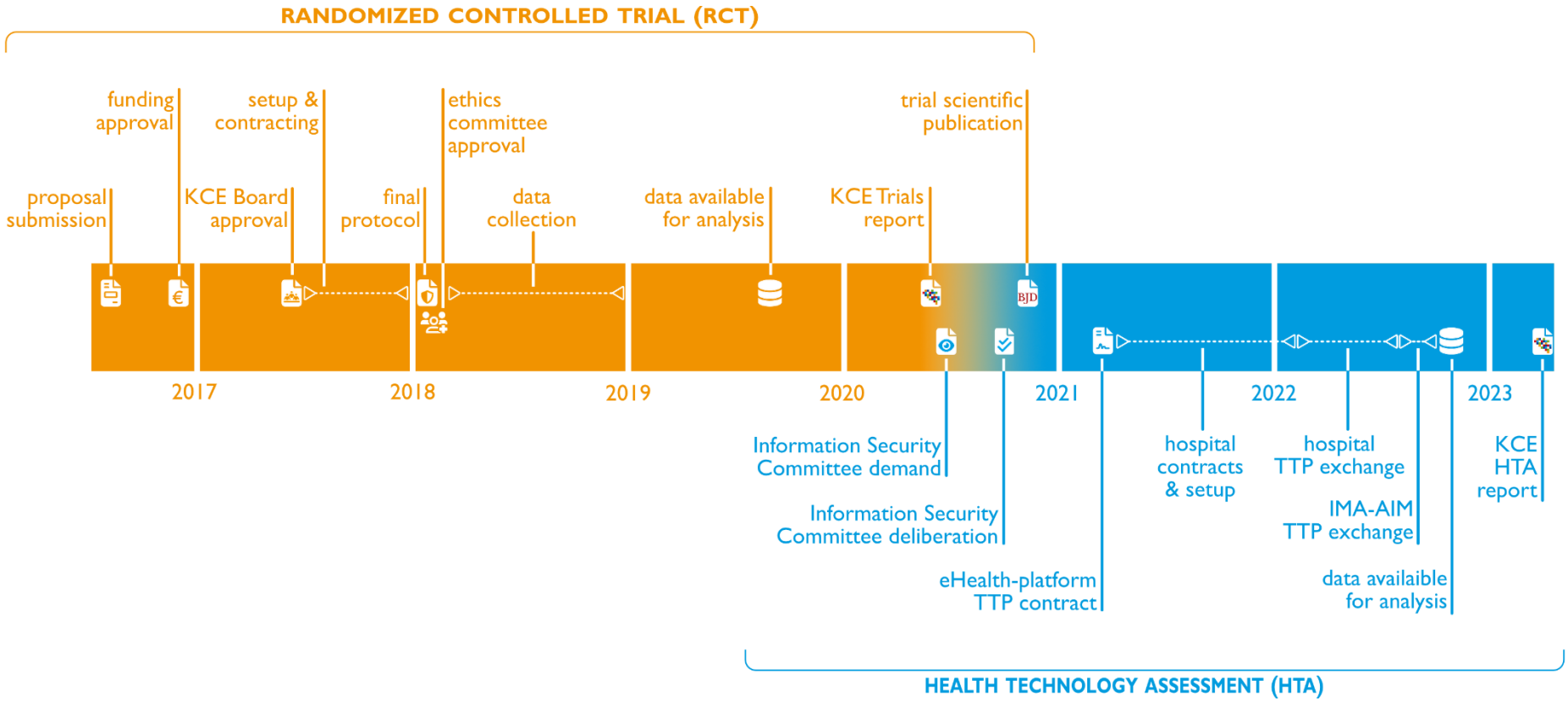


Table 28 – From clinical trial design to HTA report: description of key events

Research	Key event	Description
RCT	Proposal submission	After KCE Trials opened a call for comparative clinical trial proposals on selected topics in the 2016 commissioned workstream, the pressure ulcer RCT proposal was submitted.
RCT	Funding approval	All proposals submitted follow a review process by KCE Trials consisting of, amongst others, an assessment of the importance and relevance for the Belgian health care system, the appropriateness to answer the research question, and the scientific and methodologic soundness and feasibility of the proposal. The pressure ulcer RCT proposal was recommended for funding by the end of 2016.
RCT	KCE Board approval	Final validation and approval of the KCE Trials programme is done by the KCE Board of directors. The pressure ulcer RCT proposal was approved mid 2017 as part of the KCE Trials programme.
RCT	Setup and contracting	Once the final approval was obtained, the KCE Trials team and the RCT team finalised the necessary contracts, including those with the participating sites, and set up the necessary organisation for conducting the trial by the end of 2017.
RCT	Final protocol	Including all details necessary based on previous steps, the trial protocol was finalised at the beginning of 2018.
RCT	Ethics committee approval	The RCT protocol received approval from the respective hospital ethics committees in the first months of 2018.
RCT	Data collection	The RCT recruited and collected data between February and December 2018.
RCT	Data available for analysis	After data collection, the necessary steps were taken to arrive at database lock, taking into account the applicable legislation. The data were available for analysis by the third quarter of 2019.
RCT	KCE Trials report	The final analysis of the RCT was published in May 2020 on the KCE Trials website.
HTA	Information Security Committee demand	Based on the results of the RCT analysis, KCE planned a Health Technology Assessment as follow-up research, adding a cost-effectiveness analysis to the clinical effectiveness analysis described in the KCE Trials report. To obtain the necessary information both of the full hospital admission as well as follow-up, the RCT data were to be coupled to reimbursement claims data of IMA-AIM. For this linking, an a priori deliberation of the Information Security Committee (IVC-CSI) was requested. This demand was introduced mid 2020.
HTA	Information Security Committee deliberation	The IVC-CSI deliberation 20/190 (NL; FR) assessed the appropriateness and security of the linking process in the light of the admissibility, legal finality, proportionality and transparency of the request to be adequate.
RCT	Scientific publication	The RCT results were published in a scientific journal at the end of 2020.
HTA	eHealth-platform TTP contract	To link the RCT data with the IMA-AIM reimbursement claims data in a privacy preserving way, a trusted third party (TTP) was used. The procedure for the exchange of the data was concluded with the eHealth-platform, based on the IVC-CSI deliberation in the first quarter of 2021.
HTA	Hospital contracts and setup	For the remainder of 2021, we set up the necessary conditions for hospitals to participate in the HTA, including the conclusion of the necessary contracts, checks on data processing by the respective legal departments and exchange protocol for the eHealth-platform.

HTA	Hospital TTP exchange	The seven hospitals participating in the HTA exchanged the necessary but minimal data to the eHealth-platform in the first half of 2022.
HTA	IMA-AIM TTP exchange	IMA-AIM selected the requested data as described in the IVC-CSI deliberation for the RCT patients of the seven hospitals participating in the HTA.
HTA	Data available for analysis	The eHealth-platform performed the pseudonimisation of the data and had these communicated at KCE in the last quarter of 2022.
HTA	KCE HTA report	We completed the analysis and the report of the HTA in the first quarter of 2023.

It is possible to link data from RCTs to individual-level data as present in the IMA database. This is a possibility to reduce the cost of the trial and, in function of the results of the trial, still allow researchers to link further reliable information. It is necessary to examine first to what extent it is possible to collect relevant information through reimbursement data. In the case of the PU trial, it was possible through the IMA data to get a complete view of the total length of stay of the patients and to check whether there was a link between the occurrence of PUs and the use of specific interventions. If one considers that it is possible to collect specific information more efficiently through the IMA data, then it is necessary to already think about this when designing the trial. Linking with this data requires in advance three necessary steps:

- It requires an authorization by the chamber of social security and health of the Information Security Committee (see https://www.ehealth.fgov.be/ehealthplatform/nl/informatieveiligheidscomite). Examples of authorizations are available at https://www.ehealth.fgov.be/ehealthplatform/nl/sectoraal-comite/documenten.
- Acquiring information in this way, linked to other data that are obtained after informed consent, requires including all relevant information in the research protocol as well as in the informed consent, if the data collection is planned upfront.
- Linking with IMA data will require the ability to provide the patients' national numbers at some point to a trusted third party. The national number does not need to be included in the data collection itself, but participating healthcare providers or institutions need to be able to make the link between the national number and the study number (both of which are available at participating sites). The research protocol should specify how this link will be established at the level of the individual healthcare providers or institutions (e.g. both numbers can be extracted from the electronic health record; a separate secured database is created; etc.).

These are necessary conditions for successful linkage. It allows retrieving the costs at the level of the individual patient and linking them to the clinical trial data. As such, the linkage is possible with reimbursed hospital stays, reimbursed medical procedures, reimbursed pharmaceuticals in hospitals and public pharmacies, consultations with physicians (ambulatory or in hospital), reimbursed ambulatory health care, etc. However, it is necessary to first verify that a specific reimbursement code exists that can isolate the element in which the researchers are interested.

Mortality was not a final endpoint in the Belgian pragmatic RCT on PU prevention. For other studies, it might be interesting to link RCT data with the vital status of the patient available through the national registry.

This approach of linking RCT data to existing administrative databases allows for the reliable collection of information not only during the follow-up period of the trial, but also after the follow-up period. This approach has advantages as well as disadvantages. There is a delay on the availability of IMA data of about nine months. This delay must be weighed against the high reliability and more efficient way to obtain these data. The timeline in this report has also shown that the overall procedure can take a long time.

Optimizing this process should allow it to be completed more quickly. How such time savings can best be achieved is beyond the scope of this report, but it is certainly an important overarching research question that deserves further attention.

7.5 Conclusion

In conclusion, the Belgian pragmatic RCT has shown that the preventive use of silicone adhesive multilayer foam dressings on the sacrum reduced the incidence of sacral PUs in hospitalized patients at risk for PUs. While QoL was similar in both treatment groups, the improvement in QoL seems to be hampered by the development of a PU. A conservative cost-consequences analysis from a mixed perspective (including the hospital and healthcare payer perspective) shows the potential of the intervention to be break-even. This relies on the potential to reduce the length of stay when category III, IV, unstageable or DTI PUs are avoided. This potential only increases if possible discounts for dressings are also taken into account, if an extension of the length of stay is also possible for category II PUs, or if PU-related costs after leaving the hospital would also be taken into account. Therefore, the preventive use of silicone adhesive multilayer foam dressings on the sacrum for a population similar to the pragmatic trial population can be supported both from a clinical and economic point of view.

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APPENDICES

APPENDIX 1. SEARCH STRATEGY ECONOMIC EVALUATIONS

Appendix 1.1. Databases and search terms

Appendix 1.1.1. POP database

In November 2021, the EUnetHTA Planned and Ongoing Projects (POP) database was searched. This database allows HTA agencies to share information with each other on planned, ongoing or recently published projects conducted at the individual agency (https://www.eunethta.eu/pop-database/). Access to the POP database is currently restricted to EUnetHTA Partners and Associates who contribute to the POP database, which is the case for the Belgian Health Care Knowledge Centre (KCE). The terms 'ulcer*' and 'pressure wound*' were combined using the boolean or. This search provided 11 results. Only one study was relevant, i.e. the link referring to our own ongoing study.

Appendix 1.1.2. INAHTA HTA database

In November 2021, the international HTA database of INAHTA was searched (https://www.inahta.org/hta-database/). The Mesh term '"Pressure Ulcer"[mh]' provided 39 hits. This Mesh term was combined with the free text word 'pressure ulcer', resulting in a total of 53 hits.

Appendix 1.1.3. CRD databases

In November 2021, the Health Technology Assessments (HTA) database and NHS Economic Evaluation Database (NHS EED) of the Centre for Reviews and Dissemination (CRD) were also searched. Since March 2015 and March 2018, records have no longer been added to the EED and HTA databases, respectively. INAHTA has taken over this task for the HTA database (see Appendix 1.1.2). However, to identify older publications and for completeness, these two databases were also searched. Table 29 provides the details of this search strategy, resulting in 39 and 63 references in the HTA and EED databases, respectively.

Table 29 – Search strategy and results for CRD: HTA and NHS EED

Date	**17 November 2021**		
Date covered	All		
Search Strategy	1	MeSH DESCRIPTOR Pressure Ulcer EXPLODE ALL TREES	169
	2	* IN NHSEED	17613
	3	* IN HTA	17351
	4	#1 AND #3	**39 references**
	5	#1 AND #2	**63 references**
Note	From 31 March 2018, the HTA database remains available, but CRD are no longer adding new records to it. Bibliographic records were published on NHS EED until 31st March 2015 (source: https://www.crd.york.ac.uk/CRDWeb/).		

Appendix 1.1.4. Websites HTA institutes

In January 2022, the websites of HTA institutes (Table 30) were searched using the free text ‘pressure ulcer’. If the number of hits per website was high from a pragmatic point of view, a combination with ‘prevention’ and ‘cost-effectiveness’ was applied.

Table 30 – List of INAHTA member websites searched for HTA reports

Abbreviation	Institute	Country
ACE	Agency for Care Effectiveness	Singapore
AETS	Agencia de Evaluación de Tecnologias Sanitarias	Spain
AETSA	Andalusian Agency for Health Technology Assessment	Spain
AGENAS	The Agency for Regional Healthcare	Italy
AHRQ	Agency for Healthcare Research and Quality	USA
AHTA	Adelaide Health Technology Assessment	Australia
AIHTA	Austrian Institute for Health Technology Assessment	Austria
ANS	Agência Nacional de Saúde Suplementar / National Regulatory Agency for Private Health Insurance and Plans	Brazil
AOTMIT	Agency for Health Technology Assessment and Tariff System	Poland
AP-HP	Assistance Publique – Hôpitaux de Paris	France
AQuAS	Agència de Qualitat i Avaluació Sanitàries de Catalunya	Spain
ASERNIP-S	Australian Safety and Efficacy Register of New Interventional Procedures -Surgical	Australia
ASSR	Agenzia Sanitaria e Sociale Regionale (Regional Agency for Health and Social Care)	Italy
AVALIA-T	Galician Agency for Health Technology Assessment	Spain
CADTH	Canadian Agency for Drugs and Technologies in Health	Canada
CDE	Center for Drug Evaluation	Taiwan
CHQAC	Center for Healthcare Quality Assessment and Control	Russia
CONITEC	National Committee for Technology Incorporation	Brazil
DEFACTUM	Social & Health Services and Labour Market	Denmark
FinCCHTA	Finnish Coordinating Center for Health Technology Assessment	Finland
G-BA	The German Health Care System and the Federal Joint Committee	Germany
GOEG	Gesundheit Österreich	Austria
HAD-MSP	Health Assessment Division, Ministry of Public Health	Uruguay
HAS	Haute Autorité de Santé	France
HIQA	Health Information and Quality Authority	Ireland

Abbreviation	Institute	Country
HIS	Healthcare Improvement Scotland	United Kingdom
HTW	Health Technology Wales	United Kingdom
IACS	Health Sciences Institute in Aragon	Spain
IECS	Institute for Clinical Effectiveness and Health Policy	Argentina
IETS	Instituto de Evaluación Tecnológica en Salud	Colombia
IETSI	Institute of Health Technology Assessment and Research	Peru
IHE	Institute of Health Economics	Canada
INEAS	National Authority for Assessment and Accreditation in Healthcare	Tunisia
INESSS	Institut national d'excellence en santé et en services sociaux	Canada
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen	Germany
KCE	Belgian Federal Health Care Knowledge Centre	Belgium
MaHTAS	Health Technology Assessment Section at Ministry of Health of Malaysia	Malaysia
NECA	National Evidence-based healthcare Collaboration Agency	Korea
NICE	National Institute for Health and Care Excellence	United Kingdom
NIHR	National Institute for Health Research	United Kingdom
OH	Ontario Health	Canada
OSTEBA	Basque Office for Health Technology Assessment	Spain
SK-NRCHD	Salidat Kairbekova National Research Center for Health Development	Kazakhstan
SBU	Swedish Council on Technology Assessment in Health Care	Sweden
SEC	Department of HTA at the State Expert Centre of the Ministry of Health	Ukraine
SFOPH	Swiss Federal Office of Public Health	Switzerland
UVT	HTA Unit in A. Gemelli University Hospital	Italy
ZIN	Zorginstituut Nederland	The Netherlands
ZonMw	The Medical and Health Research Council of The Netherlands	The Netherlands

Appendix 1.1.5. Medline (OVID)

In January 2022, Medline (OVID) was searched. The search filter for economic studies from SIGN was used (https://www.sign.ac.uk/what-we-do/methodology/search-filters/) and added with clinical search terms (see Table 31), resulting in a total of 105 identified references.

Table 31 – Search strategy and results for Medline (OVID)

Date	**4 January 2022**		
Date covered	Ovid MEDLINE(R) 1996 to December Week 4 2021		
Search Strategy	1	Economics/	6982
	2	"costs and cost analysis"/	25295
	3	Cost allocation/	1017
	4	Cost-benefit analysis/	72928
	5	Cost control/	11317
	6	Cost savings/	10967
	7	Cost of illness/	29106
	8	Cost sharing/	2452
	9	"deductibles and coinsurance"/	1119
	10	Medical savings accounts/	542
	11	Health care costs/	39133
	12	Direct service costs/	942
	13	Drug costs/	15508
	14	Employer health costs/	675
	15	Hospital costs/	10603
	16	Health expenditures/	17186
	17	Capital expenditures/	829
	18	Value of life/	2693
	19	Exp economics, hospital/	16631
	20	Exp economics, medical/	3926
	21	Economics, nursing/	645

	22	Economics, pharmaceutical/	2690
	23	Exp "fees and charges"/	17889
	24	Exp budgets/	9298
	25	(low adj cost).mp.	42662
	26	(high adj cost).mp.	11232
	27	(health?care adj cost$).mp.	11216
	28	(fiscal or funding or financial or finance).tw.	125748
	29	(cost adj estimate$).mp.	2087
	30	(cost adj variable).mp.	38
	31	(unit adj cost$).mp.	2285
	32	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.	245596
	33	Or/1-32	561385
	34	pressure ulcer.mp.	9551
	35	decubitus.mp.	3018
	36	34 or 35	11959
	37	bandages.mp.	13906
	38	dressing.mp.	14043
	39	37 or 38	22834
	40	33 and 36 and 39	**105 references**
Note	The search term ‘pressure ulcer’ was included as a key word in the search strategy. The identified references (9551 hits) included all references identified with the Mesh term ‘Pressure Ulcer/’ (9015 hits). There also exist a subheading ‘Pressure Ulcer/pc [Prevention & Control]’ (3794 hits). However, this search term was considered to be too restrictive in comparison with the key word ‘pressure ulcer’ and did not add any additional hits. The Mesh for decubitus is ‘Pressure Ulcer/’, which is already included. Therefore, decubitus is only included as a separate keyword. ‘Foam dressing’ was considered to be too specific (291 hits). Therefore, the broader term ‘dressing’ was used (14043 hits). The suggested MeSH term ‘Bandages/’ (11494 hits) did not add any further references in comparison with the used keyword ‘bandages’ (13906 hits).		

Appendix 1.1.6. Embase

In January 2022, Embase was searched. The search filter for economic studies from SIGN was used (https://www.sign.ac.uk/what-we-do/methodology/search-filters/) and added with clinical search terms (see Table 32), resulting in a total of 562 identified references.

Table 32 – Search strategy and results for EMBASE

Date	**5 January 2021**		
Date covered	A time restriction for the period 2000-2021 was included (see search string #29)		
Search Strategy	1	socioeconomics'/exp	449444
	2	cost benefit analysis'/exp	88847
	3	cost effectiveness analysis'/exp	164400
	4	cost of illness'/exp	20255
	5	cost control'/exp	72042
	6	economic aspect'/exp	1899819
	7	financial management'/exp	496291
	8	health care cost'/exp	313545
	9	health care financing'/exp	13578
	10	health economics'/exp	958313
	11	hospital cost'/exp	41918
	12	finance'/exp OR 'funding'/exp OR fiscal OR financial	322035
	13	cost minimization analysis'/exp	3718
	14	cost*:de,cl,ab,ti	1204758
	15	estimate*:de,cl,ab,ti	1380846
	16	variable*:de,cl,ab,ti	1273890
	17	unit:de,cl,ab,ti	774693
	18	#14' NEAR/1 '#15' OR '#15' NEAR/1 '#14'	28630
	19	#14' NEAR/1 '#16' OR '#16' NEAR/1 '#14'	34705
	20	#14' NEAR/1 '#17' OR '#17' NEAR/1 '#14'	19709

	21	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #18 OR #19 OR #20	5399472
	22	'decubitus'/exp	24610
	23	'pressure ulcer'	6232
	24	#22 OR #23	25284
	25	bandage	19693
	26	dressing	44227
	27	#25 OR #26	59317
	28	#21 AND #24 AND #27	619
	29	#28 AND (2000:py OR 2001:py OR 2002:py OR 2003:py OR 2004:py OR 2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py OR 2020:py OR 2021:py)	**562 references**
Note			

After removal of all duplicates, a total of 696 references were identified (Table 33).

Table 33 – Results of search strategy

Database	
INAHTA HTA database	53
CRD HTA	39
CRD NHS EED	63
Medline	105
Embase	562
Total (incl. duplicates)	**822**
Duplicates	126
Total (excl. duplicates)	**696**

Appendix 1.2. Selection results

The PRISMA flow chart is presented in the report (Figure 9 in part 4.3). After de-duplication, 696 references remained. Based on title and abstract, 663 references were excluded. Of the remaining 33 references, eight references were included based on full-text evaluation, one could not be retrieved and another 24 references were excluded with reason (Table 34). Reference lists of retrieved articles were also searched and one additional reference[27] was identified. For one article,[24] three underlying (HTA) reports[28-30] were identified when searching the websites of HTA agencies (Table 7 in part 4.3). The underlying reports are looked at simultaneously when reviewing this economic evaluation.

Table 34 – Excluded references

	Excluded references identified in databases	Reason for exclusion
1	Bayoumi A, John-Baptiste A, Chen MH, Chen W, Farahati F, Krahn M, et al. The cost-effectiveness of prevention strategies for pressure ulcers in long-term care homes in Ontario: projections of the Ontario pressure ulcer model. 2008.	Intervention
2	Black J. A paradigm shift: changing the perception of unavoidability. Journal of Wound Care. 2016;25(1 Suppl):S3.	Design (no primary economic evaluation)
3	Butcher M, Thompson G. Dressings can prevent pressure ulcers: Fact or fallacy? The problem of pressure ulcer prevention. Wounds UK. 2009;5(4):80-93.	Design (no primary economic evaluation)
4	Centre for Reviews and Dissemination. Preventing pressure ulcers. England: University of York; 2014. Available from: https://www.york.ac.uk/crd/publications/effectiveness-matters/preventing-pressure-ulcers/	Design (no primary economic evaluation)
5	Davies P. 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. 2016;25(1 Suppl):S1, S4-23.	Design (no primary economic evaluation)
6	Fleurence RL. Cost-effectiveness of pressure-relieving devices for the prevention and treatment of pressure ulcers. International Journal of Technology Assessment in Health Care. 2005;21(3):334-41.	Intervention
7	Forni C, D'Alessandro F, Gallerani P, Genco R, Bolzon A, Bombino C, et al. Effectiveness of using a new polyurethane foam multi-layer dressing in the sacral area to prevent the onset of pressure ulcer in the elderly with hip fractures: A pragmatic randomised controlled trial. International Wound Journal. 2018;15(3):383-90.	Design (no primary economic evaluation)
8	Gefen A, Santamaria N. Comment on 'Effectiveness of a multi-layer foam dressing in preventing sacral pressure ulcers for the early acute care of patients with a traumatic spinal cord injury: comparison with the use of a gel mattress'. International Wound Journal. 2017;14(5):882-4.	Design (no primary economic evaluation)
9	Makai P, Koopmanschap M, Bal R, Nieboer AP. Cost-effectiveness of a pressure ulcer quality collaborative. Cost Effectiveness and Resource Allocation. 2010;8:11.	Intervention
10	Mervis JS, Phillips TJ. Pressure ulcers: Prevention and management. Journal of the American Academy of Dermatology. 2019;81(4):893-902.	Design (no primary economic evaluation)
11	Padula WV, Mishra MK, Makic MB, Sullivan PW. Improving the quality of pressure ulcer care with prevention: a cost-effectiveness analysis. Medical Care. 2011;49(4):385-92.	Intervention
12	Padula WV. Effectiveness and Value of Prophylactic 5-Layer Foam Sacral Dressings to Prevent Hospital-Acquired Pressure Injuries in Acute Care Hospitals: An Observational Cohort Study. Journal of wound, ostomy, and continence nursing : official publication of The Wound, Ostomy and Continence Nurses Society. 2017;44(5):413-9.	Design (retrospective observational cohort study)
13	Palfreyman SJ, Stone PW. A systematic review of economic evaluations assessing interventions aimed at preventing or treating pressure ulcers. International Journal of Nursing Studies. 2015;52(3):769-88.	Design (no primary economic evaluation)
14	Saab I, Solomon JF, Allen L, Siddiqui A. Hydrocellular foam is a cost-effective dressing for preventing pressure ulcers: A randomized controlled study. Journal of the American College of Surgeons. 2015;221(4):S114.	Abstract

	Excluded references identified in databases	Reason for exclusion
15	Santamaria N. The clinical effectiveness of multi-layer silicone dressings in preventing ICU acquired pressure ulcers: A randomised controlled trial. Annals of Intensive Care. 2018;8(1).	Abstract
16	Schuurman JP, Schoonhoven L, Defloor T, van Engelshoven I, van Ramshorst B, Buskens E. Economic evaluation of pressure ulcer care: a cost minimization analysis of preventive strategies. Nursing Economics. 2009;27(6):390-400, 15.	Intervention
17	Serrano J, Paiva CF, Dong F, Wong D, Neeki M. Sacral Pressure Injury Prevention in Trauma Patients: Silicone-Bordered Multilayered Foam Dressing. Journal of trauma nursing : the official journal of the Society of Trauma Nurses. 2020;27(4):246-9.	Design (no primary economic evaluation)
18	Shannon RJ, Brown L, Chakravarthy D. Pressure ulcer prevention program study: a randomized, controlled prospective comparative value evaluation of 2 pressure ulcer prevention strategies in nursing and rehabilitation centers. Advances in Skin and Wound Care. 2012;25(10):450-64.	Intervention
19	Sullivan J, Woo K. Comparing the Cumulative Incidence of Pressure Injuries Using Multilayer Foam Dressings in Seriously Ill and Frail Patients: A Quality Improvement Project. Surgical technology international. 2018;33((Sullivan J.) Nursing Practice, Quality & Education, Beverly Hospital, Beverly, MA, United States):53-7.	Not available
20	Torra IBJE, Rueda Lopez J, Camanes G, Herrero Narvaez E, Blanco Blanco J, Balleste Torralba J, et al. Preventing pressure ulcers on the heel: a Canadian cost study. Dermatology Nursing. 2009;21(5):268-72.	Intervention
21	Ucar O, Celik S. Comparison of platelet-rich plasma gel in the care of the pressure ulcers with the dressing with serum physiology in terms of healing process and dressing costs. International Wound Journal. 2020;17(3):831-41.	Intervention
22	Woods S. Aderma dermal pads in the prevention of pressure ulcers. Wounds UK. 2012;8(4):148-51.	Design (no primary economic evaluation)
23	Xakellis GC, Frantz RA, Lewis A, Harvey P. Cost-effectiveness of an intensive pressure ulcer prevention protocol in long-term care. Advances in Wound Care. 1998;11(1):22-9.	Intervention
24	Xakellis GC, Frantz RA, Lewis A, Harvey P. Translating pressure ulcer guidelines into practice: it's harder than it sounds. Advances in Skin and Wound Care. 2001;14(5):249-56, 58.	Intervention
25	Xakellis GC, Frantz RA. The cost-effectiveness of interventions for preventing pressure ulcers. Journal of the American Board of Family Medicine. 1996;9(2):79-85.	Intervention
Excluded reference from reference list		**Reason for exclusion**
	Padula WV, Pronovost PJ, Makic MBF, et al. Value of hospital resources for effective pressure injury prevention: a cost-effectiveness analysis. BMJ Qual Saf. 2019;28(2):132-141.	Intervention
Excluded references from HTA websites		**Reason for exclusion**
	Canadian Agency for Drugs and Technologies in Health (CADTH). Skin Care Management: Guidelines and Cost-Effectiveness. Ottawa: CADTH Health Technology Assessment. 19 August 2010.	Design (no primary economic evaluation)

	Excluded references identified in databases	Reason for exclusion
	Canadian Agency for Drugs and Technologies in Health (CADTH). Emerging Technologies for the Prevention of Pressure Ulcers in Acute Care Settings: A Review of Clinical and Cost-Effectiveness and Guidelines. Ottawa: CADTH Rapid Response Report. 12 September 2016.	Design (no primary economic evaluation)
	Canadian Agency for Drugs and Technologies in Health (CADTH). Polyurethane Foam Dressings for the Prevention of Pressure Ulcers: Clinical and Cost-Effectiveness and Guidelines. Ottawa: CADTH Rapid Response Report: Summary with Critical Appraisal. 3 April 2017.	Design (no primary economic evaluation)
	Holte HH, Underland V, Hafstad E. Systematic reviews on preventing pressure ulcers. Oslo: Norwegian Knowledge Centre for the Health Services (folkehelseinstituttet - FHI). 2016.	Design (no primary economic evaluation)
	National Clinical Guideline Centre. Pressure ulcer prevention: The prevention and management of pressure ulcers in primary and secondary care. Clinical Guideline 179. Commissioned by the National Institute for Health and Care Excellence (NICE). April 2014.	Wrong intervention (A cost-effectiveness analysis was performed for negative pressure wound therapy and repositioning) No primary economic evaluation of the relevant intervention

APPENDIX 2. ECONOMIC EVALUATIONS: DATA EXTRACTION SHEET

Table 35 – Data extraction sheet

	Elements to be extracted from the original economic evaluation
1	Reference (including all authors)
2	Conflict of interest and/or study funding
3	Country
4	Study question
5	Type of analysis (analytic technique) - e.g. cost-effectiveness analysis, cost-utility analysis, …
6	Design - e.g. Markov model, decision tree, …
7	Population
8	Intervention
9	Comparator
10	Time horizon
11	Discount rate for costs and/or effects
12	Perspective
13	Costs: Cost items included; Measurement of resource use; Valuation of resource use; Data sources; Currency and cost year; Other aspects…
14	Outcomes Endpoints taken into account and/or health states; Valuation of health states; Treatment effect and Extrapolation; Utility assessment (Quality of Life); Data sources for outcomes; Other aspects…
15	Uncertainty - Scenario analysis; Sensitivity analysis
16	Assumptions
17	Results Cost-effectiveness and/or cost-utility (base case); Scenario analysis; Sensitivity analysis; Other aspects…
18	Conclusions The conclusion of the authors (which can be discussed in the actual critical appraisal)
19	Remarks- e.g. limitations of the study

APPENDIX 3. QUALITY OF LIFE: EQ-5D-5L RESULTS

Table 36 – EQ-5D-5L frequencies and proportions reported by dimension and level (baseline)

	Total population (n=1624)	Patient without PU (n=1548)	Patient with PU (n=76)	Patient with sacrum PU (n=56)
Unconscious patients	88 (5.42%)	82 (5.3%)	6 (7.89%)	4 (7.14%)
Mobility				
No problems	102 (6.28%)	101 (6.52%)	1 (1.32%)	1 (1.79%)
Slight problems	75 (4.62%)	75 (4.84%)	0 (0%)	0 (0%)
Moderate problems	168 (10.34%)	158 (10.21%)	10 (13.16%)	7 (12.5%)
Severe problems	354 (21.8%)	341 (22.03%)	13 (17.11%)	10 (17.86%)
Unable	837 (51.54%)	791 (51.1%)	46 (60.53%)	34 (60.71%)
Self-care				
No problems	163 (10.04%)	162 (10.47%)	1 (1.32%)	1 (1.79%)
Slight problems	70 (4.31%)	68 (4.39%)	2 (2.63%)	2 (3.57%)
Moderate problems	141 (8.68%)	135 (8.72%)	6 (7.89%)	5 (8.93%)
Severe problems	295 (18.17%)	282 (18.22%)	13 (17.11%)	10 (17.86%)
Unable	867 (53.39%)	819 (52.91%)	48 (63.16%)	34 (60.71%)
Usual activities				
No problems	119 (7.33%)	117 (7.56%)	2 (2.63%)	2 (3.57%)
Slight problems	101 (6.22%)	97 (6.27%)	4 (5.26%)	3 (5.36%)
Moderate problems	153 (9.42%)	149 (9.63%)	4 (5.26%)	3 (5.36%)
Severe problems	281 (17.3%)	269 (17.38%)	12 (15.79%)	10 (17.86%)
Unable	882 (54.31%)	834 (53.88%)	48 (63.16%)	34 (60.71%)
Pain/discomfort				
No problems	283 (17.43%)	274 (17.7%)	9 (11.84%)	6 (10.71%)
Slight problems	360 (22.17%)	348 (22.48%)	12 (15.79%)	9 (16.07%)
Moderate problems	503 (30.97%)	474 (30.62%)	29 (38.16%)	22 (39.29%)

Severe problems	321 (19.77%)	309 (19.96%)	12 (15.79%)	8 (14.29%)
Unable	69 (4.25%)	61 (3.94%)	8 (10.53%)	7 (12.5%)
Anxiety/Depression				
No problems	665 (40.95%)	638 (41.21%)	27 (35.53%)	21 (37.5%)
Slight problems	454 (27.96%)	431 (27.84%)	23 (30.26%)	16 (28.57%)
Moderate problems	283 (17.43%)	270 (17.44%)	13 (17.11%)	10 (17.86%)
Severe problems	112 (6.9%)	107 (6.91%)	5 (6.58%)	4 (7.14%)
Unable	22 (1.35%)	20 (1.29%)	2 (2.63%)	1 (1.79%)

Table 37 – EQ-5D-5L frequencies and proportions reported by dimension and level (day 3)

	Total population (n=1400)	Patient without PU (n=1333)	Patient with PU (n=67)	Patient with sacrum PU (n=48)
Unconscious patients	64 (4.57%)	57 (4.28%)	7 (10.45%)	5 (10.42%)
Mobility				
No problems	37 (2.64%)	36 (2.7%)	1 (1.49%)	1 (2.08%)
Slight problems	91 (6.5%)	88 (6.6%)	3 (4.48%)	3 (6.25%)
Moderate problems	177 (12.64%)	168 (12.6%)	9 (13.43%)	8 (16.67%)
Severe problems	328 (23.43%)	315 (23.63%)	13 (19.4%)	9 (18.75%)
Unable	703 (50.21%)	669 (50.19%)	34 (50.75%)	22 (45.83%)
Self-care				
No problems	46 (3.29%)	44 (3.3%)	2 (2.99%)	2 (4.17%)
Slight problems	72 (5.14%)	71 (5.33%)	1 (1.49%)	1 (2.08%)
Moderate problems	141 (10.07%)	137 (10.28%)	4 (5.97%)	4 (8.33%)
Severe problems	273 (19.5%)	262 (19.65%)	11 (16.42%)	9 (18.75%)
Unable	804 (57.43%)	762 (57.16%)	42 (62.69%)	27 (56.25%)
Usual activities				
No problems	47 (3.36%)	46 (3.45%)	1 (1.49%)	1 (2.08%)

Slight problems	69 (4.93%)	66 (4.95%)	3 (4.48%)	3 (6.25%)
Moderate problems	140 (10%)	138 (10.35%)	2 (2.99%)	1 (2.08%)
Severe problems	320 (22.86%)	305 (22.88%)	15 (22.39%)	11 (22.92%)
Unable	760 (54.29%)	721 (54.09%)	39 (58.21%)	27 (56.25%)
Pain/discomfort				
No problems	200 (14.29%)	194 (14.55%)	6 (8.96%)	5 (10.42%)
Slight problems	442 (31.57%)	424 (31.81%)	18 (26.87%)	11 (22.92%)
Moderate problems	423 (30.21%)	403 (30.23%)	20 (29.85%)	15 (31.25%)
Severe problems	228 (16.29%)	214 (16.05%)	14 (20.9%)	10 (20.83%)
Unable	43 (3.07%)	41 (3.08%)	2 (2.99%)	2 (4.17%)
Anxiety/Depression				
No problems	596 (42.57%)	576 (43.21%)	20 (29.85%)	14 (29.17%)
Slight problems	435 (31.07%)	411 (30.83%)	24 (35.82%)	16 (33.33%)
Moderate problems	206 (14.71%)	196 (14.7%)	10 (14.93%)	8 (16.67%)
Severe problems	71 (5.07%)	68 (5.1%)	3 (4.48%)	2 (4.17%)
Unable	28 (2%)	25 (1.88%)	3 (4.48%)	3 (6.25%)

Table 38 – EQ-5D-5L frequencies and proportions reported by dimension and level (end of study)

	Total population (n=1356)	Patient without PU (n=1290)	Patient with PU (n=66)	Patient with sacrum PU (n=49)
Unconscious patients	37 (2.73%)	31 (2.4%)	6 (9.09%)	4 (8.16%)
Mobility				
No problems	91 (6.71%)	90 (6.98%)	1 (1.52%)	1 (2.04%)
Slight problems	189 (13.94%)	184 (14.26%)	5 (7.58%)	5 (10.2%)
Moderate problems	286 (21.09%)	274 (21.24%)	12 (18.18%)	9 (18.37%)
Severe problems	293 (21.61%)	279 (21.63%)	14 (21.21%)	10 (20.41%)
Unable	460 (33.92%)	432 (33.49%)	28 (42.42%)	20 (40.82%)
Self-care				

No problems	96 (7.08%)	96 (7.44%)	0 (0%)	0 (0%)
Slight problems	175 (12.91%)	172 (13.33%)	3 (4.55%)	3 (6.12%)
Moderate problems	222 (16.37%)	214 (16.59%)	8 (12.12%)	6 (12.24%)
Severe problems	232 (17.11%)	224 (17.36%)	8 (12.12%)	6 (12.24%)
Unable	594 (43.81%)	553 (42.87%)	41 (62.12%)	30 (61.22%)
Usual activities				
No problems	65 (4.79%)	64 (4.96%)	1 (1.52%)	1 (2.04%)
Slight problems	127 (9.37%)	122 (9.46%)	5 (7.58%)	4 (8.16%)
Moderate problems	257 (18.95%)	252 (19.53%)	5 (7.58%)	4 (8.16%)
Severe problems	302 (22.27%)	291 (22.56%)	11 (16.67%)	9 (18.37%)
Unable	568 (41.89%)	530 (41.09%)	38 (57.58%)	27 (55.1%)
Pain/discomfort				
No problems	305 (22.49%)	295 (22.87%)	10 (15.15%)	9 (18.37%)
Slight problems	476 (35.1%)	452 (35.04%)	24 (36.36%)	18 (36.73%)
Moderate problems	385 (28.39%)	369 (28.6%)	16 (24.24%)	11 (22.45%)
Severe problems	124 (9.14%)	115 (8.91%)	9 (13.64%)	6 (12.24%)
Unable	29 (2.14%)	28 (2.17%)	1 (1.52%)	1 (2.04%)
Anxiety/Depression				
No problems	654 (48.23%)	625 (48.45%)	29 (43.94%)	23 (46.94%)
Slight problems	411 (30.31%)	393 (30.47%)	18 (27.27%)	10 (20.41%)
Moderate problems	185 (13.64%)	175 (13.57%)	10 (15.15%)	9 (18.37%)
Severe problems	51 (3.76%)	49 (3.8%)	2 (3.03%)	2 (4.08%)
Unable	18 (1.33%)	17 (1.32%)	1 (1.52%)	1 (2.04%)

APPENDIX 4. NOMENCLATURE CODES

Appendix 4.1. Flap surgery

Code	French description	Dutch description	Cost*
275030	Curetage avec ou sans biopsie, d'un os profond (os iliaque-fémur-omoplate-humérus)	Curettage met of zonder biopsie van een diepliggend been (heupbeen-dijbeen-scapula-humerus)	240.67€
220253	Cure chirurgicale de phlegmon profond	Volledige heelkundige behandeling van diepliggende phlegmone	79.10€
250180	Plastique à lambeau pédiculé, temps principal	Huid- of fascio-cutane flap, hoofdbewerking	275.65€
250224	Lambeau pédiculé cutané ou fascio-cutané réalisé en un temps sur une surface égale ou supérieure à 100 cm²	Huid- of fascio cutane flap, in één bewerking over een oppervlakte gelijk of groter dan 100 cm²	413.47€
251963	Prélèvement d'un lambeau perforateur (ex : DIEP ou SGAP) et préparation du pédicule en vue du transfert microchirurgical	Vrijmaken van perforatorflap (vb : DIEP of SGAP) en klaarmaken van de vaatsteel voor microchirurgisch transfert	551.30€
251860	Lambeau musculaire, temps principal ou unique	Spierlap, hoofdbewerking	441.04€
251904	Lambeau musculo-cutané	Spierhuidlap	551.30€

** Cost on the 01/01/2023, source: NIHDI*

Appendix 4.2. Complicated dermatological dressing

Code	French description	Dutch description	Cost*
145305	Pansement dermatologique compliqué pour lésions étendues, en période d'hospitalisation	Ingewikkeld dermatologisch verband voor uitgebreide letsels, tijdens ziekenhuisverpleging	11.26€
145272	Pansement dermatologique compliqué pour lésions étendues	Ingewikkeld dermatologisch verband voor uitgebreide letsels	2.81€

** Cost on the 01/01/2023, source: NIHDI*

APPENDIX 5. HIERARCHICAL MODEL FOR LENGTH OF STAY

First, a multivariate regression model was constructed where all the variables were treated as fixed factors (Table 39).

Table 39 – Multivariate model regression analysis for log(length of stay).

	Final model	
	Estimate ± Std error	p-value
Intercept	2.83 ± 0.246	<.0001
Age (year)	0.001 ± 0.002	0.51
Surgery	-0.073 ± 0.064	0.25
BMI (kg/m²)	-0.002 ± 0.004	0.65
Sex (ref=male gender)	0.006 ± 0.039	0.87
Diabetes	0.002 ± 0.046	0.97
Baseline PU	-0.246 ± 0.074	<0.001
Braden risk score	0.006 ± 0.010	0.53
Multilayer foam dressings group (ref=SoC)	-0.091 ± 0.040	0.024
Site 1	0.040 ± 0.081	0.62
Site 2	0.279 ± 0.069	<.001
Site 3	0.078 ± 0.079	0.32
Site 4	0.049 ± 0.102	0.63
Site 5	0.240 ± 0.068	<0.001
Site 6	0.153 ± 0.067	0.023
Site 7 (ref)		
ICU ward	-0.175 ± 0.068	0.010
Development of PU	0.250 ± 0.135	0.064
Development of PU* SoC	-0.131 ± 0.181	0.47

Adjusted r²=0.0164, AIC=3144.9, BIC=3150.1

As the centre and ICU ward were variables used as hierarchical levels with patients nested within, they are treated as random factors in a multilevel regression model. The lower BIC or AIC suggest that the hierarchical model regression is a better fit than the multiple regression model. Nevertheless, with an adjusted R^2 of 0.016, we choose not to further interpret the results.

Table 40 – Hierarchical model regression analysis for log(length of stay).

	Final model	
	Estimate ± Std error	p-value
Intercept	2.977 ± 0.227	<.0001
Age	0.001 ± 0.002	0.59
Surgery	-0.088 ± 0.064	0.17
BMI	-0.001 ± 0.004	0.72
Gender (ref=Male)	0.004 ± 0.039	0.92
Diabetes	0.004 ± 0.046	0.92
Baseline PU	-0.251 ± 0.074	<0.001
Braden risk score assessment	-0.002 ± 0.009	0.86
Multilayer foam dressings group (ref=SoC)	-0.092 ± 0.040	0.022
Development of PU	0.247 ± 0.135	0.068
Development of PU* SoC	-0.130 ± 0.181	0.47
Random effect: estimated covariance siteID	<0.001	
ICU within siteID	0.012	
Residual	0.49	
AIC model	3136.1	

Model likelihood ratio test: Chi square=18.6, p<0.001; Akaike information criterion (AIC): 3140.4, Bayesian information criterion (BIC): 3140.3

APPENDIX 6. THE CHEERS CHECKLIST

The aim of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS)[52, 53] statement is to provide recommendations, in the form of a checklist, to optimise reporting of health economic evaluations. The 28 items checklist is provided in Table 41.

Table 41 – CHEERS 2022 checklist

Topic	No.	Item	Location where item is reported
Title			
	1	Identify the study as an economic evaluation and specify the interventions being compared.	Title
Abstract			
	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	Not applicable for this HTA report
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Chapter 1 & Chapter 2
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	See original research protocol
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Part 3.1.4 & 3.2.1
Setting and location	6	Provide relevant contextual information that may influence findings.	Part 3.1.2
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Part 3.1.5 & 3.1.6
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Part 6.1.2 & 6.2.3
Time horizon	9	State the time horizon for the study and why appropriate.	Part 6.1.3
Discount rate	10	Report the discount rate(s) and reason chosen.	Part 6.1.3
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Part 6.1.4
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Part 3.1.7
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Part 3.2.1
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Part 6.2.2.
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Part 6.2.2

Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	Not applicable (part 6.1.4)
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Not applicable
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	Part 7.2.3
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	Not applicable
Characterising uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.	Part 6.2.2.2 & Part 6.2.3
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	See original research protocol
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Part 6.2.1 & part 6.2.2
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Part 6.2.3
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Part 7.2.1
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	Not applicable
Discussion			
Study findings, limitations, generalisability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Discussion
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	Not applicable
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	See colophon

From: Husereau D, Drummond M, Augustovski F, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Explanation and Elaboration: A Report of the ISPOR CHEERS II Good Practices Task Force. Value Health 2022;25. doi:10.1016/j.jval.2021.10.008