Heel Pressure Ulcers: Contributory factors and their impact on quality of life and role at the end of life in the adult population

By

Alisen Zandilintombi Dube

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BIRMINGHAM CITY University

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Dissemination and Publications

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Heel Pressure Ulcers; risk factors for developing heel pressure ulcers, their impact on quality of life and their prognostic value in end of life.

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- Pressure Ulcer Prevention Conference-University Hospitals Coventry and Warwickshire 01/05/2018.
- Wounds UK 2018 annual meeting 5-7 November 2018 (poster presentation).
- Pressure ulcer prevention awareness- Birmingham City University 14/11/2018.
- West Midlands Tissue Viability Nurse meeting on 05/12/2018.
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Publications

1. Alisen Dube, Sarahjane Jones, Maxine Lintern, Mark Radford. A systematic review of risk factors associated with heel pressure ulcer development in adults. PROSPERO 2017 CRD42017071459
2. Dube A, Sidambe V, Verdon A, Phillips E, Jones S, Lintern M, Radford M. Risk factors associated with heel pressure ulcer development in the adult population: A systematic literature review. J Tissue Viability. 2022 Feb;31(1):84-103. doi: 10.1016/j.jtv.2021.10.007. Epub 2021 Oct 28. PMID: 34742635.

List of Abbreviations

ABPI	Ankle Brachial Pressure Index
AMTS	Abbreviated Mental Test Score
aSSKINg	Assessment, Surface, Skin inspection, keeping patients moving, Incontinence and Nutrition / Hydration, giving information
CIS	Consultee Information Sheet
CKD	Chronic Kidney Disease
CRF	Case Report Forms
CRRS	Clinical Results Reporting System
CTIMPs	Clinical Trials of Investigational Medicinal Products
DeNDRoN	Dementia & Neurodegenerative Diseases Research Network
DTI	Deep Tissue Injury
DUS	Doppler ultrasound
EoL	End of Life
EPUAP	European Pressure Ulcer Advisory Panel
HF	Heart Failure
HPU	Heel Pressure Ulcer
HPU PIG	Heel Pressure Ulcer Public Involvement Group
HRA	Health Regulatory Authority
HRQoL	Health-related quality of life
HPU	Heel pressure ulcer
GSF	Gold Standard Framework
KM	Kaplan Meier
MCA	Mental Capacity Act

MMSE	Mini-Mental State Examination
NICE	National Institute of Health and Care Excellent
NHS	National Health Service
NPUAP	National Pressure Ulcer Advisory Panel
NRS	Numeric rating scale
OR	Odds Ratio
PAD	Peripheral Artery Disease
PAINAD	Pain Assessment in Advanced Dementia
PH	Proportional Hazard
PIPPA	Pan Pacific Pressure Injury Alliance
PIS	Patient Information Sheet
PPRAG	Patient and Public Research Advisory Group
PRO	Patient Reported Outcomes
PURPOSE T	Pressure Ulcer Risk Primary or Secondary Evaluation Tool
PU	Pressure Ulcer
PVD	Peripheral Vascular Disease
RAT	Risk Assessment Tool
REC	Research Ethics Committee
SBP	Systolic Blood Pressure
SD	Standard deviation
SNAQ-RC	Short Nutritional Assessment Questionnaire for Residential Care
SPICT	Supportive and Palliative Indicators Tool
SSKIN	Surface, Skin inspection, Keeping patients moving, Incontinence and Nutrition / Hydration

TBPI	Toe Brachial Pressure Index
TVN	Tissue Viability Nurse
WOC	Wound Ostomy Continence

Abstract

Pressure ulcer prevention remains a persistent challenge in healthcare, affecting patients across all age groups, from neonates to the elderly. Pressure ulcers occur as damage to the skin and/or underlying tissue over bony prominence areas because of sustained pressure and/or shear. Heel pressure ulcers (HPUs) are the second most common type of pressure ulcer, following those at the sacrum, in most healthcare settings. There is limited evidence to support the prevention of heel pressure ulcers in the adult population. Furthermore, emerging evidence suggests differences in risk factors associated with pressure ulcers based on the specific anatomical site affected. This study therefore aims to identify and quantify the relationship between risk factors and HPUs presence and to investigate their impact on health-related quality of life (HRQoL) and prognostic significance at the end of life (EoL).

This research employed an exploratory single-centre observational study design, grounded in a pragmatic philosophy and utilising three distinct methodologies, as outlined below.

Phase 1: Risk factors for developing heel pressure ulcers in the adult population: a systematic literature review.

Phase 2: Factors associated with the presence of heel pressure ulcers in the adult population: a matched case-control study.

Phase 3: the impact of heel pressure ulcers on HRQoL and their prognostic significance in EoL.

This thesis is the first to conduct a systematic literature review on risk factors associated with HPUs in the adult population. The review identified a significant lack of evidence, with 76.9% of the studies rated as moderate to poor quality, highlighting the need for further research. A total of 103 participants took part in Phases 2 and 3, compromising 53 patients with heel pressure ulcer(s) and 50 without. A conceptual framework for risk factors is proposed to aid in identifying those at risk and support the timely implementation of preventive strategies. HPUs negatively impact the quality of life and significantly increase healthcare resource use in acute settings. Applying evidence-based risk assessment tools (RATs) can help improve patient outcomes.

Individuals of ethnic minority backgrounds and those lacking capacity remain underrepresented in HPU research, which denies them evidence-based care and further perpetuates health inequalities. Engaging patients and the public can be essential for ensuring research is inclusive and reflects the needs of those it aims to serve. Future research needs to prioritise ethnic minority backgrounds and those lacking capacity to make HPU risk assessment and prevention processes relevant to their care.

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Chapter 1 Introduction to the Study

1.1 Introduction

Pressure ulcers (PUs) remain an unresolved challenge within healthcare, affecting patients of all ages from neonates to the elderly. They are associated with debilitating pain, reduced quality of life for both patients and their families, and substantial financial costs for the National Health Service (NHS). PUs are localised skin or tissue damage over bony prominences, caused by sustained pressure and/or shear. They more commonly affect individuals with impaired mobility, poor nutrition and multiple morbidities, including a current or prior history of PUs (NHS Improvement, 2018). This chapter presents an overview, outlining the rationale, aims, objectives, design, and a structure of this thesis.

1.2 Study rationale.

The incidence and prevalence rates of pressure ulcers (PUs)remain high and vary across different anatomical locations and populations, with sacral and heel PUs consistently identified as the two most common types in adult populations (Li, Z. et al., 2020). This underscores the need for further research, particularly focused on heel PUs (HPUs), as existing literature often emphasises PUs in general, despite HPUs being the second most common type after sacral PUs (Coleman et al., 2013; Li, Z. et al., 2020). Gaining insight into the biology and natural history of HPUs, including factors associated with HPU development, is essential to inform innovative preventative strategies that can target the at-risk populations in a timely manner, thereby reducing HPUs incidence in the adults. Improved understanding and new interventions could enhance quality of life and health outcomes for patients by providing harm-free care. Prior to this research, no systematic literature review existed

on the risk factors for HPU development in the adult population. Moreover, there is limited evidence base on the impact of HPUs on health-related quality of life (HRQoL) and their potential predictive value at of life (EoL).

1.3 Research Aims and Objectives

1.3.1 Aim

The overarching aim of the study was to identify and quantify the relationship between risk factors and heel pressure ulcers (HPUs) presence and investigate their impact on health-related quality of life (HRQoL) and prognostic value in end of life (EoL).

1.3.2 Objectives

1. Identify the risk factors associated with HPU development and quantify their relationship.
2. Investigate the effect of HPUs on HRQoL at baseline (recruitment), 3 and 6 months.
3. Determine the prognostic value of HPUs in EoL.

1.4 Research Design

To fully address the study aims and objectives, this research is divided into three main phases which utilise different study designs. The first phase is a systematic review, critically appraising the literature on risk factors for HPU development in the adult population. The second phase is a case matched controlled study to further elucidate the risk factors for HPU development as identified from the literature review and other potential contributory factors. The third phase is a prospective cohort study used to quantify the impact of HPU on patients' HRQoL and their relationship with mortality. Patient and public involvement has been paramount to the design and delivery of this research.

1.5 Thesis Outline

Figure 1-1 outlines the structure of this thesis. Chapter 1 (current chapter) provides a summary overview of the thesis, rationale, aims and objectives and study design. Chapter 2 summaries the existing literature on HPUs, their impact on quality of life and association with mortality. A systematic literature review on risk factors associated with the development of HPU is presented in Chapter 3 (Phase 1), which comprises the aim, methods, results, and discussion of the existing literature. This is followed by Chapter 4 which presents the research methods including ethical and legal considerations applicable to this study. Chapter 5 describes the study protocols for phase 2 and 3 of this thesis. Study findings from phases 2 and 3 of the study are laid out in Chapter 6 and are discussed in Chapter 7. The study findings, limitations, and strengths from the previous chapters are discussed in Chapter 7 in relation to the wider literature facilitating the development of a HPU Risk Factors framework. Finally, Chapter 8 concluded the thesis by outlining recommendations for future research, policy, clinical practice, and education.

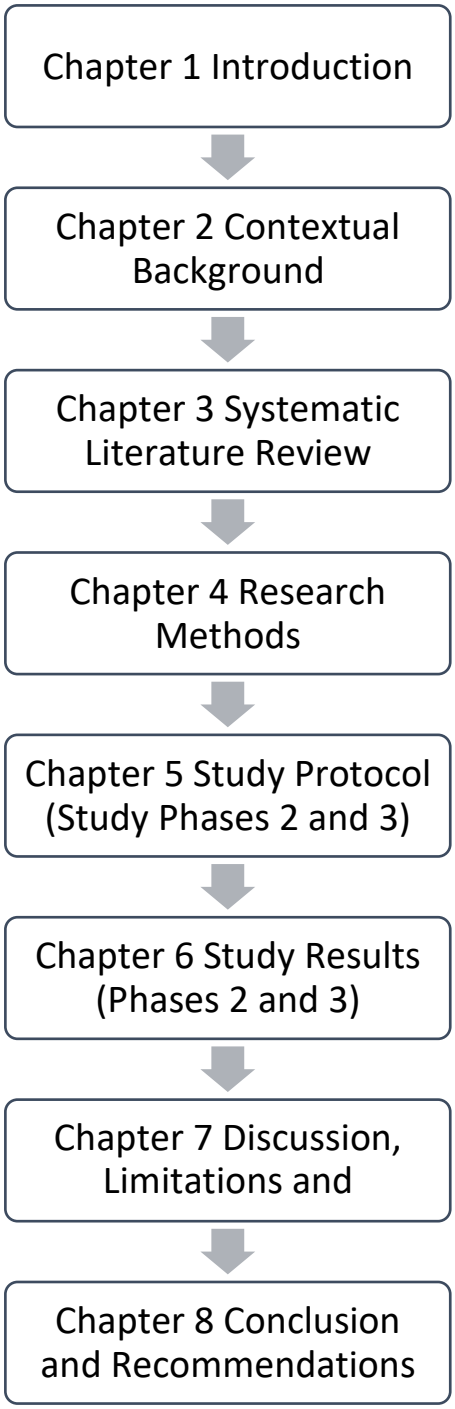


Figure 1-1 Thesis outline.

Chapter 2 Contextual Background

2.1 Introduction

Pressure ulcers (PU) continue to pose an unresolved patient safety concern, with variable incidence and prevalence rates across different healthcare settings, and prevalence rates reaching as high as 13.3% among hospitalised patients (Li, Z. et al., 2020). These chronic wounds cause distress and pain to those affected, negatively impacting the quality of life for both patients and their caregivers. Additionally, PUs cost the NHS approximately £540 million annually, and this economic burden is expected to rise with an ageing population (Guest et al., 2018). Existing evidence tends to emphasise PUs across all anatomical sites or focus on specific patient populations, with less attention given to heel pressure ulcers (HPUs) (Coleman et al., 2013; Rao et al., 2016; Sardo et al., 2023; Serrano et al., 2017; Tubaishat et al., 2018). HPUs are the second most common type, following sacral PUs (Li, Z. et al., 2020; Sardo et al., 2023; Tubaishat et al., 2018). Therefore, this literature review chapter examines pressure ulcers (across all anatomical sites) and specifically focuses on HPUs, emphasising risk assessment tools (RATs), the impact of HPUs on health-related quality of life (HRQoL), and their prognostic value at end of life. The gaps identified in the literature have informed the subsequent chapters of this thesis.

2.2 Pressure Ulcers

Pressure ulcers (PUs), also referred to as “pressure injuries” or previously as “decubitus” or “bedsores”, involve localised damage to the skin and underlying soft tissue, usually over a bony prominence or in areas affected by medical devices (NHS Improvement, 2018). This is the standard PU definition adopted in all NHS settings within England. The NHS Improvement (2018) definition aligns with international guidelines such as those from EPUAP/ NPUAP/PIPA (European Pressure Ulcer

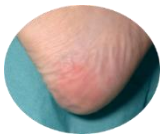
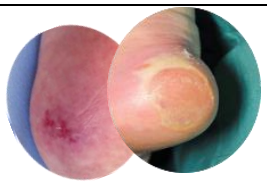
Advisory Panel et al., 2019). The EPUAP/ NPUAP/PIPA (2019) definition makes it clear that pressure and shear are key players in the development of PUs. Other PU definitions highlight the complexity of PU development and the multifactorial risk factors involved, many of which are still under investigation (Bennett, 2004; National Pressure Ulcer Advisory Panel et al., 2014; National Pressure Ulcer Advisory Panel et al., 2018). The shape of the bone surfaces and lack of soft tissue at bony prominence anatomical sites expose them to external forces because of interactions that occur between the weight bearing tissues and support surfaces. PUs commonly occur over the buttocks, heels and sacrum because of intense and/or prolonged pressure or pressure in combination with shear in individuals or patients with reduced mobility. The tolerance of soft tissue to pressure and/or shear in at-risk areas may also be affected by many other factors such as co-morbidities, nutrition, perfusion, and the state of the skin (Coleman et al., 2013; Tubaishat et al., 2018). This suggests that PU prevention might be achievable by minimising the impact of such factors. While PUs may be avoidable with correct strategies in place, patients and their carers may continue to perceive them as an inevitable consequence of ill health, old age, and medical treatments (Bennett, 2004; García-Sánchez et al., 2019). Either way, further research is still required to understand the risk factors and educate patients and their carers as well as healthcare professionals on how to identify at-risk individuals using frameworks such as risk assessments tools and management to reduce PU incidence rates. Ultimately, reducing PU incidence and prevalence rates will enable provision of harm free care thus improving patient's quality of life (QoL) and their healthcare experiences.

PUs or damage caused by pressure or pressure in combination with shear forces can range from intact skin with non-blanching redness (category 1) to an open ulcer with

full thickness tissue loss exposing bones, tendons or muscles; Table 2-1 summarises the different PU categories as defined by the NPUAP/EPUAP/PPPIA (National Pressure Ulcer Advisory Panel et al., 2014). Deep tissue injury (DTI) and unstageable categories provide further clarification for PUs that are difficult to classify on initial assessment (Appendix 1 and Table 2-1 provides further descriptions and images on the distinct categories respectively). It is worth noting that the while PU classifications are constantly evolving with new evidence, there exist several variations of the classifications in literature: NPUAP Classification (2016), WHO ICD-11(2018) and NPUAP/EPUAP International Classification (2019) being the three most commonly used classification (Edsberg et al., 2016; Pacific, 2019; World Health Organization, 2018). Whilst they are mostly similar, variations in classification systems exist. For instance, NPUAP/EPUAP International Classification states that subcutaneous fat may be visible in stage 3 PUs while the NPUAP (2016) refers to a stage three as full-thickness loss of skin, in which adipose is visible (Kottner et al., 2020). Damage in intact darker skin tones may be difficult to detect, thus can affect the healthcare professionals' ability to prevent further deterioration. As a result, individuals with darker skin tones, for instance those from Asian or Black ethnic backgrounds, are likely to present with more severe PU categories (categories 3 and above) (Harms et al., 2014; Li, Y. et al., 2011; Oozageer Gunowa et al., 2018) possibly due to late detection. For instance, in the Li et al. (2011) study, involving nursing homes in the United States; rates of category 1 PUs were 2.1% and 1.2% among white and black residents compared to 2.4% and 5.5% for categories 4 PUs. Categories 3 and above take longer to heal and have a higher risk of secondary complications particularly in the presence of conditions such as diabetes and cardiovascular diseases which are more common in Asian and Black communities (Alfonso et al., 2019; Guest et al., 2018). Healthcare

professionals need to be aware of such disparities to minimise further health inequalities amongst ethnic minority patients.

Table 2-1 Pressure Ulcer classification as outlined by European Pressure Ulcer Advisory Panel et al., 2019

Category 1	**Category 2**	**Category 3**
 *Intact skin with non-blanchable redness.*	 *Partial-thickness skin loss with exposed dermis but without slough*	 *Full thickness skin loss but bone, tendon or muscle are not exposed.*
Category 4	**Deep Tissue Injury (DTI)**	**Unstageable**
 *Full thickness loss of skin & tissue exposing bone, muscle, or tendon.*	 *Persistent non-blanchable deep red, maroon, purple discoloration* (*may also look like blood-filled blister)*	 Obscured *(with necrosis of slough)* full-thickness skin & tissue loss

2.2.1 Pressure Ulcer Pathophysiology and Aetiology

The aetiology of pressure ulcers involves a complex interplay of extrinsic and intrinsic factors, which are essential for identifying individuals at risk and implementation of preventative strategies. Extrinsic factors include prolonged pressure, friction, and shear forces from contact with a supporting surface, while intrinsic factors encompass compromised tissue perfusion, altered sensory perception and decreased mobility (Anrys et al., 2019; Makori et al., 2023; Manderlier et al., 2019). PU formation is often attributed to restricted blood supply to the affected area due to sustained external forces, resulting in tissue ischemia and eventual necrosis (Gefen, 2007). The development of PUs involves a cascade of events initiated by continuous pressure on the skin and underlying tissues (Gefen et al., 2022). Figure 2-1 illustrates the sequence of processes in PU development as a result of prolonged pressure over bony prominence (Gefen et al., 2022). Pressure intensity, duration and tissue tolerance are key factors contributing to pressure damage. When external forces exceed the arterial capillary pressure of 32 mm Hg, blood flow to the affected area is compromised leading to tissue ischemia and necrosis (Zaidi and Sharma, 2023). Ischemia triggers a series of cellular responses aimed at restoring normal blood flow and oxygen delivery. However, prolonged pressure impairs this compensatory mechanism resulting in a state of hypoxia and accumulation of metabolic byproducts, ultimately causing tissue damage (Gefen et al., 2022). An exposure to conditions such as diabetes or vascular disease reduces tissue tolerance to external forces thus making the skin and underlying tissues vulnerable to pressure and or shear damage. Understanding how the role of the extrinsic factors in combination with intrinsic factors is important for developing targeted prevention and treatment approaches as well as the processes of identifying those at risk.

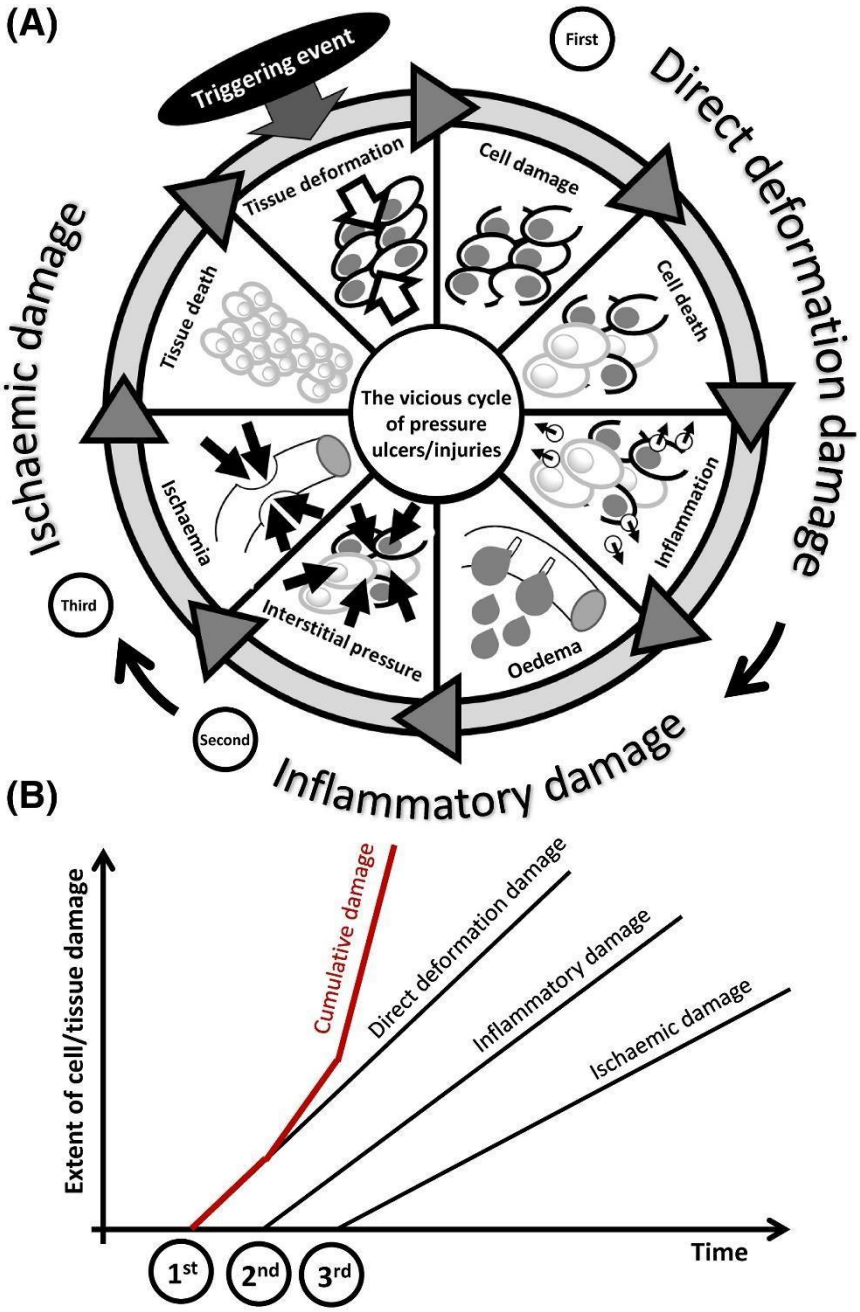


Figure 2-1 Schematic description of PU formation as result of sustained mechanical deformations. Source: (Gefen et al., 2022).

2.2.2 Pressure Ulcer Incidence and Prevalence rates

PUs remain a constant patient safety challenge across healthcare settings despite several advances in PU knowledge, preventative technology, national and local guidance, and initiatives such as ‘Stop the Pressure’ (National Wound Strategy, 2024). In the UK, PUs are one of four most common preventable harms affecting anyone

from newborns to those at the end of life (NHS Digital, 2017; NHS Improvement, 2018). PU incidence and prevalence rates continue to be uncertain due to variations in study populations, different classification tools, underreporting, inconsistent exclusion or inclusion of category 1 PUs and a lack of quality assurance processes to reduce misdiagnosis (Tubaishat et al., 2018). Misdiagnosis of PUs, particularly those affecting the heels remains a major challenge for clinicians as they struggle to distinguish between diabetic foot ulcers, and HPUs (Ousey et al., 2011). Prevalence studies conducted around 2007 and 2008 reported variable rates ranging from between 9.2 to 18.1% depending on clinical setting and geographical location (Vanderwee et al., 2006; Vanderwee et al., 2009). A recent meta-analysis, which included 39 studies from various countries primarily developed ones such as the UK (Li, Z. et al., 2020), reported a pooled estimate of 13.3% among hospital patients in low-risk studies dating back to 2008. Data from these studies show that PU prevalence rates remain high globally, despite technological advancements in PU prevention, management and updated guidelines.

In England alone, PU prevalence rates based on Safety Thermometer data from August 2012 and January 2019 (Figure 2-2), showed an initial decrease from approximately 6% to 4.5% in PU categories 2 to 4. However, from December 2013 onwards the reduction in the overall trend is barely noticeable. In recent prevalent studies across England and Wales reported rates are as high as 9.04% and 8.9% respectively (Clark et al., 2017; Stephenson et al., 2021). These rates suggest the PU prevalence rates across England and Wales are barely reducing, possibly because prevention and management interventions are ineffective (Clark et al., 2017; Stephenson et al., 2021). In 2018/19 in England, the national incidence rate was reported at 0.9% based on the Safety Thermometer data which accounts for

approximately 1,700 to 2,000 new PUs per month (NHS Digital, 2017). It is worth noting that the Safety Thermometer at the time of reporting was the only source of national PU data and it had its own shortcomings including the lack of standardised data collection processes across different organisations that result to underreporting of harm (Buckley et al., 2014; Smith et al., 2016). In a qualitative study with frontline and senior staff, participants felt that the NHS Safety Thermometer was more suited for acute settings as community nurses did not have the same access to information required (Brewster et al., 2018). Although the PU prevalence rates in England appear to be lower compared to the pooled average of 13.3% reported in Li et al. (2020), these rates are unacceptable considering that developing a PU while under the care of healthcare professionals is considered as harm and the negative impact PUs have on both the affected and their families' QoL and healthcare experience. Unfortunately, these statistics are expected to rise with the aging population and increase in prevalence of chronic diseases such as diabetes and vascular disease. Therefore, PUs cannot be ignored and require further research to improve both their prevention and treatment interventions.

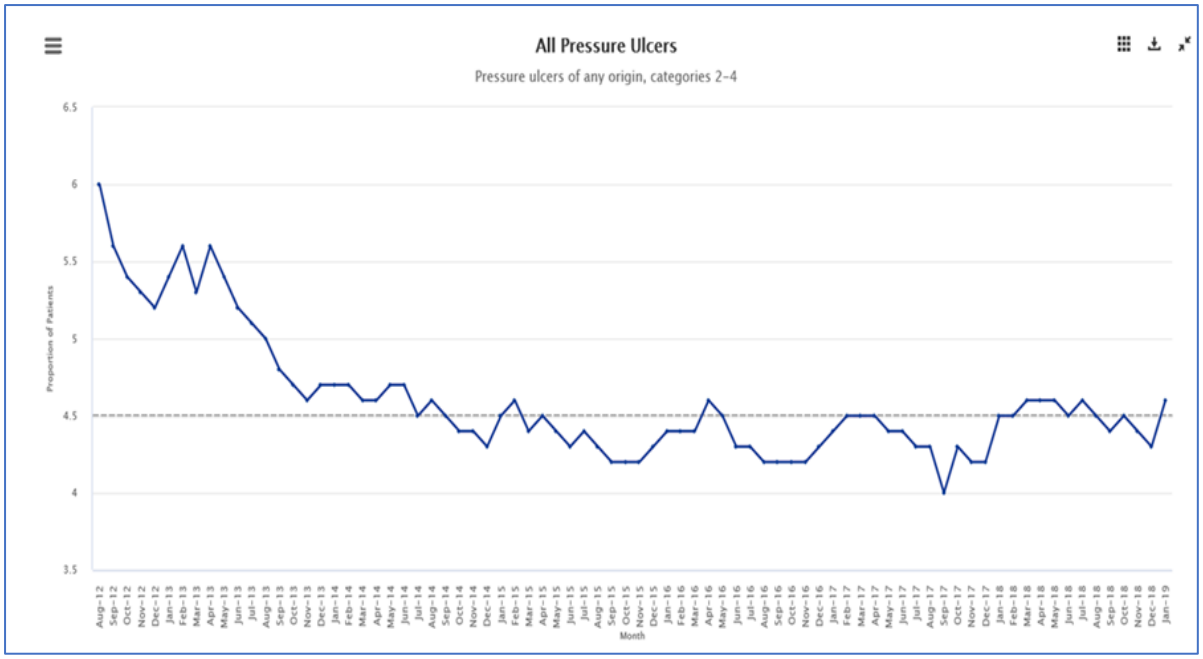


Figure 2-2 Pressure ulcer prevalence rates using Safety Thermometer data from August 2010 to January 2019. Source: (NHS Digital, 2017).

2.2.3 Pressure Ulcer Costs

PUs continue to be a patient safety challenge as well as costing the NHS millions of pounds every year. Guest et al. (2018) reported that PUs accounted for at least 6% of all wounds costing about £530 million, with the cost of managing a healed and unhealed PU, after adjusting for comorbidities, estimated at £2,343 and £4185, respectively. In the early 2000s, the cost of treating a complicated PU category 1 was estimated at £1,064 per patient compared to £10,551 per patient for a category 4 (Bennett, 2004). In 2013, the cost of healing PUs ranged from £1, 214 to £14 108, with a rise of at least 10% in the mean cost from those estimated by Bennett et al. (2004), possibly reflecting the increase in cost of treatment, complexity of wounds and patient's needs (Dealey et al., 2012). These costs were consistent with those reported by Guest et al. (2018), with all three studies confirming the link between PU severity and cost increase (Bennett, 2004; Dealey et al., 2012; Guest et al., 2018). Complex

and severe PUs (category 4) are estimated to cost more, with the cost of treating a patient with a category 4 ulcer that develops osteomyelitis estimated to cost at least two times more than treating a non-complicated category 4 (Dealey et al., 2012). The cost of treatment is dominated by nursing time as they are required for monitoring and risk assessment, dressing wound change and repositioning (Dealey et al., 2012; Guest et al., 2017). In Dealey et al. (2012) study nursing time accounted for at least 90% of all costs associated with healing a PU, however in more severe wounds the incidence of wound complications, such as infection leading to delayed healing and possible hospital admission were the main contributors of the cost associated with healing severe PUs (Dealey et al., 2012).

The average healing time ranges from 28 days for category 1 to over 150 days for category four, with most of the estimated time and cost attributed to nurse-related activities such as dressing change (Dealey et al., 2012; Guest et al., 2018). Increased hospital length of stay also contributes to the high cost associated with PUs (Palese et al., 2015). On average patients, with a PU(s) are likely to stay in the hospital 10 days longer than those without a PU with elderly patients staying the longest (Theisen et al., 2012). In addition to being a financial burden to the NHS, increased hospital length of stay can negatively impact patient's QoL, while PUs increase morbidity and mortality rates (Braga et al., 2013; Brem et al., 2010).

2.2.4 Pressure Ulcers Risks Assessment Tools

Prevention is better than treatment in many ways and if achievable, it would be considerably better for patients and their families and be cheaper for the NHS in the long run. This makes improving and maximising PU prevention a key aspect of patient safety. To resolve the challenge, there is a need to understand the complexities surrounding PU development including the associated underlying risk. There is a long-

standing debate among healthcare professionals on whether pressure ulcers are preventable with a unanimous consensus amongst a multidisciplinary group of professionals that at least most pressure ulcers are avoidable or preventable (Black et al., 2011). PUs have previously been defined as avoidable or unavoidable depending on whether all the necessary preventative measures are implemented in a timely manner (Schmitt et al., 2017). A patient is considered to have an avoidable PU if there are obvious omissions of care observed, and an unavoidable PU would be the opposite. This assumes that evidence used to inform the decision-making process is based on high-quality research and healthcare professionals' knowledge of PU risk and formation. However, evidence suggests that staff knowledge could be a barrier to successful PU prevention care (Greenwood and McGinnis, 2016; Kariwo et al., 2023; Stephenson et al., 2021); this is likely because staff may not be well informed on the different aspects that make up preventative care and/or their knowledge is based on poor quality evidence. For instance, in the Kariwo et al. (2023) study community staff identified as less confident in identifying early signs of tissue damage in patients with darker skin tones which would impact their ability to prevent further damage.

Detection of individuals or patients at risk plays an important early role in the prevention of PUs. Across the UK, the SSKIN (Surface, Skin inspection, Keeping patients moving, Incontinence and Nutrition / Hydration) care bundle is widely used in NHS settings to underpin and support PU prevention/care and has been shown to reduce PU incidence in acute settings (Stephenson et al., 2021). Though the implementation of the SSKIN bundle has promising benefits on patient outcomes and is cost-effective (McCoulough, 2016; Oni, 2022; Young, 2021), among experts and healthcare professionals the care bundle has been criticised for not including two key aspects of PU prevention, risk assessment and information giving, thus it has recently

been amended to aSSKINg (Higgins, 2021; Young, 2021). Despite being widely used in UK NHS settings, Stephenson et al. (2021) reported overall compliance with the framework of lower than 90%, with compliance for risk assessment expected to be even lower given the low compliance with meeting the National Institute of Health and Care Excellent (NICE) completion timeframe requirements (Stephenson et al., 2021). Furthermore, the same study found less than 15% of at-risk patients received adequate prevention care, possibly because nursing professionals not being fully aware of the risks and how preventative strategies are designed to minimise the impact of these risk factors (Stephenson et al., 2021). In Stephenson et al. (2021) study, the lack of staff knowledge was identified as a contributing factor to the low compliance rates, consequently impacting the delivery of successful PU prevention care (Greenwood and McGinnis, 2016; Stephenson et al., 2021).

Several national and international guidelines exist, and all recommend the use of a validated risk assessment tool (RAT) in assessing a patient's risk of developing PUs. There are numerous validated tools available for use in clinical practice (Moore and Patton, 2019; Pancorbo-Hidalgo et al., 2006) and prior to 2023 in England there was no up-to-date standardised pathway for implementing these guidelines, therefore pressure ulcer prevention including the choice of RATs varied between NHS Trusts. PU RATs are frameworks developed based on a collection of identified factors that are predictors of PUs and are used in the process of identifying and managing patients at risk of developing PUs (Fletcher, 2017). In clinical practice, the use of a validated RAT is recommended by both national and international guidelines to measure and quantify the level of risk and inform the prevention strategy to be implemented (European Pressure Ulcer Advisory Panel et al., 2019; NICE, 2014). There is evidence that if prioritised alongside implementation of prevention strategies, use of RATs can

achieve greater incident rates reductions (Gleeson, 2016). This assumes that PU risk factors are known and incorporated into RATs as guided by evidence and utilised as intended. In contrast, other evidence exists that suggests these tools may lack sensitivity and specificity with some studies suggesting clinical judgement to be superior to risk assessments (European Pressure Ulcer Advisory Panel et al., 2019; García-Fernández et al., 2014; NICE, 2014; Sharp et al., 2019). In a cross-sectional study across 36 hospitals in England, Braden scales, PURPOSE T, PRAT and Waterlow were found to be the four most common risk assessments used within NHS settings (Stephenson et al., 2021). Amongst the four most used was PURPOSE T, a recent addition with Braden Scale and Waterlow having been developed in the late 1980s. Patient demographics and disease incidence and prevalence rates have since changed drastically which challenges the suitability of risk assessment tools such as the Braden and Waterlow. PURPOSE T is an evidence-based risk assessment (Coleman et al., 2018) which comes with elaborate guidance and complemented with best practices such as the National Wound Care Strategy for PU prevention and management which provides elaborate risk assessment guidance aimed at enhancing nurses' clinical judgements (Fletcher, 2023; National Wound Care Strategy Programme, 2023). PURPOSE T, although validated and increasingly replacing the Braden Scale and Waterlow in clinical practice, requires further research to investigate its effectiveness in reducing PU incidence rates particularly for the most common PUs (that is those affecting the buttocks, sacrum, and heels).

Table 2-2 provides a comparison of risk assessment tools commonly cited in literature and it is evident that there is inconsistency in risk factors considered across the five risk assessment tools listed in Table 2-2 except for mobility which is measured in all five. Despite emerging evidence suggesting that peripheral arterial disease (PAD)

may be a predictor for HPU development (Meaume and Faucher, 2008a; Twilley and Jones, 2016) this is not considered in most RATs in their current state. Despite the Braden scale being a commonly used tool in HPU research studies, it does not consider vascular-related conditions as predictors for PU. An additional common theme across most RATs is that they do not distinguish assessment by anatomical sites, a possible reason why PUs on the heel and other sites like the sacrum remain highly prevalent. Poor mental state or cognitive impairment conditions that commonly affect those at risk of PUs are not considered in the most used risk assessment tools. On the contrary, Norton Scale, a less used RAT, includes mental state as a risk factor for PU development. PUs affect different anatomical sites with different tissue constituents and exposure to different external forces of varying magnitudes depending on the individual's position and comorbidities, thus further making PU development a complex process which is unlikely to be covered within a single risk assessment tool.

As well as understanding the aetiology of PUs it is also important to understand prognostic/ risk factors associated with their development to develop and implement strategies that instigate positive patient outcomes. Current evidence suggests that there is no single risk factor associated with PU development including HPU (Coleman et al., 2013; Dube et al., 2022). As alluded to above, risk assessment tools are developed using existing information on contributory or predicting factors associated with PU development, thus understanding risk factors is an important aspect of developing risk assessment tools. The researcher has undertaken systematic literature review as presented in Chapter 3 to summarise and quantify risk factors associated with the presence of HPU as no previous review could be identified. None of the currently existing risk assessment tools are designed to assess the risk of

developing HPUs. Thus, HPUs are the focus of this thesis, particularly looking at the risk factors associated with their presence in a quest to reduce their incidence in the adult population and improve patients' outcomes including health-related quality of life.

Table 2-2 A comparison of pressure ulcer risk assessment tools

Risk assessment tool	**Mobility**	**Vascular disease**	**Diabetes**	**Neuropathy**	**Nutrition**	**Skin Integrity Atrophy, colour etc**	**Mental state**	**Deformity Charcot, OA, Surgery, Trauma**	**History of ulceration**
Waterlow (Waterlow, 1985)	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No
Braden Scale (Bergstrom et al., 1998)	Yes	No	No	Yes	No	Yes	No	No	No

Risk assessment tool	**Mobility**	**Vascular disease**	**Diabetes**	**Neuropathy**	**Nutrition**	**Skin Integrity Atrophy, colour etc**	**Mental state**	**Deformity Charcot, OA, Surgery, Trauma**	**History of ulceration**
PURPOSE T (Coleman et al., 2014)	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes
Norton (Norton et al., 1962)	Yes	No	No	No	No	No	Yes	No	No

2.3 Heel Pressure Ulcers

Heel pressure ulcers (HPUs) remain the second most common PU after sacral PUs and therefore are the focus of this thesis (Li, Z. et al., 2020). HPUs are injuries caused by pressure, pressure in combination with shear or frictional forces when the heel is in contact with a support surface. The heel refers to the area of the foot that includes the calcaneus tuberosity and its medial and lateral processes. These structures are part of the calcaneus (heel bone) and play a crucial role in providing support and stability to the foot. It has minimal avascular fat, and no muscle or fascia thus it is anatomically disadvantaged and at high risk of skin and tissue damage due to sustained exposure to external forces (Gefen, 2007). Furthermore, without specific HPU prevention equipment in place, the heel is likely to be in contact with a support surface and exposed to external forces (pressure and or shear and friction) regardless of an individual's position (lateral, sitting, standing with footwear, or supine, except when one is in the prone position, as shown in Figure 2-3). The heel has blood supply from mostly the posterior tibial and peroneal arteries and these arteries are under the constant pressure of the body weight whilst individuals are lying in supine or semi-recumbent, or lateral positions (Faglia et al., 2013). These blood vessels are expected to continue to supply blood despite frequent and prolonged exposure to pressure and shearing forces. All these factors contribute to high incidence and prevalence rates of HPUs in combination with diseases such as diabetes, vascular disease and neuropathy further compromising the vascular function in these areas thereby increasing the risk of developing a pressure ulcer.

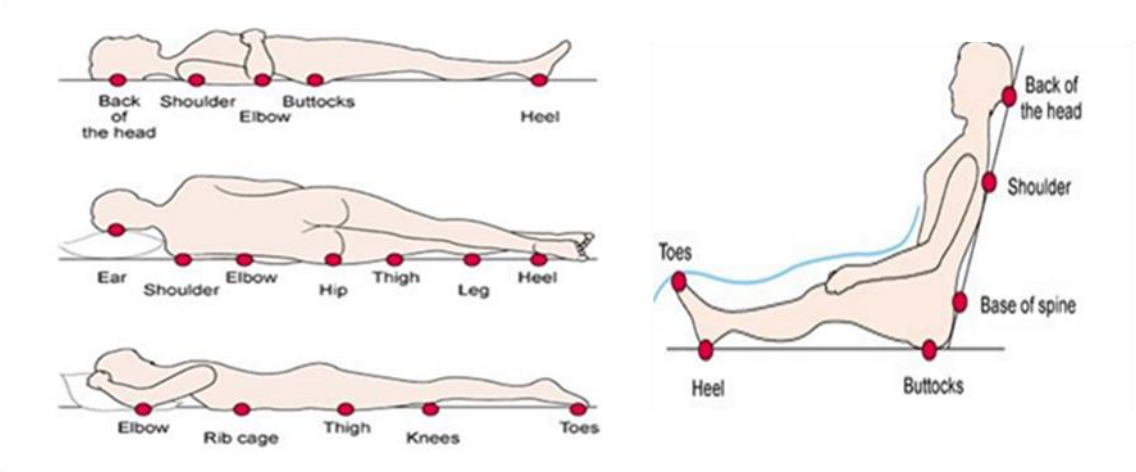


Figure 2-3 Common sites for pressure ulcers. The original diagram was created by the Tissue Viability Society, Cancer Help UK. Source: (University Hospitals Coventry and Warwickshire NHS Trust, 2014).

HPU are the second most common PU in most healthcare settings accounting for at least 20% of all pressure ulcers, with some acute settings recording as high as 38.4% (Vanderwee et al., 2011). In an international prevalence study across five different countries acute hospitals HPU accounted for 26% of all PU (Vanderwee et al., 2006). In studies conducted across England and Wales HPUs were also reported as the second most common after buttock or sacrum accounting for 13.2% and 27.3% respectively (Clark et al., 2017; Stephenson et al., 2021). In the researcher's hospital between April 2017 and August 2018, a period leading to the start of this study, over 900 category 2 or above (including hospital and community-acquired) were reported and over 30% of these were on the heel. In another acute hospital within the United Kingdom, PU prevalence rates ranged from 9.9 to 13.5% over a 5-year period while HPU accounted for 19 to 22% of all PUs across the same study period (McGinnis and Stubbs, 2014). Like PU (all anatomical sites included), HPU prevalence and incidence rates vary across different populations with the highest rates being reported in the elderly populations (Campbell et al., 2010; Delmore et al., 2015; Gaubert-Dahan et al.,

2013; Tourtual et al., 1997). Categories 1 and 2 are the most observed PU on the heels with categories 4 becoming less common, this might suggest that prevention strategies may need to focus on the prevention of categories 1 and 2 to continue reducing HPU incidence rates (Eberhardt et al., 2021; Santamaria et al., 2018). There is overwhelming evidence to suggest that HPUs remain an unsolved challenge within healthcare. It is likely that heel PUs, along with those on the buttocks and sacrum, are the primary contributors to the consistently high PU incidence and prevalence rates observed across various settings and population groups.

Much of the existing literature on PUs fails to differentiate results by anatomical location, often treating them as a single heterogeneous group. The number of studies specifically focused on the prevention and management of HPUs is relatively low in volume compared to those investigating PUs across all anatomical sites (Blackburn et al., 2020; Coleman et al., 2013; Dube et al., 2022). This volume decreases further when considering studies on risk factors for HPUs, despite HPUs remaining the second most common PU across clinical settings and patient populations. evidence suggests that risk factors for PU development may differ by anatomical site. Additionally, effective HPU prevention and management require dedicated devices (CLP heel devices, off-loading supports, and heel-specific low friction equipment) alongside specialist mattresses (Greenwood et al., 2022). Further research focusing on HPU data separately from PUs at other anatomical sites is essential to better understand why HPUs consistently rank as the second most common type.

2.3.1 Impact of HPU on Health-Related Quality of Life

Pressure ulcers depending on the severity of the ulcers can take more than four weeks to heal thus becoming chronic wounds which can cause continued significant pain and distress for patients. More severe cases (categories 3 and above) are at increased

risk of complications including infections therefore they can contribute to longer hospital stays requiring specialist care (Dealey et al., 2012; Guest et al., 2017). As a result, PUs are commonly associated with poor quality of life (QoL). Where QoL is defined as an individual's perception of their position in life in the context of the culture and value systems in which they live and about their goals, expectations, standards, and concerns (The World Health Organisation Quality of Life Group, 1996). Traditionally, QoL as a patient reported outcome (PRO) has been widely used in the evaluation of clinical interventions, however, more recently it has become an important measure of health service delivery. Increased patient empowerment has also led to the growing use of QoL assessments in clinical practice; where they are also used to provide vital information on the impact of diseases with the information progressively used to inform patient education in the management of conditions such as cancer (Greenhalgh et al., 2018; Nic Giolla Easpaig et al., 2020). The impact of diseases on quality of life is measured using tools designed to measure health-related quality of life (HRQoL) such as EQ5D-5L and Short Form 36 (SF-36) questionnaires.

PUs have been reported to negatively impact patients' health-related quality of life (HRQoL), affecting emotional, physical, mental and social aspects across various settings (hospital, care home or home) (de Souza et al., 2015; García-Sánchez et al., 2019; Spilsbury et al., 2007). In quantitative studies, patients with PUs reported lower HRQoL scores compared to those without PUs, a finding further supported by qualitative studies offering a deeper understanding of PU impact (Gorecki et al., 2009; Roussou et al., 2023). Older patients with PUs reported worse HRQoL scores than younger patients. Overall, these studies confirm that the presence of a PU negatively affects a patient's QoL. However, these studies seldom include the perspectives of informal carers (family or friends) who look after patients with cognitive impairments.

One study focusing primarily on patients with category 1 and 2 PUs (69%) found no significant difference of HRQoL, as measured using SF-36, between those with and without PUs (Franks et al., 2002). Another study found that hospital patients with PU(s) (mainly categories 2) reported higher SF-36 general health scores compared to those in long-term care facilities or at home with primarily category 3 PUs (de Souza et al., 2015). This evidence suggests that category 1 and 2 PUs may cause less noticeable changes in affected individuals' lives compared to those living with more severe PUs.

Some qualitative studies indicate that participants struggled to distinguish the effects of comorbidities from those of PUs themselves (Hopkins et al., 2006). However, Essex et al. (2009) demonstrated that, after adjusting for comorbidities, patients with PUs showed poorer HRQOL using both the EQ5D (visual analogue scale scores and EQ-5D index) and SF-36, specifically in physical functioning, role limitation due to physical issues, and vitality. The evidence from the quantitative study (Essex et al., 2009) demonstrates the negative impact PU have on HRQoL as this was confirmed in the same study using two separate questionnaires.

There is existing quantitative and qualitative knowledge as synthesised in two systematic literature reviews (Gorecki et al., 2009; Roussou et al., 2023) to demonstrate the adverse effect PUs have on the HRQoL of patients, however, none of the research reported specifically on the impact of HPU and their longitudinal impact. Although some qualitative studies involved carers it is not clear if they looked after individuals with PU who had cognitive impairment; for quantitative studies, they specifically excluded those with patients with cognitive impairments. Therefore, this thesis focused on the impact of heel pressure ulcers (HPU) on an individual's ability to live a fulfilling life as measured using EQ-5D-5L. Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

2.3.2 Pain Associated with Heel Pressure Ulcers

Pain is associated with chronic wounds and is a commonly reported symptom by patients living with a PU (García-Sánchez et al., 2019). Studies that have explored the impact of PUs on HRQoL also explored pain which has been highlighted as a contributor to poor HRQoL outcomes (de Souza et al., 2015; Gorecki et al., 2011; Spilsbury et al., 2007). For instance, in a study with mostly PUs category 1 and 2 which are less likely to be painful, HRQoL was found not to be different between patients with a PU and those without PU (Franks et al., 2002) whereas more severe ulcers were associated with poor HRQoL (Hopkins et al., 2006). This result conflicts with another study (McGinnis and Stubbs, 2014) which found that pain as reported by patients with pressure ulcers and living in the community was not associated with PU severity, instead pain was reported to be of neuropathic and inflammatory type. Several studies have found that patients with PU reported their pain to be exacerbated by movements or PU-related interventions such as dressing change or repositioning or the use of pressure redistribution surfaces (Hopkins et al., 2006; Spilsbury et al., 2007). In a qualitative study by Spilsbury et al. (2007) over 90% of their participants reported experiencing pain which was worsened during positioning and treatment.

In a qualitative study exploring home care of PU, with 50% of the patient participants having a PU on the heel and 60% of all PUs being a category 2, one of their two emerging themes included pain with all their patient participants rating their pain at least seven out of ten (where 0 represents the absence of pain and 10 is the greatest intensity of pain) (García-Sánchez et al., 2019). This might suggest that category 2 heel pressure ulcers are likely to cause severe pain in comparison to PUs on other anatomical sites. Like HRQoL outcomes, pain was not reported by the anatomical site

of the PU nor did the studies include the voice of carers looking after patients with PU who had cognitive impairments.

2.3.3 Prognostic Value of Heel Pressure Ulcers in End of Life.

The skin is the largest organ of the human body, measuring about 1.5 – 2m^2 and weighing at least 15% of the total body weight. The skin is split into two layers the epidermis and dermis, it serves as a physical barrier against the external environment, maintaining homeostasis and protecting against pathogens (Wingerd, 2013). Similar to other human organs, the skin can fail under certain conditions in a process known as skin failure. In this state the skin's ability to maintain its function is compromised. Skin failure can be attributed to various factors including underlying medical conditions that can lead to compromised blood flow and oxygenation such as end-stage organ failure, sepsis and advanced cancer. In addition, extrinsic factors such as prolonged pressure, friction, shear, and moisture can also contribute to skin failure by disrupting the skin's integrity.

Skin failure is a relatively new concept that has gained recognition in tissue viability and is central to many debates around PU and the end of life. Skin failure can be described as an event in which the skin and underlying tissue die due to hypoperfusion that occurs concurrently with severe dysfunction or failure of other organ systems (Langemo and Brown, 2006). Many other skin failure definition variations exist which suggest that they can be of different manifestations (White-Chu and Langemo, 2012). The definition by White-Chu and Langemo (2012) specifically distinguishes skin failure from PUs by stating that it occurs without the presence of pressure and/or shear, whereas pressure, shear, or both are responsible for pressure ulcer development. However, in clinical practice, it is difficult to differentiate wounds that are caused by pressure from those related to organ failure as they tend to occur concurrently

(Langemo and Brown, 2006). In most cases, skin failure is commonly diagnosed when patients have already developed a PU in the presence of other organ failure or event of death (Curry et al., 2012).

There is evidence that suggests a link between HPUs and EoL, for instance, a study by Brown (2003) found that at least 16% of patients with HPUs were in their EoL stages. In addition, in another study by McGinnis et al. (2014) investigating prognostic factors for the healing of HPU, at least 48% of the study population had died within 18 months (McGinnis et al., 2014). There is also anecdotal evidence suggesting that at least 40-50% of patients with HPUs die within 12 to 18 months of diagnosis. Unfortunately, the majority of existing HPU studies exclude many patients due to either being too unwell or approaching the end of life, hence there is a paucity of evidence to verify the possible link between HPU and EoL. End of life is defined as likely to die within 12 months including death within a few hours or days (General Medical Council, 2010).

Recognising organ failure can be crucial for timely medical intervention, for organ failure including liver, kidney, heart and lung, there are vastly well-known symptoms which include generic and specific organ symptoms. Rarely, the known organ failure symptoms particularly refer to the skin in particular that of the heel.

This thesis was to be used for hypothesis-generating, to investigate whether developing an HPU may indicate when patients are approaching EoL stages and whether HPU could be a sign of skin failure in EoL patients. Instead of treating Pus as a homogeneous group. Further research will be required to confirm the findings of this study.

2.4 Summary

Pressure ulcers remain an unsolved patient safety concern. Despite heel pressure ulcers being the second most common PUs, there is a lack of research exploring their impact on health-related quality of life and their prognostic value in end-of-life as presented in this section. Furthermore, risk profiling is guided by risk assessment tools that are generic to all PUs and risk factors are inconsistently measured across different PU risk assessment tools. The next chapter synthesises the existing literature on risk factors for developing heel pressure ulcers, identifies gaps in knowledge and informs the data collection aspects of this thesis as well as future risk assessments.

Chapter 3 Systematic Literature Review (Study Phase 1)

3.1 Introduction

This chapter presents Phase 1 of this thesis, a systematic literature review examining risk factors for the development and presence of heel pressure ulcers (HPUs) in the adult population. The content of this chapter has been peer-reviewed and published in the Journal of Tissue Viability Society (Dube et al., 2022). The published article is included in Appendix 2 and 3, along with an accompanying email outlining the publishing agreement and scholarly communication rights. Accordingly, this chapter reproduces the published article verbatim.

3.2 Aim

The main aim of this systematic review was to identify risk factors for developing HPUs in the adult population and quantify the relationship between identified risk factors and HPU development.

3.3 Review Questions

What are the risk factors for developing heel pressure ulcers as identified from a systematic review of the current literature?

What is the overall strength of association between each risk factor and the development of heel pressure ulcer based on this systematic review?

What are the heel pressure ulcer incidence and prevalence rates from eligible studies (cohort and cross-sectional studies respectively)?

3.4 Methods

The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines for writing systematic reviews and meta-analyses (Moher et al., 2009).

3.4.1 Inclusion Criteria

Type of studies: the review included all cohort, case control and cross-sectional studies investigating risk factors for developing HPUs (grade/category/stage 1-4, Suspected/Deep Tissue Injury (S/DTI) and unstageable as defined by the NPUAP et al. (2014) (National Pressure Ulcer Advisory Panel et al., 2018) guidelines or similar). For the purpose of this review, and to be in line with the new (NHS Improvement, 2018) PU recommendations, HPU severities are described as categories (replacing all previous terminologies i.e., grade or stage). Only studies published in English were reviewed with no restrictions on date of publication.

Outcome measures: included the presence or development of HPUs (categories as defined by the NPUAP in their 2014 guidelines (National Pressure Ulcer Advisory Panel et al., 2018) guidelines or similar) and/or identification of a risk factor under investigation.

Participants: Study populations were defined as adult patients aged 18 years or above in any care setting (i.e., primary, or secondary).

3.4.2 Exclusion Criteria

All studies not meeting the eligibility criteria were excluded accordingly at different stages as depicted in **Error! Reference source not found.**.

3.4.3 Electronic Searches

A systematic literature search was conducted in PUBMED (1809-March, 2020), EBSCO- MEDLINE (from 1879-March, 2020), CINHAL (1937-March, 2020), Ovid-EMBASE (1947-March, 2020), Cochrane Library (from 1946-March, 2020), NICE/NHS evidence (from 1880-March, 2020), PROQUEST, TRIP databases, Scopus (from 2004 -March, 2020) and Web of Science (from 1900-March, 2020) using keywords, Medical Subject Headings (MeSH), and other index terms, as well as combinations of these terms and appropriate synonyms. The syntax was designed specifically for each database, guided by the Cochrane handbook and also adopted from previously published PU systematic literature reviews (Clegg and Palfreyman, 2014; Coleman et al., 2013; Higgins et al., 2021). Search terms focused on the terms heel, pressure ulcer(s), pressure sore(s), decubitus, pressure injury, risk factors, contributory factors, predictors, adult, hospital, community, and their synonyms (see Appendix 4.1 for examples of database search strategies). Reference lists of all included studies were inspected for further relevant studies.

3.4.4 Selection of Studies

The main reviewer (AD) screened titles and abstracts for relevant articles prior to appraising the full texts. Identified articles were managed using EndNote X8; reasons for all full text paper screen exclusions were documented. The second reviewer (SJ) independently re-inspected all identified titles and abstracts to ensure reliability of selection. Where disputes arose, the full report was reviewed for a detailed scrutiny. SJ also reviewed full articles of studies that met the review criteria to ensure reliability of selection. Any disagreements were to be resolved by discussion, or by attempting to contact the study authors for clarification. Both reviewers were in agreement with

the screening outcome. Clarification was sought from authors of one potential eligible study, but as no response was received, the study was therefore excluded.

3.4.5 Data Extraction

AD and SJ extracted data independently from all included studies using a predefined form. Study authors were contacted for missing data or clarification were appropriate; Twilley and Jones (2016) study data were available for further analysis as part of the review (Twilley and Jones, 2016). A third reviewer (EP) was available to help resolve any disagreements, however, for this review the authors were in agreement and no further clarification was required. Data were extracted onto standard, predesigned forms. Study-specific aims and objectives - study location, design, population, sample size, eligibility criteria, methodology and outcome measures (relative risk estimates, mean difference, odds ratio (OR), risk ratio (RR), hazard ratio (HR), p-values and confidence intervals (CI) - as presented by study authors were also extracted or calculated by the reviewers.

3.4.6 Assessment of Risk of Bias and Quality Assessment of Included Studies

Currently there is no standardised method of assessing risk bias for systematic reviews of risk factors. Therefore, each eligible study was assessed for risk of bias using the assessment framework for ascertaining quality in prognostic studies (QUIPS) (Hayden et al., 2013) in conjunction with STrengthening the Reporting of Observational studies in Epidemiology (STROBE) guidance. STROBE offers guidance on methodological considerations in the analysis and publication of observational studies (Altman, 2001; von Elm et al., 2014). The risk of bias assessment rated the relevant methodological parameters of studies across six areas: study participation (clear eligibility criteria to assess risk of selection bias), attrition (withdrawals and dropout rates as appropriate), risk factor measurement (validity and reliability of data

collection tools used and providing clear definitions or descriptions of risk factors), outcome measurement (validity and reliability of outcome measurement with clear definitions), study confounders (clearly identified and adjusted for using appropriate methods), statistical analysis and reporting (use of correct statistical methods, and appropriate model building approaches as appropriate).

Predesigned risk of bias assessment forms designed following the QUIPS tool were utilised and within each of the six domains a range of questions were rated based on the adequacy of reporting as either ‘yes’, ‘partial’, ‘no’ or ‘unsure’. Based on these ratings, each domain was consequently assessed for its potential overall risk of bias as being either high, medium or low after considering all parameters within each domain. Results of the risk of bias assessment were used to provide classification of overall study quality. Overall study quality was achieved by aggregation, and where numbers were equal, the higher bias classification was recorded. Studies were therefore classified as ‘high quality’ if the overall risk of bias was deemed low, ‘moderate quality’ if the risk of bias was deemed moderate and ‘low quality’ if the overall risk of bias was deemed high. Risk of bias and quality were assessed by two independent reviewers (AD, SJ). To maximise quality, the third reviewer (EP) extracted data from five randomly selected articles and reviewed these articles for risk of bias and methodological quality.

3.4.7 Data Synthesis

Although a meta-analysis was initially planned, it was not conducted due to the clinical and statistical heterogeneity of the eligible studies. As a result, the findings are presented in a narrative form including a summary of main findings and quality assessment results in the form of tables. Risk factors for HPU development were grouped into categories as guided by other similar systems (Anrys et al., 2019;

Coleman et al., 2013). Coding was conducted by two independent reviewers (AD, SJ); disagreements were resolved by discussion and consensus was achieved.

3.5 Results

3.5.1 Search Outcome

Of the 3,012 titles and abstracts retrieved, 1,258 were duplicates. Based on the review selection criteria, 1,754 abstracts were screened, and 35 full texts were retrieved and reviewed. Figure 3-1 shows the flowchart of this selection. Of the 35 potentially suitable articles, 22 were excluded. Reasons for exclusion at full article review were non-English articles (n=4, two were duplicates), case series (n=7), theoretical study (n=1), HCPs as study participants (n=1), conference papers of eligible studies/letter to editor (n=7), HPU classification not following the EPUAP criteria (n=1) and no response from study author clarifying study eligibility (n=1).

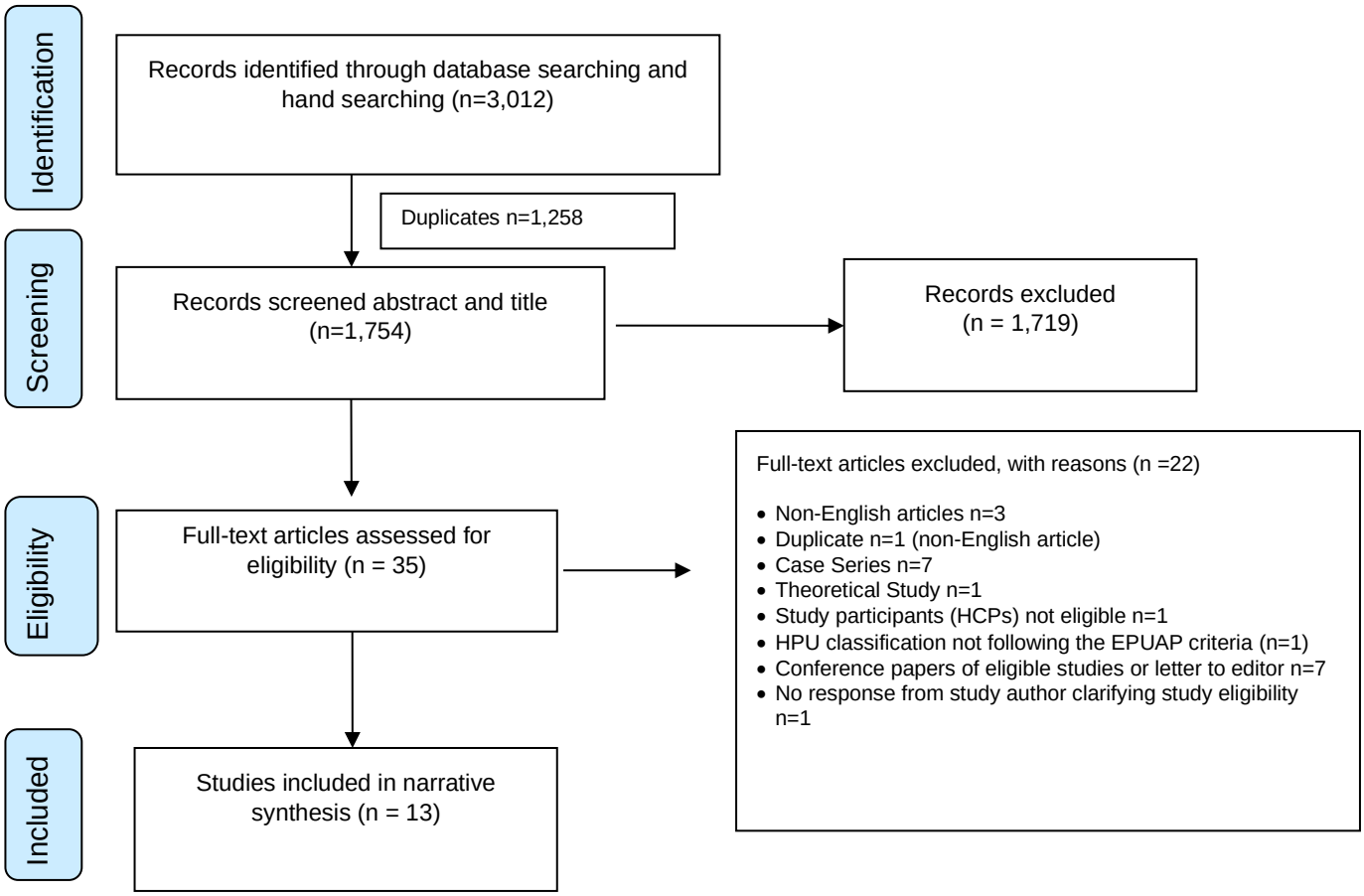


Figure 3-1 PRISMA Flow diagram.

3.5.2 General Study Characteristics

Thirteen studies met the eligibility criteria, which recruited a total of 9,228 participants with a median age of 73 years (range 41.0-101). Three studies reported two separate analyses using different study populations within the same paper (Delmore et al., 2015; Delmore et al., 2019; Tourtual et al., 1997). The main analyses in all three studies were aimed at identifying potential HPU risk factors using multivariable logistic regression analysis. The second analyses used different study populations to clarify and validate the statistical significance of findings from the main analyses. For the purpose of this review, these studies were analysed and reported once. Therefore, a total of thirteen studies are reported in this review. Delmore et al., (2015; 2019) were

conducted by the same authors, the latter being a replicate study using separate multicentre data and a larger sample size. For this review, they are reported as separate studies distinguished by the year of publication. Muntlin-Athlin et al., (2016) and Manderlier et al (2019) were secondary analyses of HPU risk factors based on data collected from a randomised controlled trial (RCT) and a cross-sectional point-prevalence survey, retrospectively (Manderlier et al., 2019; Muntlin Athlin et al., 2016) Appendix 4.2 provides further study characteristics of all eligible studies.

Five eligible studies were published in the United States of America (USA), two in France and three in the UK, and Canada, the Netherlands and Sweden produced one study each. Duncan et al. (2003) (n=53) and Delmore et al. (2015) (n=417) did not report gender distribution amongst their study participants (see Appendix 4.2). Edwards et al. (2006) reported gender for only 68% of HPU participants and none for the control group (Edwards et al., 2006). For the eleven eligible studies that reported gender distribution of study participants, 57.1% (5270/9228) were female. Tourtual et al. (1997), Demers (2005) and Delmore et al. (2019) were the only studies to report ethnicity for their study participants: the majority of the were reported as either white-20.5% (571/2780), or as other ethnic background 66.4% (1846/2780).

Median HPU incidence rate was 17.4% (range: 2.9% to 29.5%) based on the incidence rate from the four prospective and two retrospective cohort studies (Campbell et al., 2010; Demers, 2005; Duncan et al., 2003; Edwards et al., 2006; Muntlin Athlin et al., 2016; Tourtual et al., 1997). Median prevalence was 11.7% (range: 1.5% to 20.8%) based on the two cross-sectional studies and two retrospective case control cohort studies (Delmore et al., 2019, 2015; Manderlier et al., 2019). Across all studies, the participant population was diverse and included: patients from hospital wards with high

HPU prevalence, a geriatric rehabilitation centre, major abdominal surgery, elective or trauma orthopaedic surgery, nursing homes and patients receiving community care.

All eligible studies defined HPUs based on NPUAP et al. (2014) (National Pressure Ulcer Advisory Panel et al., 2018) or similar guidelines that were available at the time the studies took place. Only three studies did not report the number of HPUs by severity (Delmore et al., 2015; Demers, 2005; Muntlin Athlin et al., 2016). In total, 10.1% (935/9228) of participants were either recruited with or developed a HPU during study follow-up. Of the studies that reported HPUs by severity: 38.8% (306/788) were category 1; category 2- 27.4% (216/788) category 3- 7.5% (59/788); category 4- 5.5% (43/788); Unstageable- 18.4% (145/788) and DTI- 2.4% (19/788). Only three out of nine studies that reported HPU by severity observed unstageable and DTI HPUs; the patient population in these studies were heterogeneous (Clegg et al., 2009; Delmore et al., 2019; Manderlier et al., 2019). Tourtual et al. (1997) and Campbell et al. (2010) study participants developed superficial HPU (either a category 1 or 2), except for one participant from the Tourtual et al. (1997) study who developed a category 3 HPUs.

3.5.3 Quality of Studies

Appendix 4.3 provides a summary of the risk of bias and quality assessments. The review only included studies of observational design that investigated risk factors for HPUs only; four were prospective cohort studies (Campbell et al., 2010; Duncan et al., 2003; Muntlin Athlin et al., 2016; Tourtual et al., 1997), two were retrospective cohort studies (Demers, 2005; Edwards et al., 2006), three were cross-sectional studies (Clegg et al., 2009; Gaubert-Dahan et al., 2013; Manderlier et al., 2019), two were retrospective matched case control cohort studies (Delmore et al., 2019, 2015), and two were prospective matched case control studies (Meaume and Faucher, 2008; Twilley and Jones, 2016) (see Appendix 4.1 for full study characteristics).

Three studies (Clegg et al., 2009; Demers, 2005; Edwards et al., 2006) performed and reported descriptive analysis results based on participants who had HPUs. Four out of eleven (36.4%) studies performed multivariable logistic regression analysis in addition to descriptive statistics (Delmore et al., 2019, 2015; Manderlier et al., 2019; Tourtual et al., 1997). The rest of the eligible studies either performed parametric or non-parametric analyses (chi-squared, t-test and Whitney Mann-U tests) or just reported ORs as appropriate. Not all studies that reported on measures of association included CIs or p-values as appropriate; where adequate data was reported, reviewers attempted to calculate these based on the extracted data, as highlighted in Appendix 4.2.

Only three studies (Delmore et al., 2019; Manderlier et al., 2019; Twilley and Jones, 2016) were classed as high quality, seven were of moderate quality (Campbell et al., 2010; Delmore et al., 2015; Duncan et al., 2003; Gaubert-Dahan et al., 2013; Meaume and Faucher, 2008; Muntlin Athlin et al., 2016; Tourtual et al., 1997) and three were of low quality (Clegg et al., 2009; Demers, 2005; Edwards et al., 2006) (see Appendix 4.2). Two high quality studies (Delmore et al., 2019; Twilley and Jones, 2016) and three moderate quality studies (Campbell et al., 2010; Duncan et al., 2003; Tourtual et al., 1997) reported on their sample size assumptions and/or calculations. Of the four eligible studies that performed additional multivariable analysis, only Delmore et al. (2019) and Manderlier et al. (2019) had sufficient numbers of HPUs (events) per risk factor (i.e.10 events per risk factor) in their final logistic regression model.

The main issues contributing to high risk of bias and consequently rendering 10/13 studies moderate to low quality: were their retrospective study design, lack of comparator group, study participants only being high risk patients and already experiencing HPUs, lack of sample size calculations, selection bias, inadequate

reporting and statistical analysis issues. All of these issues may have influenced the accuracy of the study results, interpretation and generalisability. As a result, the evidence from low quality studies could not be utilised to inform the decision as to whether to accept or reject these variables as potential risk factors for developing HPUs. It was evident from the review that most of the eligible papers did not follow the STROBE recommendations. STROBE recommendations were developed to facilitate critical appraisal, interpretation of results and consequently enable direct translation of research into clinical practice (von Elm et al., 2014). As a result, most of the studies were rated as manifesting moderate risk of bias across the six subdomains of the QUIPS tool.

3.5.4 Risk factors

In total, 51 different variable names were identified from the 13 eligible studies. These were categorised into 16 risk factor domains as summarised in Appendix 4.4. Although some studies used standardised measures (e.g., validated risk assessment tools), there was still a lack of consistency across the tools utilised, measurement scales, or classification of diseases investigated. The Braden scale (PU a risk assessment tool) was the most used validated measurement scale. All variables identified in this review are listed in Appendix 4.4 according to the specification in each of the eligible studies. Appendix 4.4 highlights the heterogeneity of variables utilised across different studies. Lack of consistency in measuring and reporting of variables made it difficult to synthesise review results using quantitative methods.

Nine risk factors (body mass index, smoking status, pre-albumin, blood urea, creatinine, systemic infection, end-stage renal disease, vasopressor and corticosteroid use) were only investigated in one low quality study (Clegg et al., 2009).Thirty two other remaining variables were examined in at least one or more

moderate quality studies (Duncan et al., 2003; Gaubert-Dahan et al., 2013; Muntlin Athlin et al., 2016; Tourtual et al., 1997) as potential contributory factors for HPU development using descriptive and univariate analyses. Haemoglobin, respiratory rate and the use of HPU preventative measures emerged as significant in one moderate quality study (Campbell et al., 2010) which involved patients undergoing either elective orthopaedic or hip surgery.

The MNS subscales: physical activity and incontinence emerged as significant in the Muntlin-Athlin et al. (2016) study only however this study did not adjust for another potential confounders in their analysis. Mental status, although measured differently in the Campbell et al. (2010) and Muntlin-Athlin et al. (2016) (moderate quality studies), emerged as significant in both studies. Length of surgery and perioperative analgesia were considered in moderate to low quality studies only (Clegg et al., 2009; Delmore et al., 2015; Duncan et al., 2003) and results were either statistically insignificant or not reported.

Sensory neuropathy as defined by the Braden subscale (Tourtual et al., 1997) or using the neuropathy symptom score (NSS) and neuropathy disability score (NDS) (Gaubert-Dahan et al., 2013) were also found to be significant in univariate analysis. Only the Braden subscale 'sensory perception' item was further considered in a multivariable analysis, however did not emerge to be statistically significant (Tourtual et al., 1997). Overall, almost all moderate quality studies did not adjust for confounding factors (with the exception of Tourtual et al., (1997)). The studies were also inconsistent in reporting measures of association, and inadequately reported on sample size assumptions, statistical analysis plans, p-values, and CIs. All of these factors impacted on the review authors' ability to fully assess the studies' potential risk of bias and interpretation of results. Consequently, there is no conclusive evidence to

support whether these variables are risk factors for HPU development, given that the studies were of moderate quality.

A total of 10 potential risk factors were examined in at least one high quality study (Delmore et al., 2019; Manderlier et al., 2019; Twilley and Jones, 2016) that involved hospital, nursing home, community-dwelling, and rehabilitation patients. A disease status of either diabetes or lower limb vascular disease emerged as statistically significant in more than one high quality study. The Delmore et al. (2015) (moderate quality) and Delmore et al. (2019) (high quality) studies found that hospital patients with diabetes were at least 1.4 times (95%CI: 1.0; 7.2) more likely to develop a HPU compared to those without diabetes.

Lower limb vascular disease emerged as statistically significant in two high quality studies (Delmore et al., 2019; Twilley and Jones, 2016) and two moderate quality studies (Delmore et al., 2015; Meaume and Faucher, 2008). Participants diagnosed with lower limb vascular disease were at least 3.1 times (95%CI: 1.3; 60.2) more likely to develop a HPU compared with those without lower limb vascular disease. There is some evidence to suggest that diabetes and vascular disease are risk factors for HPU. However, this evidence comes from only one high quality study for diabetes and two high quality studies for lower limb vascular disease. The second high quality study to report on lower limb vascular disease as statistically significant (Twilley and Jones, 2016) was a small explorative study and its analysis did not adjust for other potential risk factors.

Physical conditions: age >65years, Braden subscales ‘moisture, friction and shear’, immobility/mobility (Braden and MNS subscales), nutritional status, perfusion issues, mechanical ventilation and surgery, all emerged as statistically significant in at least

one high quality study. Age emerged as an independent risk factor in only one high quality study (Delmore et al., 2019). Patients older than 65 years were more likely to develop HPUs compared to younger patients (OR: 3.3; 95%CI: 2.4-4.6). Malnutrition/ impaired nutritional status was considered in two high quality studies (Delmore et al., 2019; Manderlier et al., 2019), however, the two studies involved different study populations (hospital inpatients and nursing/community care patients, respectively). Malnutrition only emerged as statistically significant in one of the two high quality studies (Delmore et al., 2019), in this study, hospitalised patients suffering from malnutrition had an increased risk of developing HPUs by a factor of 6.9 (95%CI: 4.1-11.5). The Manderlier et al. (2019) study was only aimed at examining what they considered 'modifiable patient-related risk factors', defined as patient characteristics that are sensitive to interventions used by HCPs to prevent HPU development'. Therefore, differences in study populations and variables examined could have contributed to some of the disparities between the Delmore et al. (2019) and Manderlier et al. (2019) study results.

Perfusion issues, mechanical ventilation and surgery were examined in only one high quality study (Delmore et al., 2019) involving hospitalised patients; all three variables emerged as highly significant (p-value< 0.001). Perfusion issues were defined by the presence of conditions that affect blood to peripheral extremities - excluding vascular disease, which was considered separately. Patients that had evidence of perfusion issues (e.g., cardiovascular disease, myocardial infarction, hypovolemic shock) were at least 2.8 times more likely to develop HPUs compared to patients without perfusion issues.

Participants on mechanical ventilation were at least seven times more likely to develop a HPU compared to those not on mechanical ventilation (OR: 7.7; 95%CI:4.2-14.3; p-

value <0.001) (Delmore et al., 2019). Participants who had surgery during their hospital stay had an increased risk of developing a HPU by a factor of 1.8 (95%CI: 1.3-2.5) compared to those who did not have surgery (Delmore et al., 2019). Types of surgery reported were divided into seven categories: vascular, orthopaedic, neurosurgery, intestinal, cardiovascular, and genitourinary and gynaecology. Cardiovascular surgery was the most common amongst those that developed HPU, accounting for 27.9% of all surgeries.

Mobility/immobility was considered in one high quality (Manderlier et al., 2019) and three moderate quality studies (Delmore et al., 2015; Muntlin Athlin et al., 2016; Tourtual et al., 1997). Manderlier et al. (2019) defined mobility using the Braden subscale. In Delmore et al. (2015) (moderate quality), immobility was associated with health conditions that impaired the ability to mobilise, for example, plegia, cardiovascular accidents, lower extremity fractures, and orthopaedic surgeries, whereas Muntlin-Athlin et al. (2016) (moderate quality study) ultilised the MNS subscale ‘mobility’ to measure patients’ ability to move independently. Although mobility/immobility was measured differently across the four eligible studies, it emerged as statistically significant in all four studies. Based on the results of a high quality study, an increase in the mobility score (as measured using the Braden subscale ‘mobility’), reduced the likelihood of developing a HPU (0.6; 95% CI: 0.4–0.8) (Manderlier et al., 2019).

The Braden subscale ‘friction/ shear’ emerged as statistically significant in one high quality study (Manderlier et al., 2019) and one moderate quality (Tourtual et al., 1997). An increase in the friction and shear score decreased the likelihood of developing a HPU (0.3; 95% CI 0.2–0.5) (Manderlier et al., 2019).

Moisture (as measured using the Braden subscale ‘moisture’ or MNS subscale ‘incontinence’), only emerged as statistically significant in one moderate quality study each Muntlin Athlin et al. (2016) and Tourtual et al. (1997) respectively. However, the Braden subscale ‘moisture’ did not emerge as statistically significant in a high-quality study (Manderlier et al., 2019). Further high-quality studies are required to investigate the impact of the identified potential risk factors in the wider patient population, in order to increase the generalisability of results and inform future practice.

3.6 Discussion

This is the first systematic literature review of observational studies investigating risk factors for developing HPUs. As evident from this review, there are too few studies focusing on this area, despite HPUs being the second most common type of PU. Understanding the biology and natural history of HPUs is paramount in order to optimise prevention strategies. Risk factors can be barriers to healing, and in worse case scenarios, they can instigate life threatening outcomes if they are not addressed and corrected in a timely manner. Evidence based prevention strategies, including educational programs, empower both patients and their carers to manage their risk - especially outside of care settings.

Most of the studies reviewed provided descriptive results or univariate analysis, which did not adjust for other potential risk factors or consider the impact of living with several comorbidities to their study population. There was also evidence of selective reporting, as studies mostly reported statistically significant results. The problematic use of less robust designs and analytical techniques has previously been highlighted by Clegg and Palfreyman (2014) in their review on elevation devices used to prevent HPUs. These have also been common themes in this review - with serious implications on the quality and generalisability of specific study results. It was also evident that many

of the studies did not follow STROBE recommendations, which made it difficult to synthesise the evidence. Despite observational studies often being criticised for their vulnerability to being influenced by unknown confounding factors, well-designed observational studies can also complement RCTs in hypothesis generation, defining clinical questions and establishing future research questions (Guyatt et al., 2011; Song and Chung, 2010). The results of this review can therefore be used to generate hypotheses for further research studies investigating risk factors for developing HPUs.

Only three (27.2%) eligible studies were rated high quality (Delmore et al., 2019; Manderlier et al., 2019; Twilley and Jones, 2016). Their study populations and research questions were different, which may have contributed to a difference in the risk factors that emerged as statistically significant. In total, the review identified 16 risk factor domains, however due to the small number of eligible studies, this meant that each potential risk factor was evaluated in three or less studies of high to moderate quality. In light of this review, it is not surprising that current clinical practice recommendations and guidance do not provide substantial specific guidance on risk assessment and prevention of HPUs (National Pressure Ulcer Advisory Panel et al., 2018; NICE, 2014). It is therefore imperative that future research addresses these limitations and focuses on risk factors for HPUs in order to reduce their prevalence and incidence rates.

In this review, HPU incidence and prevalence rates were estimated as 17.4% (2.9-29.5%) and 11.7% (1.5-20.8%) respectively; however, the actual rates remain unclear due to heterogeneity of study populations, designs and quality of the studies. for instance, this review involved retrospective review of medical notes, or they lacked quality assurance processes for their outcome measure, this affected studies that used skin assessments to diagnose HPUs. Diagnosis of HPUs remains a challenge in

practice due to the misclassification of wounds affecting lower limbs; that is, many clinicians lack the ability to distinguish between diabetic foot ulcers, vascular related ulcers, and PUs (Kottner et al., 2009). For retrospective studies included in this review, this could potentially have contributed to an under or overestimation of HPUs due to lack of documentation or misclassification of HPUs by clinical staff.

HPUs, like any other PU, have multifactorial contributory factors (Coleman et al., 2013). However, the actual risk factors associated with HPU development may be different due to the anatomy and anatomical position of the heel in the body, as suggested in biomechanical and other studies (Gefen, 2010; Kottner et al., 2020; Luboz et al., 2015). This review found that age >65 years, diabetes, malnutrition, surgery, mechanical ventilation, perfusion issues, vascular disease (Delmore et al., 2019) and Braden subscales 'friction and shear', 'mobility' (Manderlier et al., 2019) emerged as significant risk factors in the presence of other variables using multivariable analysis from two high quality studies. These results are consistent with the aetiology of HPUs (European Pressure Ulcer Advisory Panel et al., 2019). Braden subscales 'friction and shear', and 'mobility' only explained 16.6% of the variance in the prevalence of HPUs amongst nursing home patients or those receiving community care (Manderlier et al., 2019). Delmore and colleagues were able to correctly identify 74% of their validation sample as either with or without HPUs using their regression model, which included: vascular disease, diabetes, malnutrition, surgery, mechanical ventilation, and perfusion issues (Moher et al., 2009). It is evident from the results of the two separate final regression models by Delmore et al. (2019) and Manderlier et al. (2019), that other contributory factors exist that were not explored in either study. Although both studies were the two largest, they involved different population samples.

The Braden scale has six subscales (sensory perception, moisture, mobility, activity, nutrition and friction and shear) and was the most used risk assessment tool (RAT) in the eligible studies. Subscales 'friction and shear' and 'mobility' or a Braden scale 'total score ≤ 18' emerged as significant in high to moderate quality studies. The MNS was the only other RAT to be considered by one moderate quality study included in this review. RATs are key to PU prevention, as recommended in both national and international guidelines (European Pressure Ulcer Advisory Panel et al., 2019; National Pressure Ulcer Advisory Panel et al., 2018; NICE, 2014). In clinical practice there are numerous other validated RATs (for example Waterlow, Ramstadius, and PURPOSE T) available for use, and it is up to clinicians and their employers to decide upon which one to use. Although using validated RATs is recommended, they have also been criticised in the literature for their inability to reduce PUs and have been found to be inferior compared to clinical judgement (Moore and Patton, 2019; Pancorbo-Hidalgo et al., 2006). A possible explanation for their poor performance may include how RATs are implemented in practice. Clinicians may perhaps focus on the final risk score, rather than the individual's risk profile, as identified by the RAT.

Mental status is another potential risk factor that needs further investigation given that one in three older people are living with some form of cognitive impairment (e.g., dementia, Alzheimer's, or severe Parkinson's disease), and more than half have severe dementia (Wittenberg et al., 2024.). These conditions are likely to affect individuals' concordance with HPU preventive strategies. Current national and international guidelines (National Pressure Ulcer Advisory Panel et al., 2018; NICE, 2014) recommend offloading both heels to prevent and treat HPUs. Where there are concordance issues, this strategy may be inadequate, and clinicians must use their clinical judgement on which device to use.

Perioperative analgesia (neuraxial blocks or peripheral nerve blocks; PNB) and sensory neuropathy were also considered as potential risk factors for HPU development. Patients exposed to these types of analgesia/anaesthesia are more likely to develop HPUs due to the temporary loss of mobility and peripheral sensation. For example, in pregnant women, (although the incidence is rare) (Armstrong et al., 2013; NHS resolution, 2018) and older patients the risk of developing HPU is likely to increase whilst the perioperative analgesia is still effective. Regrettably, there is a paucity of high-quality evidence to support whether perioperative analgesia or sensory neuropathy contribute to HPU development, and therefore would require further elucidation.

3.6.1 Strength and Limitations

This study has several limitations. Generalisations and inference require caution as the included studies were mostly rated as moderate quality, due to poor study designs, analysis, and reporting. Risk factors identified as independent predictors of HPUs were only examined in one high quality study (Delmore et al., 2019; Manderlier et al., 2019; Twilley and Jones, 2016). Clinical and statistical heterogeneity of studies and poor reporting standards affected the ability to quantitatively synthesis any extracted data. A strength of this review is that it incorporated a quality assurance phase, involving a further risk of bias and quality assessment of a random selection of 50% of eligible studies by an independent third reviewer.

Finally, at least 60.0% of all reported HPUs in the eligible studies were either category 1 or 2. Only one study investigated risk factors associated with category 3 or 4. Therefore, it could be argued that the risk factors investigated or identified in this review were associated with the development of superficial HPUs. More severe HPUs are likely to have different aetiology. Furthermore, due to poor reporting and the lack

of conclusive evidence, the review was not able to fully quantify the relationship between risk factors and HPU development. More people are living longer with multiple comorbidities, including those affected by cognitive impairment. It is imperative that future research studies focus on investigating risk factors, incidence, and prevalence rate for HPUs. This will help ascertain whether current HPU preventative measures are fit for purpose.

3.6.2 Implications for Practice and Future Research

- Heels remain the second most common site for developing pressure ulcers, with an estimated incidence rate of at least 17% and 11% prevalence rate. The results of this review suggest that current HPU preventative interventions may require further improvement in order to reduce the incidence rates.
- Several potential risk factors for developing HPU have been identified in this review however only 3 studies were of high quality and involved heterogenous populations. Therefore, due to paucity of high-quality evidence, clinicians should continue using their clinical judgement whilst reacting to individual patients' risk when evaluating and implementing HPU prevention strategies.
- This is the first systematic literature review of risk factors associated with development of HPUs, there is lack of high-quality studies to inform evidence-based practise. Therefore, further research is required to inform clinical practice and reduce harm.

3.7 Summary

This is the first systematic review of observational studies investigating risk factors for HPUs. There is a paucity of high-quality evidence on risk factors for developing HPUs, despite being the second most common type of PU. Age, Braden subscales 'friction and shear' and 'mobility', diabetes, vascular disease, malnutrition, mechanical

ventilation, perfusion issues and surgery were identified as potential risk factors, after adjusting for other factors. However, further research is required to elucidate these risk factors in addition to well-designed studies to increase the body of evidence. Other risk factors related HPU development may also exist - including BMI, haematological measures, other comorbidities, and smoking status, which requires further investigation. The results of this review have been used to inform the design of the phase 2 (matched case control study) of this study which is outlined in chapter 5.

Chapter 4 Methodology

4.1 Introduction

Chapter 2 has summarised the current literature on the importance of pressure ulcers (PUs) while focussing on heel pressure ulcers (HPUs), their impact on health-related quality of life (HRQoL) and prognostic value in determining end of life (EoL). This study aimed to synthesise the existing evidence on HPU risks factors through a systematic literature review (Chapter 3), provide further evidence on already identified risk factors and potentially detect additional risk factors and investigate the impact of HPUs on a) health related quality of life (HRQoL) and b) prognostic value in end of life (EoL). Scientific validity and reliability of any research study is founded in the design, conduct and analysis of the study. Furthermore, consideration is given to philosophical positions, which examine the fundamental questions of what reality is and how we come to know it. This chapter provides the rational for the choices made with regards to study design, ethical implications, processes and analysis and the researcher's world view.

This study aims to identify and quantify the relationship between risk factors and HPUs presence and investigate their impact on health-related quality of life (HRQoL) and prognostic value in EoL among the adult population. The researcher presents a pragmatic paradigm which reflects their interpretation of reality and emphasises the practical application of research findings to a real-world setting by prioritising external validity and generalisability of the study. In line with the pragmatic paradigm, public involvement played a vital role in ensuring the research questions and outcomes reflected the needs of the patients and the National Health Service (NHS). In addition, the pragmatic paradigm encourages the inclusion of a diverse patient population through its flexible research designs that mimic real-world conditions. Following the

pragmatic paradigm, a three-phase research design is proposed and presented in Figure *6-1*; a systematic literature review, matched case control and prospective cohort study are used to achieve the research aim.

4.2 Research Philosophy

The philosophical perspective encompasses the ontological and epistemological assumptions, research approach, designs and methods that will be used to investigate a specific phenomenon. Ontology and epistemology constitute fundamental philosophical perspectives that underpin our understanding of existence and knowledge. Ontology seeks to answer the fundamental questions about what exists and what can be said to exist (Creswell and Creswell, 2018). Epistemology is concerned with the nature of knowledge, belief, and justification. It seeks to explore questions surrounding the nature of truth, the limits of human knowledge and methods by which knowledge can be acquired (Creswell and Creswell, 2018). While ontology and epistemology are distinct branches of philosophy, they are deeply intertwined in shaping our understanding of the world (Guba and Lincoln, 1994). The nature of reality, as explored in ontology, influences our conceptions of what can be known and how knowledge is acquired, as examined in epistemology. Equally, our methods of acquiring knowledge and the limitations of human understanding, shape our perceptions of what exists, and the nature of reality as explored in epistemology and ontology respectively.

Research is a systematic inquiry aimed at generating new knowledge, understanding, and solving problems (Burns, 1997). At the centre of any research lies a set of assumptions, beliefs and values that guide the researcher's study approach. The guiding frameworks of any research are captured in the concept of paradigms, which play a crucial role in shaping the research process. Paradigms provide researchers

with lenses through which they perceive the world, conduct their investigations, and interpret findings. Importantly, they influence the choice of research questions and methods, data, analytical techniques, and the interpretation of findings (Patel, 2015). They are not fixed but evolve over time in response to new information, experiences, and perspectives. Many paradigms exist that are used in health research including positivism, constructivism, and pragmatism (Bunniss and Kelly, 2010). Positivist researchers emphasise the importance of objectivity, quantifiability and generalisability of a single reality and therefore, are more likely to use quantitative methods to measure this reality (Alharahsheh and Pius, 2020; Park et al., 2020). Constructivists (interpretivists) value multiple perspectives, contextuality and reflexivity in research, emphasising the subjective and socially constructed nature of reality and therefore are more likely to use qualitative methods (Bryman, 2016). Pragmatists advocate for interdisciplinary and flexible approaches to research that are constantly renegotiated and interpreted. Therefore, pragmatism emphasises practicality and problem solving using the best methods available (Andrew and Halcomb, 2007). In a pragmatic approach patients are involved in research in a unique way to the other paradigms which reflects the pragmatism's focus on consequences (Cherryholmes, 1992). That is, patients are consulted, involved, and can lead in research projects (Hildebrand, 2011), such involvement allows the research to be patient oriented thus taking such a pragmatic approach. Although each of the paradigms offer unique perspectives on the nature of knowledge and reality, common to all is the need for rigour, transparency and integrity of the research processes, data collection and analysis.

Public involvement played a fundamental role in the design of this study (as described in Chapter 5) by ensuring real-world applicability of the research findings, therefore a

pragmatic approach was deemed appropriate. The pragmatic paradigm places a strong emphasis on research that addresses relevant questions and outcomes, reflecting the genuine needs and preferences of patients and service providers (Hothersall, 2019). The use of public involvement in this study follows similar methodology used in another study (Allemang et al., 2021) in which a patient oriented doctoral study focused on the readiness and experiences of adolescents with co-occurring health and mental health issues exiting paediatric services. The use of such methodologies upholds democratic values, collaborative approaches to problem solving and pursuit of social justice (Allemang et al., 2022) concepts of importance in modern day healthcare. As the pragmatic paradigm focuses on consequences and impact, it therefore, encourages the inclusion of diverse patient populations, acknowledging the importance of conducting research across different demographic groups thus ensuring generalisability of findings (Cherryholmes, 1992; Hildebrand, 2011). Furthermore, the pragmatic paradigm favours the use of flexible research designs that mimic real world conditions allowing for a more accurate and arguably more meaningful assessment of the health conditions in clinical settings. The pragmatic nature of the research process is reflected throughout the lifespan of the study with public involvement resulting in changes in research processes to make the study more applicable to the real world. Therefore, the study utilised a quantitative research design with research processes informed by both literature and public involvement. Public involvement is an emerging concept in health research, and even more so in doctoral research, and is discussed further in section 4.5.

4.3 Research design

Health research needs to be scientifically robust, valid, reliable, and replicable. In order that these criteria are met, different well known and accepted methodologies that are

recommended in the literature can be utilised (Blencowe et al., 2015; Mann, 2012; Song and Chung, 2010a). Meta-analysis and systematic literature reviews sit at the top of the hierarchy as adopted by Cochrane and NICE guidelines (European Pressure Ulcer Advisory Panel et al., 2019; Higgins et al., 2021; Murad et al., 2016; NICE, 2014). These two methods synthesise previous research, quantify outcomes, and make recommendations for evidence-based practice. With respect to the proposed research question on HPU risk factors, no previous systematic review had been completed or published. Therefore, the author conducted a systematic literature review to synthesise the existing evidence on risk factors for HPU development in the adult populations (Chapter 3 – Phase 1 study), identified gaps in literature, and this informed the research processes as discussed in Chapter 5. Randomised clinical trials (RCTs) are next in line after systematic literature reviews and meta-analysis, these are designed to reduce allocation and selection bias by randomly allocating participants to either an experimental or control group and are often referred as the 'gold standard' for evaluating treatment outcomes (Bhide et al., 2018; Munnangi and Boktor, 2023; Saturni et al., 2014). However, RCTs are designed to compare two or more interventions, and to investigate causality (Hariton and Locascio, 2018), therefore would not be appropriate for the research questions proposed in this thesis which are aimed at investigating risk factors, impact of HPUs and predictive value of PHUs in EoL with no proposed intervention.

After RCTs comes observational studies (case-control, cohort and cross-sectional studies-either prospective or retrospective), these studies are mainly associated with epidemiological research as their main goal is to identify and investigate relationships between health conditions and different variables (Mann, 2003; Ressing et al., 2009). Despite observational studies often being criticised for their vulnerability to being

influenced by unknown confounding factors, well-designed observational studies can also complement RCTs in hypothesis generation, defining clinical questions and establishing future research questions (Munnangi and Boktor, 2023; Song and Chung, 2010). Cross-sectional studies, also known as prevalence studies, examine the data on disease and exposure at one point in time (Mann, 2012), for this reason a cross-sectional design cannot provide a comprehensive evaluation of the cause-and-effect relationship despite being relatively quicker to conduct compared to other designs. Instead, various literature suggests the use of case-control or cohort designs to evaluate relationships between risk/prognostic factors and health conditions (Blencowe et al., 2015; Mann, 2012; Song & Chung, 2010) such as the research question proposed in this thesis.

Case- control studies measure the effect of exposure in cases (those with a specified condition such as heel pressure ulcer (HPU) compared to controls (without HPU) and is suitable for rare conditions (Yang et al., 2010). In this type of design, it is possible to adjust for well-known confounding factors at the design stage by matching participants in both groups using a few selected factors such as age and sex (Rothman et al., 2011; Song and Chung, 2010). Confounding factors are variables that are related to both outcome and other risk factors and can result in a false positive outcome (Bhandari et al., 2011). For instance, in studies by Meaume and Faucher (2007) and Twilley and Jones (2016) investigating the relationship between peripheral arterial disease (PAD) and HPUs; participants were matched based on gender and age in both studies. In these studies, age and gender are well known confounding factors as they are related to both PAD and other predictors of HPU development, therefore were adjusted for by ensuring that cases and controls were matched based on the two variables. To identify and quantify risk factors for HPUs in the adult

population a matched case control design is proposed. Using a matched case control design has the advantage of sampling cases and controls from the same population as well as providing unbiased estimates with considerable cost savings (Breslow, 1996; Kupper et al., 1981).

Cohort studies are best suited for determining the incidence and natural history of a health condition and are commonly used where RCTs are unethical or infeasible (Mann, 2003). In this type of design, a group of selected participants with certain characteristics is followed up to determine the incidence or mortality with a specific disease (Song and Chung, 2010) however, similar to case-control studies, cohort studies are associated with distinct types of bias, those applicable to this thesis are addressed in later sections. The longitudinal nature of cohort studies was found suitable for investigating the impact of HPUs on health-related quality of life and their predictive value in end of life over time.

Several important research questions were identified as highlighted in Chapters 2 and 3 which required further investigation. The study design choices were guided by the type of research questions to be answered. Therefore, this research study involving adult population employed three distinct methodologies divided into three phases:

Phase 1 – Risk factors for developing heel pressure ulcers: systematic literature review (published by Dube et al., 2022).

Phase 2: Factors associated with the presence of heel pressure ulcers: matched case control study.

Phase 3: the impact of heel pressure ulcers on health-related quality of life and their prognostic value in end of life.

Figure 4-1 presents the study flow for Phases 2 and 3 in the order they took place.

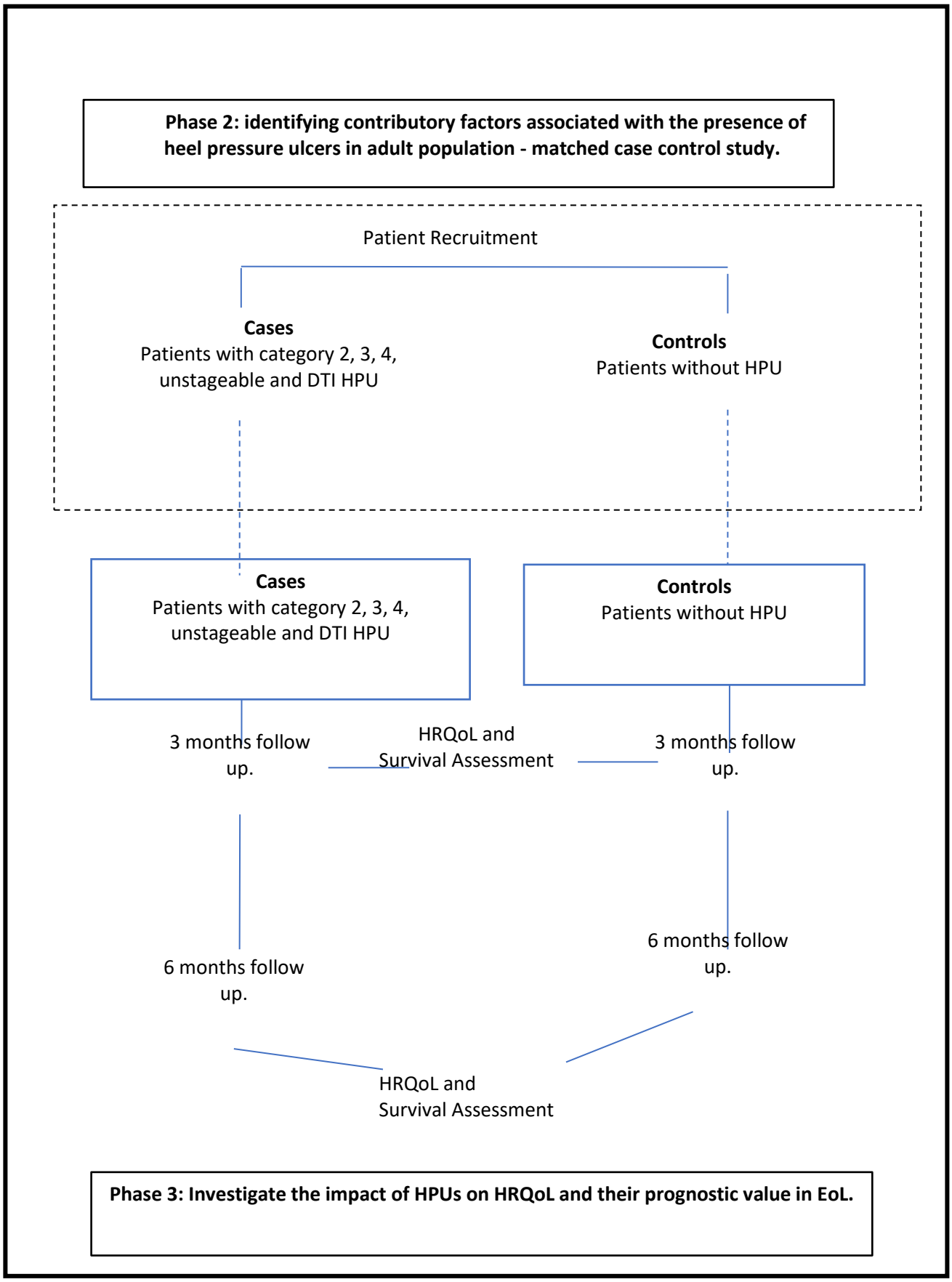


Figure 4-1 Phase 2 and 3 study design.

4.4 Validity and reliability

Health research is a systematic approach to investigate hypotheses or ideas by collecting and analysing different types of data which should be underpinned by the need to achieve scientific rigour (Cohen et al., 2017). Validity and reliability are two key concepts researchers need to consider assuring the quality of their work (Heale and Twycross, 2015). Validity refers to the accuracy of the research findings, that is, it ensures the study measures what its intended to measure (Heale and Twycross, 2015). There are four main types of validity that apply to study designs including internal validity which ensures that the measurement includes all the constructs being studied (Ahmed and Ishtiaq, 2021). External validity refers to the degree to which the findings of a study can be generalisable to other populations and construct validity examines the extent to which the study assesses the theoretical construct it is supposed to measure (Ahmed and Ishtiaq, 2021; Heale and Twycross, 2015). Lastly, statistical validity refers to the accuracy of statistical tests used to analyse the study data. The concept of reliability refers to the consistency and stability of research findings (Bannigan and Watson, 2009). It ensures that the results are dependable and can be replicated under similar conditions. Test-retest reliability measures the consistency of results when the same test is administered to the same sample at two different times, whilst inter-rater reliability measures the consistency of results when different raters evaluate the same event (Urbina and Monks, 2023). In summary, validity focuses on the accuracy of the measurement, while reliability focuses on the consistency of the measurement.

The goal of any quantitative research is to arrive at the best possible estimates that are widely generalisable, and this lies in the validity and reliability of the data collected. There are several ways that this goal has been achieved in this study; for validity, the

researcher conducted a thorough systematic literature review as well as consulting experts in the field and patients and the public through stakeholder engagement. Where possible the researcher identified validated tools for data collection such as the Braden Scale for HPU risk assessment and EQ-5D-5L questions for measuring health related quality of life and Pain Assessment in Advanced Dementia (PAINAD) (Bergstrom et al., 1998; Devlin et al., 2018; Jordan et al., 2011). Other quantitative data were based on objective measurements such as haematological tests and age as calculated based on date of birth recorded in patients' medical records. In addition, to achieve generalisability it is vital to use appropriate sampling methods to select the study population. In this thesis, the researcher sampled using convenient sampling techniques from the hospital database which provided access to all hospital admitted patients with support from treating clinicians. Furthermore, the eligibility criteria and recruitment process were developed with public involvement which increased study inclusivity and representation of patients deemed to lack capacity who are usually underrepresented in research studies (Shepherd et al., 2019). Conversely, to enhance reliability the researcher utilised standardised procedures as guided by a pre-specified protocol (Chapter 5) which included operational definitions and a statistical analysis plan. Additionally, the researcher is a registered general nurse that undertook clinical training with support of experienced clinicians as appropriate including undertaking Doppler ultrasound assessments. HPU diagnosis was confirmed by either the researcher and or specialist tissue viability nurses to minimise diagnostic errors. Owing to these measures, due consideration was given to the study validity and reliability from the design stages and throughout the delivery of the study and analysis of the study data as reflected in Chapter 5 (study protocol).

4.5 Key Stakeholder Involvement

As discussed in the previous sections, key stakeholder involvement played a crucial role in the development, delivery, and management of this research. In this thesis, two main stakeholder groups are defined below based on their contributions, experience, expertise, and roles:

- Experts – such as clinicians, managers, and other researchers – offer a viewpoint predicated on both their personal and professional experiences in healthcare that is underpinned by their education and experience.
- The public in this context refers to patients, former patients, carers, and members of the public. Their contributions are based on their lived experience of living with or looking after someone with a particular condition.

Potentially, these two groups have different contributions, perspectives and outcome expectation as reflected by their research priorities (Owens et al., 2008). It is not difficult to understand why different groups of people have different expectations of and contributions to research. Experts' thinking, experiences and expectations of research are guided by literature or their personal and clinical experience (Staley, 2009). Therefore, their focus would be to improve patient clinical outcomes and preserve health service resources. Whereas the public focus is likely to be improving quality of life outcomes, based on their experience of living with or caring for someone with a specific condition (Barber et al., 2011). On the other hand, stakeholder groups can have overlapping research interests, particularly around promotion of independence, self-esteem, and recovery (Owens et al., 2008). Shared agendas and differences amongst stakeholders are therefore both important as they facilitate development of well-rounded research agendas for the benefit of both service users and care providers. Therefore, it is vital to ensure research methodologies facilitate

such contributions to take place. For this thesis key stakeholder involvement included patients, members of the public, and clinical experts.

Traditionally, health research has been conducted for the direct or indirect benefit of the public, with participants deemed as subjects (having been subjected to research), and research mainly focusing on improving their clinical outcomes rather than more holistic needs. More recently, there has been change in the way research is conducted with a growing interest and discussion in the literature about the public's involvement in research (Forbat et al., 2009; Health and Social Care, 2018). In this context, the public are active partners in the design, development, and delivery of the study as part of the research team rather than passive participants subjected to the trial (INVOLVE, 2012) In this thesis, patients that are involved as subjects of research will be referred to as study participants. Contributions throughout the study from active public partners will be classed as 'public involvement'.

Public involvement in health research first gained momentum in cancer studies during the 1990s (Liberati, 1997). However, it has since gained momentum and popularity across all disciplines to the extent of being incorporated into UK law in the early 2000s (Department of Health, 2005). This stems from the crucial question that, *'if research is being done for public benefit shouldn't the public contribute to determine what is important and how this knowledge can be gained?*'. Swain and colleagues suggest that it would be abusive to deny the public the opportunity to use their voices to guide their own care (Swain et al., 1998). Rose (2014) also supports this concept by suggesting that allowing public involvement in research could be 'emancipatory and empowering' for those involved. There is evidence to suggest that through such involvement a positive impact on research activities such as successful recruitment and follow-up processes, shorter research periods can be achieved (Domecq et al.,

2014; Langston et al., 2005; Staley, 2009). Furthermore, public involvement can help to make research ethical and meaningful to those it is intended for (Brett et al., 2014; Staley, 2009; Wilson et al., 2015) It provides a platform where ethical considerations can be highlighted and discussed to find ways of mitigating any potential ethical concerns in a quick and easy manner (Iliffe et al., 2013)

Public involvement can be achieved using three different approaches depending on the type of research project as summarised in Table 4-1. Public involvement in research can also be a combination of any of the three approaches, throughout the lifespan of the research project. There are several published case studies describing how public involvement can be incorporated into research projects at different stages using different approaches (Boote et al., 2010; Domecq et al., 2014; Forbat et al., 2009; Liabo et al., 2020). The nature of public involvement also depends on the type of research and the researcher's experience. Less experienced researchers might feel more comfortable with using the consultation approach. This approach is simpler, more commonly used, with the public and researchers becoming more familiar with the process and help is easily accessible from experienced research colleagues if required (INVOLVE, 2012). With more experience and a mature working relationship, researchers and the public members can work together in a collaborative manner within research projects.

Table 4-1 Summary of Public Involvement Approaches

Public Involvement approach	Roles	Examples of contributions
Consultation	The public are asked for their views on a research project at any time or at any stage of the project.	Help identify research questions. Provide views on certain aspects of the study such as developing patient information sheets (PIS) and recruitment strategies.
Collaboration	The public are active partners	Collaborate with the researchers on developing the research grant application. Membership on study advisory groups such as project steering committee.
User-controlled research	The public initiates and has decision making powers with minimal support from professional researchers	Research will be conducted by a patient to address concerns around the management of a specific condition they live with for example patient living with diabetes may choose to lead research into management of diabetes.

Consultation and/or collaborative working between researchers and the public are the most used approaches (INVOLVE, 2012) This doctoral study used consultation as a means for seeking public contributions. User-controlled research is a growing concept and was deemed unsuitable because the research is led by a community of users, and this wasn't deemed appropriate for a doctoral piece of research whereby an aspect of the assessment of the qualification was whether the study is the student's own work. Collaboration also shares this challenge, thus, key stakeholder engagement through a consultation approach to inform the design and delivery, was ultilised for this research conducted in part fulfilment of the doctoral studies. This study was underpinned by the UK Standards for Public Involvement (National Institute for Health and Care Research, 2018).

4.6 Ethical Implications

Ethics is a fundamental aspect of human research and is concerned with the rules of conduct and principles relating to moral behaviour (Swanwick, 2014). In practice, ethics is also interlinked with legal frameworks such as mental capacity, consent, and access to personal information. All types of research studies, small or large, involve making ethical decisions and ensuring that these decisions abide by the relevant legal systems. The significance of ethical issues related to a study varies depending on the intent and design of the study. Studies that present a minimal risk to participants may raise complex organisational or legal issues, for instance genetic related research would raise different ethical issues compared to a study looking at population behaviours, however the fundamentals remain the same. Fundamental aspects of research ethics are imbedded in the Nuremberg Code (1947) and Declaration of Helsinki (1964) (Boahen, 2015). They both emphasise the need for sound scientific research protocols, consent, and the requirement for an independent Research Ethics

Committee (REC) for all studies involving human subjects plus human material and data.

The key elements of ethics in research are informed consent, confidentiality, privacy, respect, responsibility (Guraya et al., 2014); however, ethical principles are not universal and are based on researchers and their communities. In the UK, these elements underpin the principles of good clinical practice in research as outlined in the UK policy framework for health and social care research (Health and Social Care, 2018). Researchers are expected to give due regard to the framework when setting up projects as the framework summarises both ethical and legal considerations that should be undertaken when setting up all research projects within health and social care. The framework's main aim is to protect the interests and safety of patients, service users and the public within health and social care as outlined in the research approval process (Principle 9) (Health and Social Care, 2018).

Research to be undertaken within NHS settings requires REC and Health Research Authority (HRA) reviews, which oversee the ethical and legal concerns of research studies respectively (Health and Social Care, 2018). The REC are expected to consider all ethical aspects of the proposed research following a formal review process and provide an outcome as described below:

- "Favourable" opinion (application approved with no further amendments)
- "Provisional" opinion (REC raises issues that requires the applicant to address before they can give a final decision)
- "Unfavourable" opinion (REC rejects the application)
- REC may also decide that application is "outside remit".

The next sections will outline and discuss the ethical and legal considerations undertaken throughout the various stages of this thesis.

4.7 Consent

Consent is a fundamental aspect of medicine and research ethics, designed to protect the rights and well-being of research participants. Informed consent is a voluntary agreement by an individual to participate in a research study, based on a clear understanding of the nature, consequences, risks, and benefits of taking part in the research (Glickman et al., 2009). Consent also covers the issues of protecting privacy, confidentiality and is given based on the agreement that these aspects are upheld. However, to achieve this, there should be mutual respect and confidence in the researcher, which can only be achieved through transparency. Participants should enter the research study freely, without coercion or undue influence. Traditional and common research models of consent involve provision of detailed information to potential participants, adequate understanding of the information provided and expression of consent (Agre et al., 2003; Pullman, 2001). In this thesis, to enable potential participants to provide informed consent, they were provided with study information sheets and had the opportunity to discuss the study with the researcher, their treating clinician and family members. Furthermore, patients were given at least 24 hours to consider the information unless they chose not to. Based on these models of consent, it is fundamental that potential participants comprehend the information given, the risks and benefits of taking part in the study as well as their perceived roles and responsibilities. To ensure participants fully comprehend the information provided, where possible researchers should use plain language, visual aids, and interactive methods (Barry and Docherty, 2018; Mental Capacity Act, 2005). However, in some instances, participants may lack the ability to provide informed consent as they fail to

understand the study information due to acute or chronic conditions that affect their cognitive ability (i.e., acute infection, dementia, Alzheimer's disease). Involving such individuals in research raises several ethical and legal dilemmas which are discussed below.

4.7.1 Mental Capacity

This research study intended to recruit all eligible patients regardless of their ability to provide consent due to cognitive impairing conditions including dementia, Alzheimer's, and Parkinson's disease. These conditions are progressive and affect an individual's ability to make autonomous decisions regarding their participation in research. Informed consent relies on the ethical and legal belief that research participants need to understand what it involves taking part in research, which relies on one's mental capacity or ability to provide that consent. Mental capacity refers to the ability to make their own decisions (British Medical Association, 2015). For individuals with full mental capacity, the process of obtaining consent is relatively straightforward whereas, for those lacking the ability to provide consent the process raises several ethical and legal complexities.

Health and social care professionals including researchers are often faced with the decisions of mental capacity. In the UK, there are three separate legislations which cover mental capacity; Adults with Incapacity Act (2000) which covers the whole of UK, Mental Capacity Act (2005) applicable to England and Wales only and Mental Capacity Act (2016) only applies to Northern Ireland. This thesis will only focus on relevance and implementation of the Mental Capacity Act (2005) as the research project took place in England. As previously discussed, for a subject to take part in a research study they need to be able to provide informed consent. This raises the

question ‘how does a researcher determine if an individual has capacity to provide consent’.

Capacity assessment was incorporated into law in 2005 as part of the Mental Capacity Act (2005), to protect the rights of people who lack the capacity to make decisions for themselves and provide help for those caring for them (Boahen, 2015). It also includes safeguards for the conduct of research, excluding clinical trials of investigational medicinal products (CTIMPs) (MCA, 2005). Prior to 2005, the Courts dealt with any issues of capacity under ‘common law’ (Nicholson et al., 2008). CTIMPs involving adults who lack capacity are regulated separately by the Medicines for Human Use (Clinical Trials) Regulations (2004) and are outside the scope of this discussion. MCA (2005) is accompanied by a code of practice which outline provisions for facilitating research involving individuals that lack capacity to consent. Clinicians are expected to have read and understand the code of practice and be able to prove that they have done so, if required.

The MCA (2005) is underpinned by five key principles as outlined in Table 4-2. In its first principle, it enforces the assumption that a person has capacity unless it is established otherwise. Whenever there is doubt on one’s capacity, the Act puts the burden of proving that one lacks capacity on the individual who needs to receive informed consent (such as a doctor, nurse or researcher) (Boahen, 2015). According to the Act, for an individual to be able to provide a decision they need to understand the ‘salient factors’, be able to weigh, retain the information, and communicate their decision and the assessor must take reasonable steps to facilitate this process. It also acknowledges that the process is decision and time specific, making it subjective and difficult to replicate in research.

Table 4-2 Five key principles of the Mental Capacity Act, 2005 (adapted from (Nicholson et al., 2008)

• Capacity is presumed unless proven otherwise.
• All practical steps to help a person to make a decision must be taken.
• An irrational decision does not equate to the absence of capacity.
• If a person lacks capacity, any decisions made must be in their best interests.
• Any decision for an adult lacking capacity made must be the least restrictive option available for their basic rights and freedoms.

The UK law also requires provision of practicable steps to support decision making process, this may have financial implications for organisations. For instance, where patients are non-English speaker's clinicians or researchers must make arrangements to provide appropriate translators for each patient as required. In cases where patients have fluctuating capacity researchers, clinicians and carers can optimise this process through liaising with each other to identify best time or day to approach the patient. However, there are no provisions in the law to continue providing support to all individuals beyond the decision-making process. For those deemed to lack capacity, support is made available to them to meet their care needs in their 'best interest'. Conversely, those deemed to have capacity can continue with their life choices including those that might be making 'unwise decisions', which might have implications for both them and the health service in the future.

Mental capacity assessment is a complex process, subject to various contextual factors as specified in the MCA (2005), when completed inappropriately can lead to impeachment of patients' rights. In clinical practice, clinicians are likely to confuse

compliance with implying having ability to make decisions or refusal of treatment as lacking capacity to consent. This is possibly because they would not have undertaken an in-depth capacity assessment i.e., not probing understanding or one's ability to weigh and use the information presented to them. This can result in serious consequences for both patients and clinicians depending on the decision to be made. Social and cultural beliefs can also affect how one makes their decisions; thus, clinicians/researchers need to be aware of their patients' beliefs and values to fully support them with their decision-making process (Pennington et al., 2018).

In literature there are several validated tools that can be used to assess patient's assess memory and specific function competences including those underpinned by the MCA (2005) principles (Gerstenecker et al., 2016; Jeste et al., 2007; Moye and Marson, 2007). These include Capacity Assessment Tool, MacArthur competence assessment tool, Mini Mental state Examination (MMSE) and Abbreviated Mental Test Score (AMTS). MMSE and AMTS assess memory and specific function competences tend to be used in research to provide quantitative data for analysis. Evidence of cognitive impairment does not necessarily mean one lacks the ability to decide; as decision making process is decision and time specific (Pennington et al., 2018). In addition, within UK law there is no requirement to retain the information beyond the decision-making process. Memory and/or function tests require an individual to retain information long term. Some individuals can score high with memory/function tests but may not be able to understand, retain, weigh or use complex information. Whilst there is evidence to suggest that lower scores on the MMSE is linked to lack of capacity, a higher score does not mean one has capacity (Karlawish, 2008). Due to the complexity and subjective nature of mental capacity assessments there is no 'gold standard',

which has implications for patients' rights, their clinical care and access to research opportunities.

In this thesis, the researcher, therefore, proposes a pragmatic approach that is sensitive to the fact that individuals might have fluctuating capacity depending on a range of things including mood, time of the day, medication. The mental capacity assessment was underpinned by the five principles of the MCA (2005) and clinical judgements of both treating clinicians and the researcher. This mental capacity assessment adopted the methodology stipulated by Warner et al (2008) which had an added value of lessening the burden of taking part in research on the part of potential participants. Pressure Ulcers more likely affect the elderly frail population and therefore using a pragmatic capacity assessment seemed sensible to minimise participant burden. As well following the functional test outlined below, the MCA (2005) requires that for a person to be deemed to lack capacity they should have an impairment or disturbance of the mind or brains. The impairment or disturbance should also affect their ability to process information. Figure 4-2 below outlines the mental capacity assessment adopted in this study and completed as outlined below.

1. Providing sufficiently detailed, salient written and verbal information to potential participants in a form they would be able to understand, including (a) the objectives of the study, (b) potential risks and inconveniences of participation, (c) Doppler ultrasound assessment procedure (d) study assessments and follow-up (e) the opportunity to withdraw at any time. Depending on the ability of the participant to assimilate information, the researcher repeated this information as necessary and at times requested the participant's carer to help impart information.

2. Allowing sufficient time for the individual to understand and retain this information. This was assessed by the researcher judging, after providing the information in various ways, whether the participant was likely to be able to meet these criteria. If the researcher felt this was unlikely the participant was deemed to lack capacity.

3. Testing whether the potential participant had retained salient information, for example, by asking them to repeat relevant information and demonstrate understanding of this.

4. Ensuring the potential participant was able to weigh this information in the balance and decide whether they wanted to participate, without coercion.

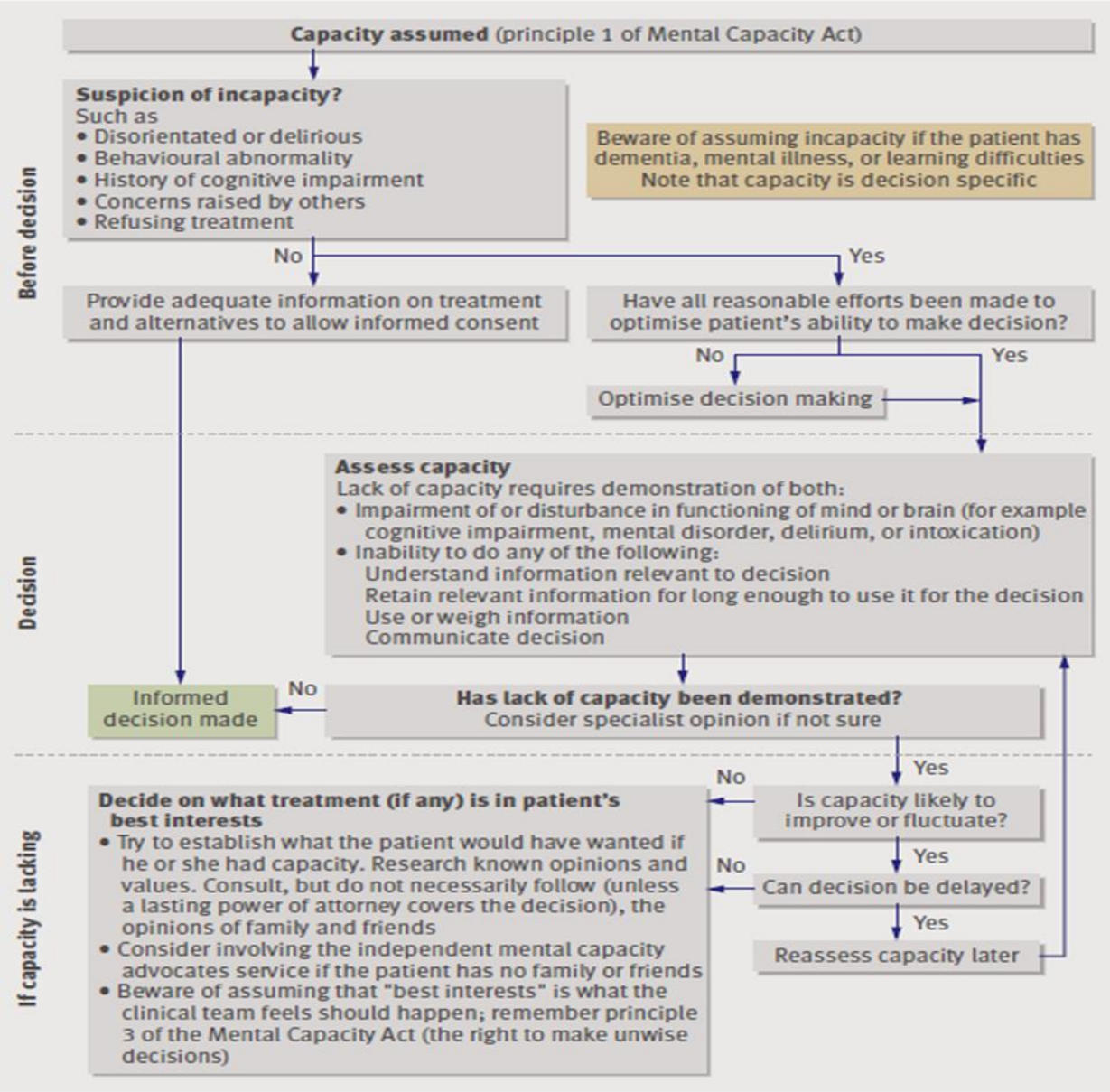


Figure 4-2 Flow diagram outlining mental capacity assessment. Source: (Nicholson et al., 2008).

Once a subject has been deemed to lack capacity the Act doesn't specify if the individual should be provided with study information for their consideration, however, it is always best practice to involve an individual in all aspects of their care. On the contrary, the Act puts weight on any sign of objection exhibited by the person lacking capacity and requires the researcher to acknowledge refusal to take part in the study. If a person has been deemed to lack capacity, there are specific processes that need

to be followed to comply with the law. In accordance with the Act, where a patient lacks capacity to consent for themselves, advice on whether to include the patient in the study needs to be sought from an appropriate consultee. Consultee can either be personal or nominated depending on the patient's circumstance; this can be anyone who has a personal relationship with the patient but is not involved in their welfare for financial benefit or involved in research (Department of Health, 2008). Examples of suitable people who might act as a personal professional consultee are a family member, carer, friend, or a court nominated deputy who has a personal relationship with the patient, treating doctor or GP. Consultees were asked to consider the patient's wishes and beliefs before they lost their cognition.

If the researcher is unable to identify a personal consultee, the Act proposes a nominated consultee, which could be any HCP involved in the patient's care to be identified to advise the researcher**.** Should participants regain capacity during the study the Act requires that they are provided with study information and asked to provide consent should they wish to continue in the study. Figure 4-3 below summarises the provisions for involving people without capacity in this research as laid out in the MCA (2005).

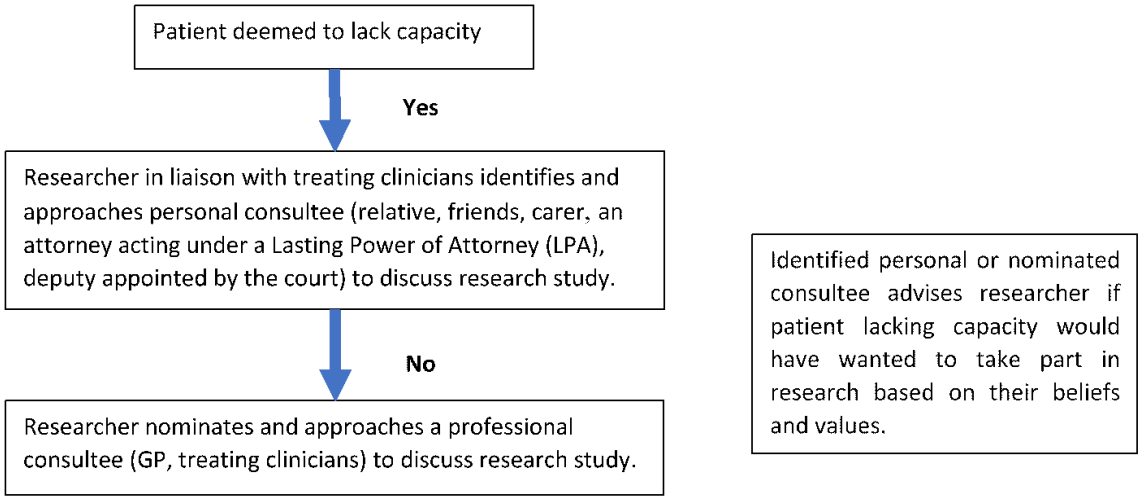


Figure 4-3 Consultee identification process for research purposes. Source: (Mental Capacity Act (2005)).

Under the MCA (2005) a research project involving adults lacking capacity requires REC approval, and the research must be linked to the impairing condition or treatment of the condition affecting the person that lacks capacity. It further requires that there must be justification for proposing to involve this group of individuals and well as provisions to consult with their carers. Without proper training and support on the Act, one can easily misinterpret the law to suggest that only studies investigating conditions like dementia are considered under this Act. However, it provides further requirements which allows other types of research to involve persons lacking capacity to consent if the research has intended benefit for the person and that the research aims to improve care and treatment of such individuals. In addition, the research project should ensure that the risk or burden are proportionate to the benefits of taking part in the study.

To ensure that this study would gain REC and HRA approval under the MCA (2005) the following justification was used: Evidence from SLR showed that HPU mainly affects elderly persons with median age range of 70-85 years, and other PU studies

suggest prevalence and incident rates increase with age (Coleman et al., 2013; Dube et al., 2022). Furthermore, one in three adults aged 65 and over are reported to be living dementia that affects their ability to make decisions, and these numbers are expected to rise with the ageing population (Alzheimer's Society, 2024). People with dementia have been reported to have a higher PU prevalence and having a PU is associated with lower survival time compared to those without dementia and PUs (Jaul and Meiron, 2017). Altered mental status has also been identified as a potential important risk factor in a previous HPU study, however, still requires further elucidation (Campbell et al., 2010). Therefore, excluding this group of patients would skew the data and the results of the study would not be widely generalisable (Bayer and Tadd, 2000). It was evident from the systematic literature review that there is paucity of evidence on the impact of cognitive impairment on the prevention of HPUs, therefore including this group of patients in this research study would further HCPs' understanding and consequently result in improvement of care provisions. NICE guidelines for dementia state that people with dementia should not be excluded from any services because of their diagnosis or age (National Institute for Health and Care Excellence, 2018) and in research this is particularly important to ensure that results are generalizable to this population group. The public were also consulted through public involvement and those consulted agreed that it was paramount for this vulnerable group of patients to be represented in this research.

4.8 Right to Approach and Withdraw from a Study

In the UK, ethics committees and HRA have the responsibility to ensure researchers in their proposals adhere to ethical principles and regulatory requirements including the right to approach potential participants and the participant's right to withdraw at any time. To maintain patients or potential participants' rights, researchers are

required to obtain approvals from the ethics committee and or HRA. Right to approach refers to the ability of researchers to approach potential participants for inclusion in their studies. All potential participants must be approached in a way that does not breach their right to privacy and data. To safeguard patient's privacy and their data, researchers must give due regard to the common law duty to confidentiality, that is patient information must not be disclosed without the consent of the patient.

Right to withdraw is a fundamental aspect of research ethics that ensures participants have autonomy and control over their involvement in research. Allowing participants to withdraw from a study at any time without providing an explanation respects their rights to make independent decisions. Respecting participants' right to withdraw upholds their well-being and ensures that there is no coercion, this is particularly important in health research where participants may be dealing with illness, vulnerability or other challenges whose outcome might depend on the input of the researcher as their treating clinician. Thus, researchers have the responsibility of clearly communicating the voluntary nature of participation and right to withdraw. Participant information sheets should include clear processes for participants to exercise their rights allowing them to prioritise their well-being and personal interest. Empowering participants to exercise their rights contributes to building trust between researchers and participants which is important for the success of any health research. In doing so, researchers should be prepared to manage the impact of participant withdrawals on the overall study integrity and validity by exploring strategies for dealing with consequences of withdrawals. Despite the impact withdrawals might have on the study, it remains imperative that researchers and the wider research community continue to prioritise and uphold the right to withdraw as an essential aspect of health research practice.

4.9 Confidentiality and Anonymity

Confidentiality refers to the protection of the identity of the participant through maintaining the data in such a way that protects their identity (Swanwick, 2014). In clinical research this involves separating personal data from other study data. Personal data is defined by GDPR (2018) as information that relates to an identified and identifiable individual. GDPR came into force in 2018 and applies to processing of all personal data, requiring organisations to have subject consent for processing their personal data (research data exempt). GDPR also requires organisations to anonymise data to protect privacy and provide secure storage for all data. All research teams are expected to abide with the GDPR and Data Protection Act (Data Protection Act, 2018; European Union, 2016).

Although GDPR exempts research work from the need to have consent for personal data, the natural sensitivity of health information including personal data and inferred vulnerability of patients poses ethical dilemmas within research. To protect and safeguard patient's privacy within common law there is duty of confidentiality which requires anyone outside of the patient's care team to have patient consent to access any confidential patient information, including personal data and health information (Marsh and Reynard, 2009). Therefore, consent is required to be able to access confidential patient information for research purposes. Requesting anonymised aggregated data from frontline care teams can mitigate the need for consent, however in exceptional circumstances this may not always be possible. Prior approval from the Confidentiality Advisory Group for England & Wales can be used in such instances (Health Research Authority, 2024).

Maintaining the confidentiality and anonymity of data may be necessary; this can be achieved by not collecting personal data at all or removing personal data and

assigning a study identification which is only known to researchers. If anonymising data at the initial point of undertaking study processes (that is, during consenting or interviews in qualitative work); in such instances it is necessary to have processes in place to separate personal data from other research data as soon as possible. There is the risk of breaching confidentiality where there are safeguarding concerns around patient care and there is need to be transparent about any breeches to potential participants and carers. Table 5-10 in section 5.16 outlines the study processes undertaken to maintain confidentiality and anonymity for all study participants.

4.10 Research Risks and Benefits to Participants

RECs are tasked with the responsibility of assessing the risk and benefits of each study proposal; thereby ensuring participant safety and that they are not disadvantaged by taking part in the study (Dixon-Woods and Angell, 2009). The researcher and their team have the responsibility of carrying out risk assessments and putting mitigating measures in place to always maintain participant safety and dignity. In studies that involve participants lacking the capacity to consent, researchers need to ensure potential risks associated with lacking capacity are identified (e.g., not being able to communicate pain or lack of understanding may lead to harm when individual decides to move during an intervention) and that these individuals do not experience extra burden compared to those who are able to understand and make decisions for themselves. Principle 8 of the UK policy framework requires researchers to be transparent in terms of associated risk and benefits of taking part in the study (Health and Social Care, 2018). This information needs to be made apparent in REC applications, and study patient/consultee information sheets and the researcher encouraged verbal discussion with potential participants.

4.11 Summary

This chapter discussed the various aspects that make up a research study, including decisions made at various stages of this thesis. The researcher positioned themselves as a pragmatist and chose quantitative methodology complimented with public involvement to address the study research questions. Three distinct designs were chosen; Phase 1 – a systematic literature review used to synthesise existing evidence as well as inform the design of the matched case control (Phase 2) study. Phase 2 – a matched case control aimed at identifying risk factors for HPU presence. Phase 3 – prospective cohort study investigating the impact of HPU on HRQoL and their predictive value in EoL. Chapter 5 outlines the study protocol utilised in the delivery and management of this thesis.

Chapter 5 Protocol (Phase 2 and 3)

5.1 Introduction

This section builds on from the previous chapters, stipulating the research protocol for transparency and replicability of the study. This chapter outlines the study research questions, data collection methods, data management and analysis of data. Also included is the key stakeholder involvement, highlighting their contributions and resulting changes. Chapters 2 and 3 provided the contextual background and systematic literature review on risk factors for developing HPUs in the adult population respectively. In Chapter 2, the researcher presents a review of the literature on all pressure ulcers (PUs) with a focus on heel PUs (HPUs), identifying the lack of evidence on HPUs, highlighting the paucity of evidence on risk assessment tools and unclear evidence on HPU prevention strategies. Although it was clear that PUs have a negative impact on health-related quality of life (HRQoL), none of the research explored the impact of HPUs on HRQoL. Furthermore, there was emerging evidence to suggest a link between HPUs and EoL status which requires further exploration (Black et al., 2011; McGinnis and Stubbs, 2014). Successful implementation of HPU prevention strategies relies on accurately identifying those at-risk using evidence-based processes. Despite HPUs continuing to be the second most common PU after sacral PUs (Clark et al., 2017; Li, Z. et al., 2020; Sardo et al., 2023; Stephenson et al., 2021), the first systematic literature review on risk factors for HPUs presence is reported in Chapter 3. The findings from the systematic literature review in conjunction with key stakeholder contributions were used to inform the design of the Phase 2 of this thesis. Phase 3 of this thesis explores the impact of HPUs on HRQoL and their predictive value in EoL, as informed by literature and stakeholder involvement.

The overarching aim of this thesis was to identify and quantify the relationship between risk factors and heel pressure ulcers HPUs presence and investigate their impact on HRQoL and prognostic value in EoL.

The thesis was therefore divided into three phases, with each phase aimed at addressing one of the three study objectives as follows:

- Phase 1 – A systematic literature review on risk factors for HPU development in the adult population as reported in Chapter 2 and published by Dube et al. (2022).
- Phase 2 – A matched case control study aimed at providing further evidence on already identified risk factors and potentially detect further additional risk factors.
- Phase 3 – A prospective cohort study which was designed to investigate a) the impact of HPUs on HRQoL and b) their prognostic value in EoL.

Phase 2 and 3 involved the same study population that was recruited in phase 2 and followed up during phase 3 of this thesis.

The Phases 2 and 3 commenced after gaining relevant approvals which included Birmingham City University Ethics and Health Research Authority approvals and confirmation of Capacity and Capability from the research site as listed in Appendix 5. A substantial amendment was made to the original ethics application and granted approval by BCU and HRA (approvals attached in Appendix 5.5).

5.2 Study setting

This study was undertaken within one of the largest acute teaching NHS trusts in the UK, comprising two hospital sites: University Hospital Coventry and Hospital of St

Cross (UCHW). The NHS Trust covers 16 different clinical specialties including accident and emergency, maternity, paediatrics, and children, with a total of 1115 beds. In 2015/16 a total of 158,189 patients were admitted to the hospital (UHCW Annual Report 2015 - 2016). The trust covers one of the most deprived regions in the country, and maintains a strong focus on delivering high quality, safe and effective patient care. In 2016, the Trust was shortlisted for a Health Service Journal (HSJ) award in the 'Using technology to improve efficiency' category for its World Class Conversations projects (Hsj.co.uk., n.d) and classified as 'Good' in its most recent Care Quality Commissioner (CQC) report (Cqc.org.uk, n.d) prior to start of the research. Participants were recruited from July 2018 to March 2020.

5.3 Key Stakeholder Involvement

In this thesis key stakeholder involvement included clinical and research experts in PUs as well as contributions from patients and members of the public, as discussed in sections below. As previously mentioned, involvement of both groups is vital as they bring a diverse and comprehensive contribution to research.

5.3.1 Expert Involvement

Key stakeholder group discussions aimed at identifying important parameters to be collected as part of the study were held prior to any research taking place. Several groups of healthcare professionals (HCPs) with interest in PUs and EoL care were identified; these included mainly tissue viability nurses (TVNs) both local to the Trust and geographical region, PU Champions (PUCs) within the NHS Trust (study site), EoL and PU research experts. Three separate group discussions with an average of five HCPs and a total of five one to one meetings with experts were held within the first year of the research project. Prior to each meeting the attendees were sent a brief presentation of the proposed study and oral presentation was also given on the day of

the meeting. Participants were asked to consider and advise on the following based on their experience and expertise:

- Anecdotal evidence from clinical practice
- Proposed research questions
- Study design
- Recruitment processes
- Data collection

In the initial stages of the research design development, the researcher also presented at several PU prevention and management forums, local and regional conferences and TVN group meetings through poster and oral presentation followed by group discussions. Including these perspectives in the study design ensured that the clinical presentation of HPUs was considered, which might not yet have made it into the academic literature.

5.3.2 Public Involvement

In addition to obtaining a clinical perspective, efforts were also made to engage the public who represented the study population. Public representatives were identified with help of TVNs and NHS Trust Research and Development (R&D)'s Delivery Manager. Those willing to contribute were asked by the researcher to complete a terms of reference form which included six questions which explored their experiences of pressure ulcers (form attached in Appendix 6). Their responses informed further discussion as part of their contribution through public involvement.

A group of public members (including previous and current NHS patients) who either had a or previously suffered PU, or a family member who had experience of caring for

someone with a PU were identified and agreed to act as public representatives on the study, a total of 4 patients and 2 carers. PUs mainly affect elderly frail individuals with multiple comorbidities, and their health conditions are likely to deteriorate with time (Jaul et al., 2018; Khor et al., 2014; Serrano et al., 2017). The four patient representatives were of similar characteristics living with multi-comorbidities. Due to the frail nature of these individuals and to reduce the burden on them, the researcher arranged one-on-one meetings with them at their most convenient time. Initial meetings were face-to-face within hospital settings with up to five follow-up meetings over 3 years. Further meetings were arranged to be through telephone or face-to-face if patients were attending outpatient appointments as appropriate. This allowed participants to respond individually at their most convenient time and avoid unnecessary travel. Initial discussion with the public representatives were open discussions guided by their responses provided on initial questions asked on the Heel Pressure Ulcer Public Involvement Group (HPU PIG) questionnaire and they were also asked to consider the following:

- Identify important questions to be answered by the research study.
- Review patient information leaflets to make sure they were written in plain English and easily understood.
- Consider ethical issues involving patients lacking capacity to provide consent and complete study questionnaires.
- Help identify ways of reaching the right study population.
- Help to ensure results are reported clearly.

Public representatives were selected from an older population as HPUs tend to affect this group of individuals (Bergstrom et al., 1998; Delmore et al., 2019; Manderlier et

al., 2019). The researcher anticipated potential loss of public representatives over the study duration to be high due to increased risk of mental deterioration and death in the population. To allow for these unfortunate events the researcher also engaged a much larger well-established Patient and Public Research Advisory Group (PPRAG) which was part of the NHS trust (study site). Through this group, the researcher was able to access support throughout the study. For the initial consultation, the researcher provided the group with PIS and consent form drafts for their review and feedback prior to the meeting. At the meeting, the researcher had an opportunity to give a presentation of the study and had a group discussion around the proposed study aims and objectives, whether patients lacking capacity should be included in the study and how best to include them and their relations. The representatives were given the opportunity to provide feedback and comments either during the meeting or through email after the meeting.

In the subsequent meeting, the researcher also provided a brief study presentation which included aims and objectives, current study processes and issues identified. The study was experiencing poor recruitment rates due to high exclusion rates of patients who could not provide consent to take part in the study due to their medical conditions. The following issues were highlighted and discussed with the PPRAG to find strategies to improve recruitment processes:

1. The researcher did not have initial ethical research approval to contact patients' families or friends through telephone to discuss the study, therefore relied on frontline staff to communicate with the patients' relations. The clinical staff were provided with research study information to convey to family/friends of patients. It was also documented in patients' nursing notes that the patients were eligible to take part in the study and the researcher

needed to discuss the possibility of taking part in the study with their respective families or friends whilst they were visiting in the hospital. In majority of the cases the messages were not conveyed, and patients were discharged before the researcher could meet with the families.

After a long group discussion, it was unanimously agreed that frontline staff were under a lot of pressure from their own clinical duties which were their priority, however as gatekeepers to accessing patients it was agreed that holding a meeting with the ward managers would be useful to raise research awareness and help them understand why the study was important from patients' perspectives. In doing so, it was hoped that this would help the frontline staff to understand why it was equally important to offer all patients the opportunity to take part in the research. A volunteer from the PPRAG attended a Ward managers' meeting with the researcher where they gave a talk and explained why it was important for front line staff to enable patients to engage with research.

2. Some patients had known relations however most of their family or friends did not live local to the hospital, hence did not visit regularly. As a result, potential participants were discharged before they could be recruited into the study. The representatives and the researcher considered three options described below to address this issue.

Option (1)

The first option was for the researcher to be the first person to approach identified consultees about the study. This option had already been rejected in the initial research ethics committee (REC) approval application, therefore only a member of the treating team was to make the initial contact with the eligible patients' relative or friend

(consultee) about the study and then introduce the researcher to the consultee provided they had given verbal consent to be approached. This approach was affecting recruitment as not all relatives or friends visited regularly or at all, and others visited out of hours when the researcher was not available. Due to the nature of the study (PhD project) there was only one researcher for the whole project which therefore made it impossible to always have someone available to meet with the patient's relative or friend at the hospital.

Option (2)

If the researcher was unable to meet with a personal consultee within the hospital setting, a member of the eligible patient's treating team would have a telephone consultation with the identified personal consultee and receive verbal consent for the researcher to contact the identified personal consultee at an identified convenient time. However, due to current staff shortages, high workload and winter pressures on the wards, ward staff would not have the capacity to take on this responsibility.

Option (3)

If there was an identified personal consultee but the researcher was not able to meet with them within the hospital setting to discuss the study, a nominated professional consultee would be identified. This could have been either the potential participant's GP or treating doctor or Advanced Clinical Practitioners not involved in this research study. The researcher would discuss the study with the professional consultee and provide them with a study information sheet (document attached in Appendix 7). In future, should the researcher have contact with a patient's personal consultee, they would be consulted about the study and requested to advise the researcher about their relative/ friend's wishes and beliefs about taking part in research.

Representatives were asked to discuss and propose ways to best address the raised issues, they also had the opportunity to email further suggestions to the researcher after the meeting. The group agreed that option (3) was more acceptable and feasible, therefore this option was incorporated as part of a substantial study protocol amendment and received a favourable opinion from REC. The support from the patient representatives contributed to a positive ethical application. Patient and public contributions and involvement in this study was bound by the values and principles as stipulated by the NIHR-INVOLVE guideline (INVOLVE, 2016) and National Standards for Public Involvement (NIHR, 2018).

The feedback from the different patient, carer and HCP groups were considered separately to identify research priorities for HPU prevention based on experiences and expert opinions. Both patients, carers' representatives and HCPs agreed that the research questions identified were important and required further investigation. The following points were raised and were also incorporated as part of protocol development: Table 5-1 below, summarises the contributions made by experts and patients' representatives as part of this research. These contributions were incorporated into the study protocol development discussions with the supervisory team.

Table 5-1 Stakeholder contributions

Experts	**Patient and Public representatives**
Minimising risk of bias: To minimise selection bias, clinicians advised to include all hospital	Reviewed and contributed to the development of patient/consultee information sheet, recruitment process and results reporting and dissemination.

Experts	Patient and Public representatives
patients in the screening process and utilise the large pool of patients.	
Eligibility criteria: to exclude patients in their last days of life no longer receiving medical intervention as advised by treating clinicians.	Representatives emphasised on the effects on PUs on QoL outcomes and pain based on their own experiences and the need to investigate these further to improve quality of care.
Research questions based on their clinical expertise e.g. investigate the relationship between HPUs and PAD severity as diagnosed using DUS.	Representatives also supported the involvement of vulnerable individuals to ensure the research remained applicable to all patients that are affected by HPUs.
Reviewed study assessment processes e.g. DUS assessment and case report forms (CRFs).	Strategies to boost recruitment rates, for instance, three options discussed above. As well as contributed to research awareness among frontline clinicians.

It is important to note that experts tend to focus on clinical outcomes whereas patients are more focussed on patient reported outcomes (Owens et al., 2008). Both perspectives were therefore vital in the research process as they complement each other whilst ensuring the research remains clinical and scientifically relevant as well as maintaining relevance to patients.

5.4 Sample, Recruitment and Consent

In order that study findings can be representative as widely as possible several factors were taken into consideration whilst developing the eligibility criteria. The process was

also supported by experts and patients through key stakeholder involvement. A convenience sampling approach was used for screening all potential case and control study population, this allowed the researcher to approach eligible participants based on the NHS Datix (incident reporting system) database for the case group and admission data available to the nurses on the ward for the control group. The study sample was recruited as part of the Phase 2 study (matched case control design) and followed up in Phase 3 study (prospective cohort design). All hospitalised patients with HPU ≥ category 2 was screened from the NHS Datix database against the following criteria:

5.4.1 Eligibility criteria

Inclusion criteria

- Patients aged 18 years and above.
- *Cases* - Patients with a category 2, 3, 4, deep tissue injury and unstageable HPU (as classified by NPUAP, EPUAP and PPPIA (2014) attached in Appendix 1 for full details of classification).
- *Controls* - patients without a HPU not meeting the exclusion criteria (matched based on recruited cases' age (±1 year), gender, mental and end of life status)

Exclusion criteria

- Patients under 18 years old
- Patients in their last days of life as advised by the medical or nursing team
- Patients contraindicated for DUS (e.g. unable to lie flat for 90 minutes due to cardiac disease or shortness of breath, contracted limbs, confusion)

- Patients that are unable to sufficiently comprehend English to provide informed consent.
- Patients unwilling to provide written informed consent.

Due to the research study being funded as part of a PhD project, resources were not available to enable inclusion of those who do not sufficiently comprehend English to provide informed consent.

To evaluate the screening process (total number of patients screened and reasons for exclusion) a screening log was kept up to date during recruitment. Participants were able to withdraw from the study at any time without giving a reason. Those participants that either declined to take part or withdrew from the research study were given the opportunity to discuss/ inform the researcher of their reasons.

5.5 Power and Sample Size

To ensure that a research study has a high chance of correctly identifying a difference between two groups (known as power), if one exists, it is important that researchers perform sample size calculations. Sample size calculations depend on p-value, power, and effect size; in practice these are conventionally set at P= 0.05 and at least 80% Power (Whitley and Ball, 2002). In a previous similar research study aimed at investigating the association between a single risk factor PAD and HPU, the study reported odds ratios (OR) of 2.40: 95% CI (0.95; 6.02), in the same study an attrition rate of 13% at 12 weeks follow-up was reported (Twilley and Jones, 2016). To detect an OR=2.0 with a 5% significance level, 80% power and 13 % attrition rate would have required a total sample of 346 participants. Unfortunately, other studies investigating other risk factors did not report their power calculations (Campbell et al., 2010; Clegg et al., 2009; Meaume and Faucher, 2008). This research intended to identify all

potential risk factors associated with HPU, currently, within the literature, it remains unclear as to how many risk factors have a clinical or statistically significant association with HPU development due to inconsistencies in reported study results (Campbell et al., 2010; Clegg et al., 2009; Duncan et al., 2003; Meaume and Faucher, 2008).

For Phase 3 the following assumptions were made: a survival rate of 50% in the control group and 20% difference between cases and control groups at 5% significance level and power= 80% and 13% attrition rate a total sample size of 104 participants were required. From January 2016 to December 2016, 240 HPU patients were reported on the NHS Trust Datix database, giving an average of at least 20 HPU patients a month. Assuming a combined eligibility and consent rate of 50%, recruitment was anticipated to last at least 12 months, depending on the actual recruitment rate this was planned to last a maximum of 24 months to ensure enough time for analysis within the project timeline. Therefore, initially the researcher had proposed a pragmatic sample size of 200 cases and 200 controls with a 24-month recruitment period; this would have allowed at least 10 potential risk factors to be investigated and also had enough power to detect an OR=2.0.

However, the recruitment rate remained poor despite substantial amendments to the protocol due to several reasons which included high mortality and discharge rates amongst the case group (to be elaborated later in Chapter 6 - Results section) thus affecting the overall study sample size. After interim power calculations and discussion with the supervisory team it was agreed to recruit as many participants as possible until the end of March 2020 and significance levels were adjusted to 10% and power=80% based on the final number of participants recruited n= 103. Unfortunately, the study experienced poor recruitment due to several reasons outlined in Chapter 6

which included patients being discharged or dying before being approached to take part in the study. In addition, recruitment was discontinued two weeks earlier than planned due to the social distancing policy imposed by the government due to the COVID-19 pandemic. Due to the paucity of evidence on HPU risk factors and non-existent evidence on the impact of HPUs on HRQoL and their predictive in EoL, this was an exploratory study guided by the available data and final sample size (Morgenthaler, 2009).

5.6 Recruitment and Consent

5.6.1 Patient Screening

In Phase 2 of this thesis a matched case control design was used, which aimed to identify and quantify the relationship between risk factors and HPU presence. Cases were hospitalised patients with HPU(s) (category 2, 3, 4, unstageable and deep tissue injury (DTI)) regardless of their origin (community or hospital acquired) and controls were patients from the same hospital without a HPU(s) who met the eligibility criteria described in section 5.4.1.

Patients with either a community or hospital acquired HPU (cases) were reported to the TVN using the Datix database by HCPs working within the participating hospital; all reported patients were screened against study eligibility by the TVN and finally by the researcher. Controls were identified and screened against study eligibility by their treating clinicians and the researcher made the final decision as to whether a patient met the eligibility criteria. With the help of the treating clinicians, eligible patients' mental capacity and EoL status were assessed by the treating clinicians and the researcher before obtaining written informed consent. Potential control participants were also screened based on the age, gender, EoL status and mental state of recruited cases.

Age was matched to the nearest ±1 year period in controls. EoL was defined as last year of life according to the NICE guidelines and participants' end of life status was assessed using the Supportive and Palliative Indicators Tool (SPICT) as recommended by the National Gold Standard Framework (GSF) for EoL (National Gold Standards Framework Centre, 2024; NICE, 2017). The EoL status was either documented in the patient's record or in the absence of a status the researcher would discuss the patient with senior members of the treating team to ascertain the patient's EoL status. For the purposes of this study a potential participant was be deemed to lack capacity in relation to their care, treatment, or research if at the material time they were unable to decide for themselves because of an impairment of, or a disturbance in the functioning of, the mind or brain as defined in the Mental Capacity Act 2005. Mental capacity assessment within clinical practice is based on whether the patient can understand the information relevant to the decision, to retain that information, to use or weigh that information as part of the process of making the decision, or to communicate their decision, as stipulated in MCA 2005 Section (3) (Mental Capacity Act, 2005). Initial mental capacity status for the purposes of matching the study participants during recruitment was based on the clinical opinion and/or previous formal diagnosis of cognitive impairment. Once participants or their nominated consultee had provided consent or assent, respectively, their mental capacity was assessed using Abbreviated Mental Test Score (AMTS) for study purposes.

To evaluate the screening process (total number of patients screened and reasons for exclusion) and ensure age and gender of those taking part were comparable to those not taking part in the study, a screening log was kept up to date during recruitment. Participants were free to withdraw from the study at any time without giving a reason.

Those participants that either declined to take part or withdrew from the research study were be given the opportunity to discuss/ inform the researcher of their reasons.

In both study groups the researcher was introduced to eligible patients and their consultees by either a trained ward nurse or TVN only after receiving initial verbal consent from the respective patients or their consultee. The researcher then discussed the full study details with the potential participants and their consultees and provided them with appropriate study information sheets as specified below.

5.6.2 Informed Consent

With the help of the treating clinicians, eligible patients' mental capacity was assessed by the researcher before obtaining written informed consent. Patients deemed to have mental capacity were provided with both verbal and written patient information sheets (PIS – attached in Appendix 8) about the study, given time to consider the information and discuss with their families or treating clinicians. Potential participants were given as long as they needed to consider the information, however, they could only be recruited into the study during their hospital admission. Potential participants were asked to provide written informed consent to participate in the study; taking part in the study was completely voluntary. If a patient, for whatever reason, was unable to provide written consent, provisions were made available to obtain recorded verbal consent using an encrypted recorder provided they agree to be recorded; however, this was not necessary for this study.

5.6.3 Consultee Declaration

This study intended to recruit all eligible patients regardless of their mental capacity. Patients may lack capacity due to cognitive impairing conditions including different types of dementia (Alzheimer's disease, Lewy body and vascular disease) and

Parkinson's disease with associated cognitive impairment. These conditions are progressive, and current treatments can only slow down and manage symptoms; it is inevitable that patients living with these conditions will not get better (Arvanitakis et al., 2019; Mitchell et al., 2009). Previous HPU studies, have reported participant median age ranges of 70-85, in addition the risk of developing PUs increases with age (Coleman et al., 2013; McGinnis and Stubbs, 2014; Meaume and Faucher, 2008; Twilley and Jones, 2016). At least one in six of over-80s are reported to be living with some form of dementia and the numbers are expected to rise with the aging population. People with dementia have been reported to have a higher PU prevalence, furthermore, having a PU significantly reduces their median survival time compared to those without dementia and a PU (Jaul and Meiron, 2017). Altered mental status is more common in the elderly the population more likely to be at risk of PU (Alzheimer's Society, 2024; Campbell et al., 2010; Sayar et al., 2009). Therefore, excluding this group of patients would skew the data and the findings of the study would not be widely generalizable. Patients that lack the capacity to consent are underrepresented in research which denies them evidence-based care and perpetuates health inequalities (Matsuda et al., 2016; Shepherd, 2020). Also, evident from the literature review (presented in Chapter 2) is a lack of evidence on the impact of HPUs in patients with cognitive impairment, thus including this underrepresented group in this research study would further HCPs' understanding and consequently result in improvements in their care.

NICE guidelines for dementia state that people with dementia should not be excluded from any services because of their diagnosis or age (National Institute for Health and Care Excellence, 2018), and this is particularly important in research to ensure that results are generalisable to people with such conditions. The public involvement group

was also consulted on this issue and agreed that it was paramount for this vulnerable group of patients to be represented in this research. This study was therefore granted ethical approval under the Mental Capacity Act (2005).

For patients deemed to lack the mental capacity to provide informed consent, effort was made to involve them as much as possible. In accordance with the Mental Capacity Act 2005, where a patient lacks the capacity to consent for themselves, agreement to include the patient in the study was sought from an appropriate consultee.

Consultees can either be personal or nominated depending on the patient's circumstance; this can be anyone who has a personal relationship with the patient but is not involved in their welfare for financial benefit or involved in research. Examples of suitable people who might act as a personal or professional consultee as guided by the legal framework are family members, carers, friends, or a court nominated deputy who has a personal relationship with the patient, treating doctor or general practitioner (GP) (Mental Capacity Act, 2005). However, according to the initial NHS REC approval personal consultees could only be involved in the study through face-to-face consultation.

A personal consultee (relative or friend) was the first point of call, where available they were provided with study information, given the opportunity to consider information and ask questions. They were asked to consider the patient’s wishes and beliefs before they lost their cognition. If the researcher was unable to identify a personal consultee, an appropriate HCP (nominated consultee) involved in the patient’s care was identified to advise the researcher**.** This process presented a challenge for the researcher as it was not always possible to meet with identified personal consultees

within hospital settings. Following a successful substantial protocol amendment, the recruitment process changed to the one described in the substantial amendment section. Should participants regain capacity during the study period they would have been provided with study information and asked to provide consent should they wish to continue in the study. The participant would be free to withdraw at this point should they wish to. However, for this study none of the patients regained their capacity in the duration of the study.

Participant consent, personal or nominated consultee agreement were documented in patient records. Copies of patient information signed consent/declaration forms were given to participants/ their consultee and filed in their medical records. Only at this point were study related procedures undertaken. Treating clinicians and participant's General Practitioner (GP) were informed that their patient was taking part in the proposed research study through discussion and a GP letter (attached in Appendix 9). The researcher always acted with compassion and in the participant's best interest.

As part of this research study any concerns identified around patient safety and care were discussed with the treating team and reported to the Safeguarding team as appropriate following the trust's safeguarding policy.

5.6.4 Substantial amendment 1.0

Between July 2018 to January 2019, the research study experienced poor recruitment rates which were attributable to:

1. High exclusion rates based on patients not being able to complete a DUS assessment.
2. Matching controls to cases based on ±1 year age range limited the recruitment process and made the screening process laborious for the researcher. Due to the

research project being part of doctoral studies the researcher was the only person involved in consenting and other study processes.

3. An initial ethical application approval was only granted on the condition that personal consultees (for potential participants unable to provide informed consent) could only be consulted whilst visiting their relation in hospital, however this proved to be difficult as either relatives were not visiting regularly, or they tended to communicate with the treating clinicians via telephone. In this instance where there was a known relative or next of kin clinicians were reluctant to act as nominated professional consultees. As a result, potential participants missed opportunities to take part in the study.

To ensure the study sample was representative of the target population and maximise generalisability of study findings, it was necessary to seek a substantial protocol amendment. This was approved in March 2019; since then, potential participants were screened and recruited as described below.

Initially, all potential participants were screened against inclusion criteria (1) and exclusion criteria (1) to assess their eligibility for a Doppler ultrasound assessment which was used to diagnose peripheral arterial disease (PAD) (a potential risk factor for developing HPU). However, if these potential participants declined to take part in the research study because they did not want to complete a DUS assessment, they were given the opportunity to take part in the study without completing the DUS assessment.

Potential participants that met exclusion criteria (1) were further assessed against exclusion criteria (2), based on the result of this screening assessment they were

either approached to take part in study without the need to complete a DUS assessment or excluded from the study completely.

Screening of potential cases continued to be undertaken by TVNs and researchers. Potential participants without HPUs (control) were identified and screened by the researcher with the help of ward nurses against the eligibility criteria described below.

Inclusion criteria (1)

- Admitted to UHCW for treatment.
- Patients aged 18 years and above.
- *Cases*-Patients with stage 2, 3, 4, unstageable HPU or DTI (NPUAP PU classification criteria which was fully adopted in April 2019 at the research site, (see Appendix 1 for full details).
- *Controls*- patients without HPUs and not meeting the exclusion criteria (were matched to cases based on gender, EoL status, mental state, and age groups (i.e., 18-19; 20-24; 25-29; 30-34; 35-39;40-44; 45-49; 50-54; 55-59; 60-64; 65-69; 70-74; 75-79; 80-84; 85+))

Exclusion criteria (1)

- Patients under 18 years old
- Patients in their last days of life as advised by the medical or nursing team.
- Patients unable to lie flat for 90 minutes due to cardiac disease or shortness of breath.
- Patients with deep vein thrombosis due to risk of pulmonary embolism
- Patients that are unable to sufficiently comprehend English to provide informed consent.

- Patients unwilling to provide written informed consent.

Exclusion criteria (2)

- Patients under 18 years old
- Patients in their last days of life as advised by the medical or nursing team.
- Patients that are unable to sufficiently comprehend English to provide informed consent.
- Patients unwilling to provide written informed consent.

Participants meeting inclusion and not exclusion criteria (1) who provided informed consent completed a Doppler ultrasound assessment as part of the research study. Those meeting inclusion and not exclusion criteria (2) were not required to complete a Doppler ultrasound assessment as part of the research study. All other study procedures I.e. recruitment, consenting and data collection processes were the same for all participants. All participants continued to receive standard care as per hospital policy.

Potential participants that satisfied inclusion criteria (1) and not exclusion criteria (1) were provided with patient/consultee information sheets (1) (see Appendix 10) which included information on the Doppler ultrasound assessment.

Potential participants that satisfied inclusion criteria (1) and not exclusion criteria (2) were provided with patient/consultee information sheets (CIS) (2) (attached in Appendix 11) which did not include Doppler ultrasound assessment information.

The consenting and recruitment process was as specified in section 5.4.3.2. In addition, following the substantial amendment, if the researcher was unable to meet with an identified personal consultee within the hospital setting, an appropriate HCP

(nominated consultee) involved in their care was identified to advise the researcher on whether the patient could take part in the study**.** If a personal consultee became contactable later, they would be provided with study information for their consideration and advise the researcher on the patient's wishes and beliefs before they lost their cognitive ability.

All study documentation involved in recruitment (PIS/CIS, consent forms, consultee declaration forms, GP letters) is outlined in Appendices 6 to 11. The substantial amendment also reflected General Data Protection Regulations changes that came into force in 2018.

5.7 Research Aims and objectives

5.7.1 Aim

The overarching aim of the study is to identify and quantify the relationship between risk factors and heel pressure ulcers (HPUs) presence and investigate their impact on health-related quality of life (HRQoL) and prognostic value in EoL.

5.7.2 Objectives

4. Identify the risk factors associated with HPU development and quantify their relationship.
5. Investigate the effect of HPUs on health-related quality of life (HRQoL) at baseline, 3 and 6 months.
6. Determine the prognostic value of HPUs in EoL.

5.8 Phase 2: Risk Factors for Heel Pressure Ulcer Presence (Matched Case Control Study).

Phase 2 of the study is a matched case control study design aimed at identifying and quantifying the relationship between risk factors and HPU development. Cases were hospitalised patients with HPUs (category 2, 3, 4, unstageable and deep tissue injury (DTI)) regardless of their origin (community or hospital acquired) and controls were patients from the same hospital without HPUs as presented in section 5.4. Participants were matched based on age, gender, EoL status and mental state of recruited cases. Age was initially matched to the nearest ±1 year period in controls, after March 2019 this was amended to 5-year gap age groups as described in section 5.4.3.4.

EoL was defined as the last year of life according to the NICE guidelines (National Institute for Health and Care Excellence, 2018) and participants' end of life status was assessed using the Supportive and Palliative Indicators Tool (SPICT) as recommended by the National Gold Standard Framework (GSF) for EoL (National Gold Standards Framework Centre, 2024; NICE, 2017).

For the purposes of this study a potential participant were be deemed to lack capacity in relation to their care, treatment, or research if at the material time they were unable to decide for themselves because of an impairment of, or a disturbance in the functioning of, the mind or brain as defined in the MCA (2005). Mental capacity assessment within clinical practice is based on whether the patient can understand the information relevant to the decision, to retain that information, to use or weigh that information as part of the process of making the decision, or to communicate his decision, as stipulated in MCA 2005 Section (3). Initial mental capacity status for the purposes of matching during recruitment was based on clinical opinion or previous

formal diagnosis of cognitive impairment. Once participants had provided consent, their mental capacity was assessed using Abbreviated Mental Test Score (AMTS).

5.8.1 Primary Outcome

- To estimate the odds ratio (ORs) for risk factors associated with HPU presence (for example, diabetes, and peripheral arterial disease (PAD)).

5.8.2 Secondary Outcomes

- Estimate the proportion of community acquired and hospital acquired HPU amongst the case study group.
- Investigate the relationship between HPUs and PAD as diagnosed using a Doppler ultrasound assessment.
- Establish whether there is a relationship between PAD severity as diagnosed using DUS and HPU.

5.9 Phase 3: Heel Pressure Ulcers: Their Impact on Health-Related Quality of Life and Prognostic Value in End of Life (Prospective Cohort Study)

Phase 3 of the study (prospective cohort design) was a follow-up of the study population recruited in phase 2, therefore research setting, and sample size were the same as phase 2. Phase 3 was divided into two as explained below.

5.9.1 Phase 3a: The impact of Heel Pressure Ulcers on Health-Related Quality of Life and Associated Pain

Phase 3a was aimed at investigating the impact of HPUs on HRQoL as defined by the EQ-5D-5L questionnaire by following-up participants at 3 and 6 months after recruitment. The study population was divided into cases and controls as defined in section 5.4.

5.9.2 Primary Outcomes

- Compare Health related quality of life between cases and controls at 6 months post recruitment.

5.9.3 Secondary Outcomes

- Estimate differences in the HRQoL between patients with HPUs compared to those without pressure ulcers as measured using the EQ-5D-5L questionnaire at 3 months.
- Estimate average pain score experienced by participants with heel pressure ulcer as measured using NRS or PAINAD at 3 and 6 months.

5.9.4 Phase 3b: The Prognostic Value of HPUs in End of Life

Phase 2b was aimed at investigating the prognostic role of HPUs in EoL by following up participants for survival at 3 and 6 months after recruitment.

5.9.4.1 Primary Outcomes

- Compare survival rates between cases and control at 6 months.

5.9.4.2 Secondary Outcomes

- Estimate and compare death rates at 3 months for cohort study cases and controls.

5.10 Study Assessments, Management, and Storage

Table 5-2 below, summarises the information collected at different assessment time points for each participant throughout the study. Further details can be found in study case report forms (CRFs) attached in Appendices 12-18.

Table 5-2 Study assessments timeline

Study assessment	**Phase 1**	**Phase 2 (follow-up)**	
	Baseline	**3-month**	**6-month**
Eligibility assessment	X		
Contact details	X	X	
Age	X		
Gender	X		
Smoking Status	X		
Ethnicity	X		
Abbreviated Mental Test Score (AMTS)	X		
Waterlow Score	X		
Braden Score	X		
[$]Location of PU	X	X	X
End of Life status	X		
Blood results (Hb, Albumin, cholesterol level - LDL)	X		
Medication	X	X	X
Comorbidities	X	X	
[$]Severity of HPU	X		X
HPU photograph	X		
Doppler ultrasound assessment	X		
EQ-5D-5L	X	X	X
Pain Assessment (NRS/ PAINAD)	X	X	X
Peripheral neuropathy assessment	X		

Study assessment	Phase 1	Phase 2 (follow-up)	
	Baseline	3-month	6-month
New HPU		X	X
[$]Healthcare professional input		X	X
[$]Treatment specific to HPUs	X	X	X
Deceased		X	X

$Only applicable to participants with a HPU

Assessments were the same across both cases and controls except for assessments related to HPUs and those not eligible for a Doppler ultrasound assessment. Two separate CRFs were available for the study at each assessment point to accommodate participants deemed to lack mental capacity. For participants lacking capacity their questionnaire booklet included a proxy version of the EQ-5D-5L and PAINAD – a tool used for pain assessment in people with dementia or cognitive impairment. Both were completed by the relevant consultee or nominated carer. In this study, pain assessments were completed by the researcher with the help of the treating team whilst participants were in hospital and their caregivers once discharged from the hospital.

5.10.1 Baseline Assessments

Baseline assessments were carried out soon after written informed consent, personal or nominated consultee agreement has been obtained. Where possible, information was retrieved from medical and or nursing records and other readily available health record databases (Clinical Results Reporting System (CRRS), VitalPac databases).

Wound assessment for cases was also completed at baseline or recorded from TVN notes if the patient's wound dressing had just been completed on the day of

recruitment. PU categorisations were confirmed by either a TVN or the researcher. All study participants continued to receive standard treatment; Doppler ultrasound and neuropathy assessments were the only additional assessments that required physical involvement for study participants.

5.10.2 Doppler Ultrasound Assessments

Vascular disease including PAD has been identified as a potential risk factor in the development of HPU according to the findings of the systematic literature review reported in Chapter 3. It was therefore the aim of this study to explore this relationship further. Doppler ultrasound (DUS) assessments performed using a handheld machine have been approved as a safe and reliable tool with high sensitivity in diagnosing PAD (NICE, 2020).

Ankle Brachial Pressure (ABP) measurements are useful for assessing the adequacy of overall arterial circulation to the legs. The brachial arterial pressures are used as systemic pressure estimates, as disease in the arms are relatively rare compared to leg arterial disease. The test uses the fact that there is a pressure drop across a significant stenosis. The researcher had the training and experience of completing DUS assessments and as such was responsible for performing DUS on all study participants that had agreed to complete this assessment, unless they had recently completed one with the hospital vascular laboratory and their results were accessible to the researcher.

In instances where patients had leg ulceration or lower limb surgery and could not tolerate ankle blood pressure assessments due to discomfort, toe pressures were performed instead. Diabetic, renal, and oedematous patients are more difficult to assess as they sometimes have calcified and hence incompressible arteries, which

may result in overestimation of the pressures within these arteries (Potier et al., 2009; Williams et al., 2005). In these patients' waveform analysis, pole test, toe pressures or duplex scan may be useful in addition to ankle brachial pressures (ABP) (Normahani et al., 2021; Vriens et al., 2018). For the purpose of this research, only toe-brachial pressures (TBP) were collected instead of ABP as deemed appropriate to minimise the burden of patients already unwell and affected by HPUs. ABP Index (ABPI) and TBP Index (TBPI) measurements were assessed following NICE (2020) guidelines using a handheld DUS kit purchased from Huntleigh Healthcare Ltd, which was also the recommended device to use within the study centre.

Participants were required to lie flat using one pillow and rested for at least 20 minutes in supine position before they could have their DUS assessments. This resting period allows the hydrostatic pressures to reach equilibrium and reduces false negative results (Vowden and Vowden, 2001). Systolic blood pressure (SBP) was measured manually using an appropriately sized cuff in both arms and ankles/ toes. An 8 MHz DUS was used to take manual measurements of SBP of the posterior tibial, dorsalis pedis, peroneal arteries, and a photoplethysmography probe was used to measure SBP on toe capillaries as appropriate. Where possible pedal pulses were palpated, and Doppler waveforms were also recorded. The assessment was anticipated to take up to one and a half hours depending on the ease of locating the participant's pulses.

Some participants experienced discomfort or became restless during the procedure and the researcher had to discontinue the assessment; therefore, these participants had no ABPI/TBPI data collected. Results of the DUS assessment were shared with their treating team in hospital and GP with recommendations for further investigations and treatment as appropriate.

5.10.3 Peripheral Neuropathy Assessment

Peripheral neuropathy on both feet was the only other additional assessment that was not standard practice for all inpatients. For this study, peripheral neuropathy assessment was performed as follows:

- A 10-gram monofilament needle was used.
- Sites tested were 1st, 3rd 5th toe, plantar surface at base of each of previous toes and middle of heel pad. A cross or tick represents the presence or absence of absent peripheral neuropathy on the study CRF documentation.
- The researcher demonstrated the monofilament test on the patient's hand and asked the patient to close their eyes for the assessment of their feet.
- The approach, skin contact and departure of the filament was undertaken in approximately 1.5 seconds.
- The researcher applied sufficient pressure to cause the filament to bend.
- The filament was not allowed to slide across the skin or make repetitive contact at the test site.
- The researcher randomly selected the test sites and time between successive tests to reduce the potential of the participant guessing.
- The participants were asked to respond ‘yes’ whenever they felt the filament.
- The filament was applied along the perimeter of and not on ulcer site, callus, scar, or necrotic tissue
- Monofilaments were not used in more than 10 patients in one session and should be left for 24 hours to recover.

Peripheral neuropathy was considered present if there was a negative response in 2 or more test sites or the participant was unable to complete the assessment due to

cognitive impairment. All neuropathy assessments were completed by the researcher whilst the participants were still in hospital.

5.10.4 Follow-up Assessment

Follow-up assessments were performed at 3 and 6 months from consent date ±4 weeks. Follow-up data was mainly for phase 3 of the study to ascertain participants HRQoL and survival data for both study groups. Proxy questionnaires were completed by a nominated consultee or nursing, or care staff as nominated by the consultee, for participants that were not able to complete questionnaires follow-up assessments due to cognitive impairment. To ensure minimum missing data and loss to follow participants were followed up where possible in person during their hospital stay or outpatient follow-up appointment. Alternatively, participants were offered telephone follow-ups at an appropriate date and time as identified by both the researcher and the participant or their nominated person. Community based treating clinicians were also contacted for follow-up data including HPU progress and treatment with permission from participants or their consultees.

Data collected at both 3- and 6-months follow-up is highlighted in Table 5-2 above, which included presence of new HPU or any other PU, and severity of HPUs. With the support of the researcher, participants or consultees completed appropriate study questionnaire booklets similar to the ones completed at baseline.

5.11 Data Collection and Storage

5.11.1 Completion of Case Report Forms (CRFs)

Case report forms (CRFs) were designed by the researcher in conjunction with the supervisory team and other HCPs (as described in section 5.3) (copies attached in Appendix 12-18). These were used in data collection and only the researcher was

involved in the data collection process throughout the study. Data collection spanned from July 2018 to September 2020. All efforts were made to minimise missing data, where appropriate attempts were made to collect study data from other NHS trusts (such as community trust) for study participants with their consent.

Data recorded on predesigned CRFs was entered on an excel spreadsheet by three research associates who had been trained by the researcher. The research associates kept strict diaries of any missing data, comments or issues which were addressed by the researcher at a later date. During analysis all data was also investigated for any outliers; if outliers were identified the appropriate data was cross checked against the medical records and amended as appropriate. After all data had been collected and entered, a random 10% of the CRFs were checked against the excel spreadsheet data for quality assurance by the researcher.

5.11.2 Data Management and Storage

All data collected was anonymised at baseline and all study participants were allocated a unique study number. Personal data collected was handled and stored in accordance with the General Data Protection Regulation (2016), participating Trust and University standard operating procedures. Participation in the study remained confidential unless the researcher had any safeguarding concerns. All data recorded on paper, such as consent forms, were stored onsite either at the participating Trust or University within buildings with restricted access. All electronic data was stored securely on university servers and was archived according to the university policy.

5.12 Statistical Analysis Plan

All statistical analysis and sample size calculations were performed using STATA 13.1 (2013) or latest version.

5.12.1 Baseline Characteristics

Descriptive analysis was used to summarise baseline data by study groups, the whole study population and any differences identified were reported accordingly. The differences were assessed using appropriate statistical tests depending on the type of data (chi-squared test, t-test). Hypothesis tests were two-sided and considered to provide evidence for a significant difference if p-values are less than 0.05 (5% significance level). The null hypothesis considered was that there was no difference between cases and controls for each of the listed variables. Table 5-3 to Table 5-8 outline the study data, how it was derived and the appropriate statistical tests.

Table 5-3 Summary of types of analysis performed on demographic and vital assessments data

Variable; summary statistic	**Derivation**	**Estimate difference; Statistical tests**
Age (years); Median (Range)	Age on admission; calculated from date of birth as reported in medical notes	Mean difference (standard deviation (sd)); t-test
Gender (Female); n (Percentages)	As reported in medical notes	Odds Ratio; Chi-square test
Ethnicity; n (Percentages)	As reported in medical notes	Odds Ratio; Chi-square test
Weight (kg); Median (Range)	On admission as reported in medical nursing	Mean difference (sd); t-test
Height; Median (Range)	On admission as reported in medical nursing	Mean difference (sd); t-test

Variable; summary statistic	**Derivation**	**Estimate difference; Statistical tests**
BMI; Median (Range)	Calculated from weight and height recorded on admission	Mean difference (sd); t-test
Pulse rate; Median (Range)	Reported in medical nursing on date of admission	Mean difference (sd); t-test
BP (systolic and diastolic); Median (Range)	Reported in medical nursing on date of admission	Mean difference (sd); t-test
Oxygen saturation; Median (Range)	Reported in medical nursing on date of admission	Mean difference (sd); t-test
AMTS; Median (Range)	Assessed on recruitment using AMTS tool	Mean difference (sd); t-test
Smoking status; n (Percentages)	As reported by participant/consultee on recruitment	Odds Ratio; chi-square test
Comorbidities (Yes); n (Percentages)	As reported in medical nursing on date of admission	Odds Ratio; chi-square test
Medication (Yes); n (Percentages)	As reported on medication administration records on recruitment	Odds ratio; chi-square test

Variable; summary statistic	**Derivation**	**Estimate difference; Statistical tests**
Reason for admission	As reported in medical and nursing on date of admission	Odds ratio; chi-square test
Peripheral neuropathy assessed on feet (Yes); n (Percentages)	As assessed on recruitment	Odds Ratio; chi-square test
Braden Scale; n (Percentages)	As assessed on recruitment	Odds Ratio; chi-square t-test

Table 5-4 Summary of analysis techniques used on haematological measurement data.

Variable	**Derivation**	**Statistical tests**
Haemoglobin (Hb); Median (Range)	On admission ± 3 months as reported on CRRS	Mean difference; t-test
Albumin; Median (Range)	On admission ± 3 months reported on CRRS	Mean difference; t-test
Pre-albumin; Median (Range)	On admission ± 3 months reported on CRRS	Mean difference (sd); t-test
Cholesterol level (LDL); Median (Range)	On admission ± 3 months reported on CRRS	Mean difference (sd); t-test
HbA1; Median (Range)	On admission ± 3 months reported on CRRS	Mean difference (sd); t-test

Table 5-5 Summary of analysis techniques used on vascular assessments data.

Variable	**Derivation**	**Statistical tests**
Pale limb (Yes); n (Percentages)	As assessed on recruitment	Odds Ratio; chi-square test
Hairless limb (Yes); n (Percentages)	As assessed on recruitment	Odds Ratio; chi-square test
Cold/cool limb (Yes); n (Percentages)	As assessed on recruitment	Odds Ratio; chi-square test
Ulcer with a punched-out appearance (Yes); n (Percentages)	As assessed on recruitment	Odds Ratio; chi-square test
Claudication (Yes); n (Percentages)	As assessed on recruitment	Odds Ratio; chi-square test
Night leg pain (Yes); n (Percentages)	As assessed on recruitment	Odds Ratio; chi-square test
Capillary refill (Yes); n (Percentages)	As assessed on recruitment	Odds Ratio; chi-square test
Dry skin (Yes); n (Percentages)	As assessed on recruitment	Odds Ratio; chi-square test
Scaly skin (Yes); n (Percentages)	As assessed on recruitment	Odds Ratio; chi-square test
Ankle flare (Yes); n (Percentages)	As assessed on recruitment	Odds Ratio; chi-square test

Skin Staining (Yes); n (Percentages)	As assessed on recruitment	Odds Ratio; chi-square test

Table 5-6 Summary of analytical technique used on Doppler ultrasound assessment data

Variable	**Derivation**	**Statistical tests**
Dorsalis Pedis pulse palpable (Yes); n (Percentages)	As assessed on recruitment	Odds Ratio; chi-square test
Posterior Tibia palpable (Yes); n (Percentages)	As assessed on recruitment	Odds Ratio; chi-square test
Peroneal palpable (Yes) n (Percentages)	As assessed on recruitment	Odds Ratio; chi-square test
Dorsalis Pedis Waveform; n (Percentages)	As assessed on recruitment	Odds Ratio; chi-square test
Posterior Tibia Waveform; n (Percentages)	As assessed on recruitment	Odds Ratio; chi-square test
Peroneal Waveform (Yes); n (Percentages)	As assessed on recruitment	Odds Ratio; chi-square test
Dorsalis Pedis Pulse Pressure; Median (Range)	As assessed on recruitment	Mean difference; t-test
Posterior Tibia Pulse Pressure; Median (Range)	As assessed on recruitment	Mean difference; t-test
Peroneal Pulse Pressure; Median (Range)	As assessed on recruitment	Mean difference; t-test

Variable	Derivation	Statistical tests
Dorsalis Pedis ABPI; Median (Range)	As assessed on recruitment	Mean difference; t-test
Posterior Tibia ABPI; Median (Range)	As assessed on recruitment	Mean difference; t-test
Peroneal Pulse ABPI; Median (Range)	As assessed on recruitment	Mean difference; t-test
Toe Pressure; Median (Range)	As assessed on recruitment	Mean difference; t-test
TBPI; Median (Range)	As assessed on recruitment	Mean difference; t-test

Table 5-7 Summary of wound assessment data: derivation and summary statistics

Variable	Derivation	Summary statistic
Size	As assessed on diagnosis by TVN and reported in nursing notes or on recruitment.	Mean (sd)
Category 2 3 4 DTI Unstageable	As assessed on diagnosis by TVN or researcher and reported in nursing notes or on recruitment.	Frequency (%)

Variable	Derivation	Summary statistic
Wound bed appearance	As assessed on diagnosis by TVN and reported in nursing notes or on recruitment	Frequency (%)
Wound exudate	As assessed on diagnosis by TVN and reported in nursing notes or on recruitment	Frequency (%)
Wound infection	As assessed on diagnosis by TVN and reported in nursing notes or on recruitment	Frequency (%)
Wound dressing applied to ulcer	As assessed on diagnosis by TVN and reported in nursing notes or on recruitment	Frequency (%)
Condition of surrounding skin	As assessed on diagnosis by TVN and reported in nursing notes or on recruitment	Frequency (%)

NB- this data was only applicable to cases-those with heel pressure ulcer(s).

5.13 Phase 2: Risk factors Associated with HPU Presence (Matched Case Control Study).

5.13.1 Primary Objective and Analysis

This study was exploratory with a primary aim of identifying independent risk factors associated with the presence of HPU and estimate their relationship using odds ratio (ORs). Diabetes, PAD, mobility, nutrition (as measured using the Braden Scale) and Braden scale are amongst the risk factors to be investigated as identified from a SLR reported in Chapter 3.

There are several ways of estimating effect size from matched case control studies, including calculating unadjusted odds ratio or using logistic regression modelling techniques to calculate adjusted effect estimates (Pearce, 2016). An inherent characteristic of any observational studies including matched case controls is their inability to fully adjust for all confounding factors (Munnangi and Boktor, 2023; Song and Chung, 2010). Matching cases to controls at design stage is one way of adjusting for known confounders; for this thesis for instance, cases and control were matched 1:1 based on age, gender, mental and EoL status, however other unknown confounders may still exist. Therefore, using unadjusted OR analysis may result in overestimation of effect size. Logistic regression analysis was better suited for this type of data as it allowed for the adjustment of confounders. Although the study design was matched case control, unconditional logistic regression was found to be best suited for this study data due to the exploratory nature of the study. Unconditional logistic regression was used to estimate the odds of having a HPU for each of the identified risk factors before and after adjusting for other independent variables.

The population for the primary analysis included all cases and controls with baseline data available at time of analysis. Participants with missing data were excluded from analysis as reported in Chapter 6. Participants were considered as cases if they had a cat ≥ 2 HPU at baseline; participants with HPUs on both limbs were counted as one event. For the logistic regression only participants without missing data for risk factors being investigated were entered into the model. STATA was the software of choice, as it performs complete case analysis.

5.13.2 Modelling Process

A list of potential covariates was compiled based on the findings from the systematic literature review reported in Chapter 3. These included diabetes, vascular disease,

PAD, Braden Scale subdomains, mechanical ventilation, and surgery; factors previously identified as significant factors for HPU (Dube et al., 2022), further details on how the variables were defined are discussed below. Univariate analysis was first performed with each variable that had a p-value ≤ 0.1 following analysis with either a chi-square test or t-test; this gave an OR, a 95% confidence interval (CI) and p value (statistical significance). Collinearity of variables that were significant at $p<0.1$ was investigated; further investigation was also carried out for those variables found to be correlated. Final decision on which variable to use was based on clinical significance and missing data less than 5%. A composite factor variable was created for variables found to be significantly correlated at 5% level. No weighting was applied while creating a composite factor due to lack of evidence to inform the process. A composite factor was created by adding together the values of the correlated variables. A multivariate logistic model was fitted for a selected group of variables at baseline which were selected using chi 2 or test followed by univariate analysis.

There are two methods of selecting variables for a model, which are either automated or manual. Automated variable selection relies on a computer program to conduct multiple testing of several variables together against a pre-specified significance level; variables are then either added or removed (forward or backward selection) from the model. However, this method can produce misleading results (narrow CI and exaggerated coefficient values) (Heinze et al., 2018). With the manual method the investigator is more in control and can use prior knowledge to inform the model selection process. Given the explorative nature of the study, a manual method was chosen as the researcher had prior knowledge of potential risk factors from the SLR; p=0.1 was used as a cut off value for selection of factors included in multivariable analysis. Table 5-8 Summary decisions made for matching variables and risk factors.

summarises decisions made for matching variables and risk factors considered in univariate and multivariable analysis; age, gender mental status and EoL status were used as matching variables. Only variables with p-values ≤ 0.05 were entered into the final model; effect estimate, 95%CI and p-values were reported for each of the variables.

Table 5-8 Summary decisions made for matching variables and risk factors.

Variable	**Derivation**
Age	Age on admission to hospital was taken from the date of birth in the medical records. Matching variable
Gender	This was taken from medical records. Matching variable
Mental Status	At time of recruitment this was based on clinical judgement of both treating clinicians and CI. After receiving consent or consultee declaration mental status was assessed used Abbreviated Mental Test Score (AMTS) which has both been validated and found to be reliable (Hodkinson, 1972) Matching variable based on clinical judgement. For analysis purposes it was considered both as a numeric and categorical variable. Score ≤ 6 considered as cognitively impaired.
EoL	At time of recruitment this was based on the Supportive and Palliative Indicators Tool (SPICT) as recommended by GSF

Variable	Derivation
	(Gold Standard Framework). End of life was defined as being in the last year of life based on the SPICT. Matching variable based on the SPICT
Braden Scale **Domains** *Sensory perception* *Moisture* *Mobility* *Activity* *Nutrition* *Friction and Shear*	Braden Scale is one of many pressure ulcer risk assessment tools used in clinical practice; a validated and reliable tool (Bergstorm, 1987). It has six domains which were individually assessed and added together to provide a final score; completion was based on patient assessment and medical records. Each of the domains were considered as a potential risk factor for HPU development, however only domains that were identified as significant in the univariate CLR were considered in the final model selection process.
Comorbidities	As recorded in medical records
PAD	Handheld DUS was used to diagnose PAD and was carried out as outlined in the NICE guidelines. Currently there is no agreed guidance to use TBPI to diagnose PAD, so for this study this was guided by the manufacturer advice, expert opinion, and guidance from NHS trust vascular laboratory. This was then coded as PAD absent if 1.3 ≤ ABPI ≥ 0.9 or present if 1.3 >ABPI <0.9. For diabetic, CKD, oedematous patients TBPI were carried out instead due to risk of false negatives, therefore this was coded as PAD absent if TBPI is >

Variable	Derivation
	0.64 and PAD present if TBPI ≤ 0.64. DUS assessment was completed on both limbs as appropriate. Participants that could not complete a DUS for a pedal pulse, for that pulse their data was recorded as missing. In addition, DUS assessments were only completed for participants that had provided informed consent or assent provided by a nominated consultee for participants deemed to lack capacity.
Peripheral neuropathy of the feet	Assessment was completed as described in section 5.8.3. A participant was classed as having peripheral neuropathy on each of the assessed toes or heel if could not feel the mono filament needle during assessment. Also, participants were assumed to have peripheral neuropathy if they could not complete the assessment due to cognitive impairment at the time of assessment.

5.13.3 Secondary Analysis

The population of analysis were all participants without missing data for the required variable. Results were reported by the study group (case/control group) as appropriate.

- Estimate the proportion of community acquired and hospital acquired HPU amongst the case study group.

  A HPU was considered community acquired if a participant was admitted to hospital with a PU to the heel or if it developed in less than 72 hours of

admission. While a participant who developed a HPU at least 72 hours post admission was classed to have a hospital acquired HPU.

- Investigate the relationship between HPUs and PAD as diagnosed using a Doppler ultrasound assessment.

  This was to investigate whether the presence of a HPU may be a symptom of undiagnosed peripheral arterial disease. A handheld doppler ultrasound was used as the main method of assessment whilst participants with CKD or diabetes diagnosis, swollen legs, or unable to tolerate a blood pressure cuff around their legs were offered a toe pressure assessment. Only participants that met the study eligibility as stipulated in section 5.3 and participants or their nominated consultee had provided consent or assent as appropriate completed a DUS assessment. Where participants were already scheduled for an assessment within the hospital vascular laboratory as part of their standard care, the participants provided consent for the researcher to contact their physicians for the DUS results. Only participants that had no previously documented PAD history were included from both the cases and control group as part of this analysis. Participants not able to complete a DUS assessment without a PAD history documented in their medical notes were classed as missing data and consequently excluded from the analysis. Participants were considered to have PAD if they had an ABPI of 1.3 >ABPI <0.9 or TBPI ≤0.64; full categorisation criteria is specified in Table 5-9.

- Establish whether there is a relationship between PAD severity as diagnosed using DUS and HPU.

  This was only applicable to participants with a HPU at baseline or identified at follow-up and had a ABPI/TBPI measurement either as part of this study or

completed by their clinical team. Those with missing data were excluded. HPU severity was defined using EPUAP pressure ulcer staging criteria (Appendix 1) and as recorded on recruitment or time of diagnosis. PAD severity was classified using the participant with HPU on both limbs, each limb was counted as a separate event with its respective DUS assessment result. Chi-squared test was used to investigate the relationship between HPU and ABPI/TBPI severity, chi-squared statistics and p-values were reported.

Table 5-9 ABPI/ATPI severity categorisation

Severity	**ABPI**	**TBPI**
Normal	0.9> ABPI <1.3	>0.7
Mild	0.8≥ ABPI ≤0.9	0.64≥ TBPI ≤-0.7
Moderate	0.5≥ ABPI <0.8	0.4 <TBPI≤0.64
Severe	ABPI <0.5	≤0.4

5.13.3.1 Sensitivity Analysis

Participants without PAD DUS assessment were recorded as missing for the PAD variable unless they had a previous diagnosis noted in their medical records. To ascertain the impact of the missing data two separate analysis were carried out as follows:

- Assuming all those with a missing PAD diagnosis had a PAD
- Assuming all those with a missing PAD diagnosis did not have PAD

The intention was to rerun the final model using the two-dataset based on the above assumptions to investigate the impact of missing data. However, this was not done as PAD was not in the final model.

5.14 Phase 3: Heel Pressure Ulcers: Their Impact on Quality of Life and Prognostic Value in End of Life (Prospective Cohort Study)

Phase 3 was a prospective cohort study involving the participants that were recruited in phase 2 of this thesis with data collection at 3- and 6-months post recruitment. This phase was subdivided into two sections and data analysed as described below.

5.14.1 Phase 3a: The Impact of Heel Pressure Ulcers on Health-Related Quality of Life and Associated Pain.

Phase 3a was aimed at exploring the impact of heel pressure ulcers (HPUs) on health-related quality of life and their associated pain using a prospective cohort study design and following participants up to six months post recruitment in the study. All summaries will be presented by study group (that is, case (participants with HPUs) and control group (participants without HPUs)).

5.14.1.1 Primary Objective and Analysis

The primary objective of Phase 3a was to compare the health-related quality of life (HRQoL) between participants with HPU and those without as measured using EQ-5D-5L questionnaire at 6 months.

HRQoL was assessed using the EQ-5D-5L; it is a well validated and reliable non-specific tool (Reenen and Jensen, 2015) which allowed assessment of HRQoL across study cross for comparison. The EQ-5D-5L questionnaire contains 5 levels evaluating mobility, self-care, usual activity, pain, anxiety/depression with a five –point Likert response scale ‘No problem to extremely affected’ and depression plus the visual analogy scale (EQ-VAS). It was developed and validated for use in all ages; it also provides a proxy measure for individuals who may not be able to complete the questionnaire due to cognitive impairment or being critically unwell (Reenen and

Jensen, 2015). Although proxy measures are known for not being reliable in this instance, they provided an opportunity for consultees or nominated individuals to provide their own perception on their patient / loved one's health. Results were interpreted with caution given that proxy assessments are not reliable measures of one's HRQoL. The EQ-5D-5L index-based score was generated by applying societal preference weights to each of the above five health dimensions according to a UK population-based EQ-5D VAS model (Devlin et al., 2018). In addition, a 0–100 visual scale (0-worst imaginable state of health; 100-best imaginable health state) was used to assess self/proxy-reported current health status. Results are presented as frequencies and graphs by study group and whether they were self/proxy reported.

5.14.1.2 Secondary Objectives and Analysis

- To estimate HRQoL for the study sample as measured using EQ-5D-5L questionnaire at baseline, 3- and 6- months.
- To calculate the difference in HRQoL (cases vs controls group) at baseline and 3 months

  Analysis followed the techniques described above in section 5.9.3.1.1.

- To estimate average pain score for the study sample as measured using numeric rating scale (NRS) or Pain Assessment in Advanced Dementia Scale (PAINAD) at baseline, 3 and 6 months.
- To calculate the difference in average pain scores (cases vs controls group) as measured using numeric rating scale (NRS) or Pain Assessment in Advanced Dementia Scale (PAINAD) at baseline, 3 and 6 months.

The NRS (0-no pain and 10-worst pain) was used to measure pain as reported by study participants, that is those without cognitive impairment. Pain scores were

summarised as means (sd), differences analysed using t-test and 95%CI and p-values were also reported for all three time points by study group.

In participants with cognitive impairment and not able to accurately use the NRS, the PAINAD tool was used. This tool has been validated and found reliable in this patient group (Warden et al., 2003). It uses non-verbal cues to assess pain; it has five domains and 3-point Likert scale (Breathing independent of vocalisation, negative vocalisation, facial expression, body language, consolability; 0-normal to 2 highest score reflecting worse pain). Using NRS/ PAINAD tools to assess pain has an added advantage in that it measures pain at the time of assessment, whereas EQ-5D-5L measures average pain on the day of assessment and is vulnerable to recall bias. Also, PAINAD tool provides promptings to assist with the assessment and for this study all participants were provided with a copy of the questionnaire to assist them in completing follow-up. Summary statistics (such as frequencies and means) and graphic presentations were used to report the results; differences were analysed using chi-squared tests and t-tests as appropriate.

5.14.2 Phase 3b: The Prognostic Value of HPUs in End of Life

The aim of phase 3b was to investigate if there is a relationship between HPUs presence and time to death; therefore, the primary endpoint was time to death. Time to death for all study participants was measured from date of recruitment until death. Death was defined as death from all causes for the purpose of this study and date of death was taken from medical records. Similar to phase 3a the population of analysis were participants recruited in phase 1 and followed up for survival up to six months from date of recruitment.

5.14.2.1 Primary Objective and Analysis

The primary objective was to estimate the difference between survival times for cases and control participants within a six-month follow-up period (that is, estimate and compare death rates at 6 months between case and control groups). Cox proportional hazard (PH) model was chosen as the primary endpoint was time to event with censored and survival data (Harrell and Harrell, 2015). Censoring within data occurs when either the event of interest (death) does not occur in the study duration or the time at which the event occurs is unknown due to loss to follow-up or withdrawal form study.

5.14.2.2 Modelling Process

The intentions of the study were to investigate the predictive value of HPUs in end of life for the study sample population using the Cox proportional hazards (PH) model which allows for multiple variables to be investigated at once to adjust for potential prognostic factors. In this study the prognostic factor of interest was the presence of HPU(s) as diagnosed using the EPUAP classification system initially by treating nurses and confirmed by either the researcher and or tissue viability nurses (TVNs). Other factors to be adjusted for would have included comorbidities and demographics on admission as described in Table 5-3 to Table 5-9. The Cox (PH) regression analysis assumes that the hazards are proportional. To test the proportional hazards assumption i.e., that the ratio of the hazard rate to the baseline hazard is constant, Kaplan Meier (KM) curves were plotted for each study group. PH modelling was not completed as the initial log rank test showed that there were no significant differences between the case and control group median survival times at 6-month follow-up.

5.14.2.3 Secondary Objective and Analysis

- To estimate and compare death rates between case and control group at 3 months.
- To estimate and compare median time to death between case and control group at 3- and 6-months follow-up.

Both the primary and secondary outcomes were summarised using median survival times and KM curves and cause of death was presented using frequency summaries by study group.

5.15 Study Management

The day-to-day management of the study and its progress was the responsibility of the researcher supported by the academic supervisory team at BCU and clinical staff from the NHS Trust. The researcher was responsible for ensuring the TVNs, ward and data entry staff were appropriately trained on the study processes and had access to up-to-date study documents. The study was officially completed when the last participant to be recruited had been followed up six months after recruitment.

5.16 Ethical considerations

A summary of the ethical considerations undertaken by the researcher is provided in Table 5-10 .

Table 5-10 Summary of ethical considerations

Right to approach	All potential participants were approached in a way that did not breach their right to privacy and data protection i.e., the researcher was not provided the contact details (personal identifiable data) of potential participations, without their prior

	verbal consent obtained by someone who has a right to be in contact with these individuals as part of their role.
Confidentiality and anonymity	Participation in the research was confidential; the researcher did not divulge the details of participants to anyone outside of the immediate research team (unless safeguarding issues are raised). All data collected was coded to ensure anonymity. Documents that include personal identifiable data was stored separately to the coded research data and only the research team was able to make the link between the two. This right to confidentiality and anonymity was made clear in the participant information sheet
Data Protection and Storage	The research team did abide with the General Data Protection Regulation. Both personal identifiable data and research data was stored securely. Electronic data was stored on the participating hospital and university's secure server that requires a staff log in to gain access. For personal identifiable data, files were password protected. Where data exists on paper or other physical forms, a lockable filing cabinet was utilised and stored within the facilities of the participating hospital and researcher's university.
Informed consent	All participants who are invited to join the study was provided with a participant information sheet. The potential participants were given time to consider their willingness to participate and sign a consent form for research records.

	For potential participants without mental capacity, they were included in the study process as much as possible, a personal or nominated consultee were also to be identified. Consultees were provided with study information, time to consider the information and advice the research team to whether their relation or patient should take part in the study after considering the potential participant's beliefs, values and wishes. Should they advise the research team that their relation or patient can take part in the study they were asked to sign a consultee declaration form for research records. Should participants had regained capacity during the study, they would have been provided with study information, their willingness to participate and sign a consent form for research records. However, this did not happen as none of the participants deemed to lack the capacity to consent regain it in the study period.
Right to withdraw	Two information sheets were produced, one for patients with capacity and one for appointed consultees (representing patients without mental capacity to provide consent). This informed them that if they decided to take part, they would still be free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, would not affect their continuing care (patients) or employment (health professionals).

Safeguarding	The data collected remained confidential as indicated, however, confidentiality would be breached in the event of a safeguarding issue or if criminal activities were uncovered. This was made clear in the participant information sheet prior to consent.

5.17 Summary

To meet the aim and objectives of this thesis matched case control and prospective cohort study designs were used as described in this chapter. The study population were recruited in phase 2 using a convenient sampling method and followed up to 6 months in phase 2 of the study. Data was collected from medical and nursing records and during interviews with patients. Data analysis included logistic regression and Cox proportional hazards regression models for identifying factors associated with the presence of HPUs and investigating the prognostic value of HPUs in EoL, respectively. Other analysis included HRQoL and pain assessments summaries for data collected over a 6-month follow-up period. The study design and data analysis were purposefully designed to minimise bias, particularly through recruitment and loss to follow-up. Chapter 6 presents the findings of this thesis based on the data analysis techniques used as described in this chapter.

Chapter 6 Results (Phases 2 and 3)

6.1 Introduction

As previously specified in Chapter 4, this study was divided into three phases with Phase 1 being a systematic literature review which was aimed at identifying risk factors for developing heel pressure ulcers (HPUs) in the adult population (published by (Dube et al., 2022) and reported in Chapter 3 of this thesis). Phase 2 was a matched case control study aimed at factors associated with the presence of HPUs in the adult population. Phase 3 was a prospective cohort study aimed at investigating the impact of heel pressure ulcers on health-related quality of life, and their prognostic value at the end of life. This chapter outlines the findings from phase 2 and 3 analyses as specified in Chapter 5. It begins with a summary of the screening and recruitment data including a patient flow chart illustrating the exclusion reasons. It then reports the baseline data by study groups (cases and controls) and for the whole study population. The baseline results include EQ5D-5L responses which were used to measure health-related quality of life. Three months and six months EQ5D-5L responses and survival rates are also presented by study groups. The results include descriptive summaries, estimated differences, 95% confidence intervals (CI) and p-values for tests conducted as applicable. A discussion of the results and contribution to knowledge are presented in Chapter 7 and 8 respectively.

6.2 Screening and Recruitment Summaries

Recruitment was initially planned for 24 months; however, it had to be interrupted earlier than initially planned due to government guidance on the COVID-19 pandemic which led to non-urgent and non-lifesaving research being temporarily interrupted. Therefore, screening and recruitment of the study population took place between July

2018 and March 2020 (a total of 20 months). Figure 6-1 provides an overview of the patient flow process for the duration of the study.

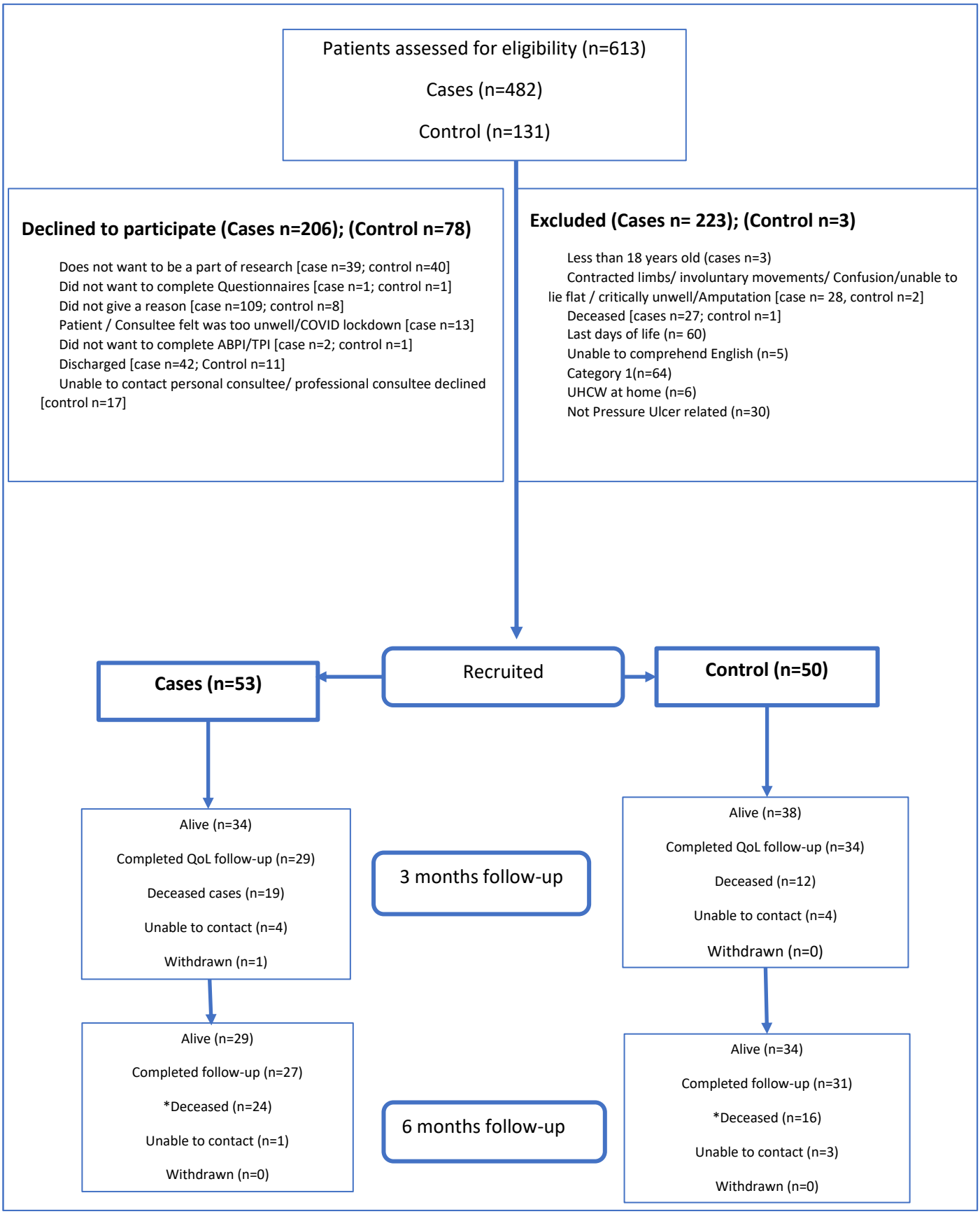


Figure 6-1 Study flow chart summarising screening, recruitment, and follow-up.

6.2.1 Screening Data Summary

In total, 613 patients were screened (those with heel pressure ulcers (HPUs) (cases n=482) vs those without HPUs (controls n=131); on average 30 patients were screened per month. Patients with HPUs were initially screened by the researcher using information reported on Datix software for patient safety, which is used for collecting and managing adverse events including HPUs, followed by a face-to-face consultation where possible. A total of 42.7% (206/482) cases were reported as declined to take part in the study; of these 72.3% (149/206) either did not want to take part in the study (26.2%; 39/149), did not want to complete study questionnaires (0.7%; 1/149), or did not provide a reason (73.2%; 109/149). A further 20.4% (42/206) of the case study population (patients with HPUs) were discharged before they could meet with the researcher to discuss or provide study consent and were therefore reported as declined to take part in the study. Discharges included those discharged home during weekends and out of hours, therefore were not screened by the researcher face-to-face. The researcher was not able to meet with the personal consultee for 14.6% (30/206) of those deemed to lack the mental capacity to provide informed consent and had an HPU. The initial study Research Ethics Committee (REC) approval required the researcher to meet with friends and families of patients deemed to lack mental capacity within hospital settings; this assumed all patients have visitors during their hospital stay. Therefore, this group of patients represented those that missed the opportunity to take part in the study due to the extra criterion imposed by the REC.

Patients with HPUs that did not meet the study eligibility criteria were excluded from taking part in this study; a total of 48.3% (223/482) patients with HPUs were excluded due to reasons described below and presented in Figure 6-1. Of the screened case population 30.6% (60/223) were excluded as they were identified as in their last days of life (<72 hours) by their treating clinicians, this was a study exclusion criterion as it was unethical to approach them and their families whilst they were going through difficult times. Another subset of the case population reported as excluded were patients with HPU(s) who died before the researcher could approach them to take part in the study, this group of patients represented 12.1% (27/223). Patients with category 1 HPUs (28.7%; 60/223) were excluded from the study according to the study eligibility criterion. Category 1 PUs are less

severe and tend to resolve within a few days to a month (Dealey et al., 2012) and within the participating site it is not mandatory to report category 1 PUs. Furthermore, category 1 PUs are more likely to be misdiagnosed and overrepresented (Kottner et al., 2009) thus were excluded from the study population.

The observed average age for screened patients was 79.3 (standard deviation (sd)-13.6), and three of the screened patients were aged over 100 years (as reported in Appendix 19). Females accounted for 62% of the total screened population. Overall recruited and non-recruited patient groups were comparable in terms of age and gender (p-values), similarly for case and control groups. Therefore, the study sample was representative of the targeted population in terms of age and gender.

6.2.2 Patient Recruitment

A total of 103 participants were recruited to take part in the study, comprising of 53 cases (those with a HPU) and 50 controls (those without HPUs). On average, five participants were recruited each month. The recruitment rate was 50% lower than the anticipated rate, due to patients or their consultee declining to take part in study activities, being discharged or deceased before the researcher could discuss the study with them. In addition, patients were excluded if they were contraindicated for a doppler ultrasound assessment or were in their last days of life as depicted in Figure 6-1. Three participants in the case group could not be matched with any controls based on their age, gender, end of life and mental capacity within the project lifetime. All participant data were included in the analysis process as applicable including the three non-matched participants' data. All recruited participants met the study eligibility as stipulated in the study protocol Chapter 5.

6.3 Study Baseline Summaries

For this thesis, all study participants for Phases 2 and 3 were recruited during Phase 3 and their baseline data was also collected in Phase 2. This section therefore presents the baseline summaries for the whole study population.

6.3.1 Participant Characteristics and Demographics

This section summarises participant characteristics and vitals as recorded on day of admission to hospital, day of assessment, or recruitment, accordingly. The average age for recruited participants was 77.9 years (sd-12.3); cases had an average age of 77.9 (11.9) and controls of 78.3 (12.4) (full results presented in Appendix 16). Over sixty percent (60%) of the total study population were females and participants living with some cognitive impairment on the day of assessment or had a formal diagnosis recorded in their medical records represented 41.7% (43/103) of the study population. Most of the study participants were of White British/Irish ethnic background (99.0%; 102/103), and 10.7% (11/103) were reported and/or documented in their medical or nursing records to be in their last year of life as defined by the Supportive and Palliative Care Tool (SPICT). Overall matching variables were comparable across the two study groups (cases vs controls) as summarised in Appendix 16.

Alcohol consumption and length of stay (LOS) (odds ratio (OR): 0.5 [95%CI 0.2; 1.2] p-value 0.07; the mean difference (MD): -39.1 days [95% CI -74.3; -3.9) were significantly different at 10% significance level. Whereas, mean differences or odds ratios for height, weight, BMI, pulse, diastolic and systolic blood pressure, oxygenation saturation, and smoking were observed not to be statistically significant at p-value= 0.1. On average the participants in the case group stayed in hospital almost twice as long as those in the control group. Further analysis using multivariable logistic regression modelling techniques was conducted with variables that achieved a p-value less than 0.1 (section 6.4 summarises findings from the multivariable analysis). The results presented in this chapter are based on unpaired data analysis (chi-squared and t-test), a sensitivity analysis using paired data analysis techniques (McNemar's and paired t-test as appropriate) found comparable results. Table 6-1 provides a summary of all participant characteristics and vital data collected as part of baseline data in Phase 2 of this study.

Table 6-1 Participant characteristics and vitals summary

Variable **Median (range)** **N (%)**	**Cases (n=53)**	**Controls (n=50)**	**Total (n=103)**	**Parameter estimate (mean difference/ odds ratio) (95% CI)**	**P-value**
Height (m)	1.7 (1.4-1.9)	1.6 (1.5-1.9)	1.7 (1.4-1.9)	0.09 (-0.03; 0.05)	0.6
Weight (kg)	65.9 (45 - 127)	65.6 (36.4 -106.2)	65.8 (36.4 - 127)	3.8 (-3.1; 10.7)	0.3
BMI (kg/m^2)	25.0 (15.6- 42.4)	25.0 (14.7- 36.2)	25.0 (14.7-42.4)	1.1 (-1.1; 3.4)	0.3
[m]Pulse (beats/min)	78.0 (50-118)	78.0 (55-110)	78.0 (50-118)	-0.2 (-5.6; 5.2)	0.9
[m]Systolic BP (mmHg)	122.0 (90-181)	128.0 (80-173)	124.5 (80-181)	-3.4 (-12.5; 5.7)	0.9
[m]Diastolic BP (mmHg)	72.0 (45-105)	75.0 (48-99)	74.5 (45-105)	-3.2 (-7.9; 1.6)	0.2
[m]Oxygen saturation (%)	97.0 (88-100)	96.0 (88-100)	96.0 (88-100)	-0.2 (-1.1; 0.7)	0.7
Smoking status					

Variable **Median (range)** **N (%)**	**Cases (n=53)**	**Controls (n=50)**	**Total (n=103)**	**Parameter estimate (mean difference/ odds ratio) (95% CI)**	**P-value**
Ex-Smoker (%)	22.0 (41.5)	21.0 (42)	43.0 (41.7)	0.9 (0.2; 4.6)	0.9
Regular Smoker (%)	5.0 (9.4)	5.0 (10)	10.0 (9.7)		
Never Smoked (%)	26.0 (49.1)	24.0 (48)	50.0 (48.6)		
Alcohol consumption status (Y %)	28.0 (52.8)	35.0 (70.0)	63.0 (61.2)	0.5 (0.2; 1.2)	**0.07***
Length of stay (LOS-days)	71.0 (15.6)	32.0 (7.5)	52.3 (9.0)	-39.1 (-74.3; -3.9)	**0.03***

m=missing data (n≤2), continuous variables -height, weight, BMI, pulse, systolic, diastolic, oxygen saturation and length of stay are presented as median and range; categorical- numbers and percentages; *variables with p-values <0.1 included in multivariable analysis.

6.3.2 Blood Test Results

Blood test data was collected for all participants based on the most recent test (3 months or less) before or since hospital admission, and at study baseline assessment. Table 6-2 provides a summary of the most recent blood tests as recorded at baseline. No pre-albumin blood test results data could be identified on the hospital system for any participants (both pre- and during hospital admission). Based on the most recent albumin and haemoglobin (Hb) blood test results, cases were observed to have significantly lower levels compared to the control group (MD: -5.7 [95% CI-8.2; -3.1], $p < 0.0001$ and -11.1 [95%CI -18.2; -4.1] $p=0.002$ for albumin and Hb respectively). In contrast, the observed difference in cholesterol levels (LDL) was not statistically significant at 10%, however, 25.2% of the LDL data was missing. In addition, haemoglobin A1 (HbA1) levels were observed not to be statistically different at 10% significance lever, however, 7.8% of the data was missing. Albumin and Hb blood results were further considered in a uni and multivariable analysis in section 6.4.

The following variables had < 8% missing data: pulse, systolic and diastolic pressure, peripheral neuropathy, Hb, albumin, and HbA1, whereas cholesterol (LDL) had 25.2% missing data. Baseline data were collected on admission to hospital or recruitment to study, blood results including cholesterol (LDL) level (highest percentage missing data) were based on the most recent recorded data either entered within three months before or on hospital admission. It is clear from the results of this study that cholesterol (LDL) level was not consistently completed given 25.2% of the participants did not have data logged in their records. The eight percent that was missing from the other variables (pulse, systolic and diastolic pressure, peripheral neuropathy) was due to participants either being aggressive during or nonconcordant with interventions, therefore the researcher was not able to obtain this data. Of the recruited participants, 48.5% (50/103) [Cases: 47.2% (25/53) and controls 50.0% (25/50)] requested to receive a lay summary of the study report. This was a mixture of patients themselves [50.0% (30/60)] or their nominated personal consultee [46.5% (20/43)].

Table 6-2 Summary of most recent blood tests as recorded at baseline.

Blood test	**Cases (n=53)**	**Controls (n=50)**	**Total (n=103)**	**Estimate Difference (95% CI)**	**P-value**
^{m}Hb	104.5 (58.0-162.0)	115.0 (82.0-158.0)	107. 0 (58.0-162.0)	-11.1 (-18.2; -4.1)	**0.002***
^{m}Albumin	29.0 (17.0-46.0)	36.0 (24.0-48.0)	33.0 (17.0-48.0)	-6.3 (-8.6; -4.2)	**<0.0001***
^{m}LDL	2.0 (0.4-5.2)	2.5 (0.9-4.2)	2.3 (0.4-5.2)	-0.1(-0.6; 0.4)	0.6
HbA1	42.5 (29-134)	42.0 (15.0-98.0)	42.0 (15.0; 134.0)	3.6 (-3.3; 10.5)	0.3

Hb-haemoglobin level; LDL-cholesterol LDL level; missing data (Hb and albumin <2%; LDL-25.2%, HbA1-7.8%); *variables with p-values <0.1 included in multivariable analysis.

6.3.3 Past Medical History and Surgery During Admission

Table 6-3 provides details of the participants medical history as reported by the participant, their consultee or recorded in their medical or nursing notes. On average, participants had five or more medical conditions reported in their hospital notes. In addition, at least 90% (43/47) of those with a formal diagnosis of diabetes mellitus had type 2 diabetes. Over 50% of the study participants had a formal diagnosis of hypertension, however, the difference between the case and control group [OR: 1.3 (0.6; 3.0), p=0.5] was not statistically significant at p-value=0.1. Eight percent of

the study population had a formal diagnosis of peripheral vascular disease (PVD) on admission; participants with HPUs (case group) were 3 times more likely to have a formal diagnosis of PVD compared to those without a HPU (control group), the observed odds ratio was not significant at p=0.1. Angina, atrial fibrillation (AF), asthma, chronic kidney disease (CKD), diabetes, and heart failure (HF) had a p-value ≤0.1, these variables were considered in a univariate and multivariable logistic regression (logistic regression summary results presented in Table 6-13).

Table 6-3 Summary of participants' medical conditions as reported in their medical or nursing records

Past Medical History Y (%)	**Cases (n=53)**	**Controls (n=50)**	**Total (n=103)**	**Estimate Difference OR (95% CI)**	**p-value**
IHD	7.0 (13.2)	12.0 (26)	19.0 (18.4)	0.5 (0.1; 1.5)	0.2
CVA	13.0 (24.5)	10.0 (20.0)	23.0 (22.3)	1.3 (0.5; 3.7)	0.6
Stroke	11.0 (20.7)	8.0 (16)	19.0 (18.5)	1.4 (0.4; 4.4)	0.5
Diabetes	33.0 (62.3)	14.0 (28.0)	47.0(45.6)	4.2 (1.7; 10.6)	**0.0005***
Type 1	2.0 (5.9)	2.0 (14.3)	4.0 (8.3)	2.5 (0.2; 38.6)	0.6
Type 2	31.0 (93.9)	12.0 (85.7)	43.0 (91.5)		
CKD	30.0 (56.6)	13.0 (26.0)	43.0 (41.8)	3.7 (1.5; 9.4)	**0.002***
Stage 3	5.0 (16.7)	6.0 (46.2)	11.0 (25.6)	-	-
Stage 4	0.0	2.0 (15.3)	2.0 (4.7)		
Stage 5	2.0 (6.7)	0.0	2.0 (4.7)		
Unknown	23.0 (76.7)	5.0 (38.5)	28.0 (65.1)		

Past Medical History Y (%)	**Cases (n=53)**	**Controls (n=50)**	**Total (n=103)**	**Estimate Difference OR (95% CI)**	**p-value**
COPD	12.0 (22.6)	8.0 (16)	20.0 (19.4)	1.5 (0.5; 4.8)	0.4
Hypertension	30.0 (56.6)	25.0 (50)	55.0 (53.4)	1.3 (0.6; 3.0)	0.5
PVD	6.0 (11.3)	2.0 (4)	8.0 (7.8)	3.1(0.5; 32.2)	0.2
Asthma	4.0 (7.6)	10.0 (20.0)	14.0 (13.6)	0.3 (0.1; 1.3)	**0.07***
Dementia	14.0 (26.4)	18.0 (36.0)	32.0 (31.1)	0.6 (0.3; 1.6)	0.3
TIA	4.0 (7.6)	3.0 (6.0)	7.0 (6.8)	1.3 (0.2; 9.2)	0.7
AF	16.0 (30.2)	7.0 (14.0)	2.0 3(22.3)	2.7 (0.9; 8.4)	**0.05***
HF	7.0 (13.2)	2.0 (4.0)	9.0 (8.7)	4.3 (0.8; 42.8)	**0.06***
Parkinson's disease	2.0 (3.8)	2.0 (4.0)	4.0 (3.9)	0.9 (0.7;13.5)	1.0
Angina	5.0 (9.4)	1.0 (2.0)	6.0 (5.8)	5.1 (0.5; 246.2)	**0.1***
Heart Attack	5.0 (9.4)	5.0 (10.0)	10.0 (9.7)	0.9 (0.2; 4.4)	0.9

PVD-peripheral vascular disease; IHD-Ischaemic Heart Disease; CVA-cerebrovascular accident; CKD-chronic kidney disease; COPD- chronic obstructive pulmonary disease; PVD- peripheral vascular disease; TIA-transient Ischaemic attack; AF- atrial fibrillation; HF-heart failure; *variables with p-values <0.1 included in multivariable analysis.

At least 12% (13/103) of the study population had a surgical procedure during their hospital stay; of these 61.5% (8/13) had surgery on one of their lower limbs (6 cases vs 2 controls). Anti-embolic stockings were only applied to 3.9% (4/103) participants with the majority being in the control group. Appendix 17 summarises the study participants' surgical and anti-embolic

stocking use data as recorded in their medical and nursing notes at the time of assessment during their hospital stay.

6.3.3.1 Composite Variables and their Link to Heel Pressure Ulcers

This section presents the results of exposure to composite variables created from comorbidities that were observed to be associated with the presence of HPUs at 10% significance level and correlated to each other. AF, angina, asthma, CKD, diabetes, and heart failure (HF) were identified as associated with the presence of HPU at 10% significance level as listed in Table 6-3. Using Chi-Square Test of Independence test results, composite variables were created for variables that were observed to have significant correlation ($p \leq 0.05$); that is a composite variable for asthma and AF and other for CKD and diabetes (see correlation coefficients reported in Appendix18). These two separate composite variables were created by adding together the values of the correlated variables. An additional composite factor was created by adding together the values of comorbidity variables that had a statistically significant association with HPU and were considered to likely affect the overall perfusion of lower limbs (that is angina, AF, and asthma). All variables used to create the composite variables were equally weighted due to lack of additional information to support the weighting process.

CKD and Diabetes were the two most significant variables from the univariate analysis (with p-values of 0.002 and 0.0002 respectively). Using composite variables for CKD and diabetes, participants exposed to CKD or diabetes were observed to be four times more likely to have a HPU compared to non-exposed participants. Majority of HPU's were recorded on the left heel (41/68); of these over 70% (30/41) were at least a DTI, category 3 or unstageable. In addition, 80% (24/30) of these categories were recorded on participants that were exposed to both CKD and diabetes. In this study, there was no evidence to support the odds ratio associated with composite variables for asthma and AF, and HF (perfusion related comorbidities) at 10% significance level as reported in Appendix 23. Therefore, these two composite variables were not considered in multivariable analysis.

6.3.4 Braden Scale and Peripheral Neuropathy Assessment

Study participants were assessed for peripheral neuropathy using a monofilament test as described in Chapter 5 section, however those with cognitive impairment and not able to comply with assessment were reported as having peripheral neuropathy. Cases were observed to be more likely to have impaired sensation on each of the eight positions assessed on their feet (both 1st, 3rd, and 5th toes and both heels). All comparisons between the study groups (case versus control group) were observed to be statistically significant at 10% level, therefore all neuropathy assessment variables were considered in the univariate and multivariable analysis. Table 6-4 below provides a summary of the peripheral neuropathy assessment.

Table 6-4 Summary of peripheral neuropathy assessment

Risk assessment domain	**Cases (n=53)**	**Controls (n=50)**	**Total (n=103)**	**Estimate Difference (95% CI)**	**p-value**
Peripheral Neuropathy Assessment:					
Right –impaired Y (%)					
[d]1st toe	34.0 (66.7)	25.0 (50.0)	59.0 (58.4)	2.0 (0.8; 4.8)	**0.09***
[d]3rd toe	39.0 (75.0)	21.0 (42.0)	60.0 (58.8)	4.1 (1.7; 10.5)	**0.0007***
[d]5th toe	39.0 (75.0)	24.0 (48.0)	63.0 (61.8)	3.3 (1.3; 8.2)	**0.005***
Heel	41.0 (78.9)	22.0 (44.0)	63.0 (61.8)	4.7 (1.8; 12.5)	**<0.0001***
Left –impaired Y (%)					

Risk assessment domain	**Cases (n=53)**	**Controls (n=50)**	**Total (n=103)**	**Estimate Difference (95% CI)**	**p-value**
[e]1st toe	38.0 (76.0)	24.0 (48.0)	62.0 (62.0)	3.4 (1.3; 8.8)	**0.004***
[e]3rd toe	39.0 (78.0)	25.0 (50.0)	64.0 (64.0)	3.5 (1.4; 9.4)	**0.004***
[e]5th toe	38.0 (76.0)	21.0 (42.0)	59.0 (59.0)	4.4 (1.7; 11.4)	**0.0005***
Heel	40.0 (80.0)	23.0 (46.0)	63.0 (63.0)	4.7 (1.8; 12.5)	**0.0003***

*variables with p-values <0.1 included in multivariable analysis.

The level of risk for developing a HPU was measured using the Braden Scale (risk assessment tool) on the day of recruitment. Using the Braden scale (subdomains sensory perception, moisture, activity, nutrition, and mobility) a score of 4 means no impairment and 1 means fully impaired. Braden scale subdomain friction and or shear can only be scored 1 to 3, with 1 being most impaired and 3 no impairment.

The difference between the average total Braden scale score for cases (participants with a HPU) and controls (participants without HPU) was statistically significant [MD: -3.9 (-5.4; -2.6), p< 0.0001]. This implies that on average cases had a lower score (high impairment) than controls. The difference in average scores for cases and controls was significant at p-value=0.1 in all six Braden scale subdomains (sensory perception, moisture, activity, mobility, nutrition, and friction and or shear). Furthermore, activity and mobility had the highest significance out of the six subdomains (see Table 6-5 for full details). The intentions of Phase 3 of this study were to replicate previous findings as reported by other studies exploring HPU risk factors. The

Braden scale (subdomains) has previously been identified as a risk factor for HPU in only one high quality study as rated by Dube et al. (2022), it will therefore be considered in the multivariable logistic regression.

Table 6-5 Summary of risk assessment profile as measured using the Braden Scale

Risk assessment domain	**Cases (n=53)**	**Controls (n=50)**	**Total (n=103)**	**Parameter estimate (mean difference or odds ratio (95% CI))**	**p-value**
Braden Scale Total	13.0 (6.0- 23.0)	19.0 (9.0 -23.0)	16.0 (6.0 -23.0)	-3.9 (-5.4; -2.6)	**<0.0001***
Braden Scale Score ≤18 (%)	48.0 (90.6)	24.0 (48.0)	72.0 (69.9)	8.3 (2.8; 27.6)	**<0.0001***
Braden Scale - Sensory perception					
Median (Range)	3.0 (1-4)	3.0 (1-4)	3.0 (1-4)	-0.5 (-0.9; -0.2)	**0.002***
Completely Limited	4.0 (7.5)	0.0 (-)	4.0 (3.9)		**0.02***
Very Limited	17.0 (32.1)	8.0 (16)	25.0 (24.3)		
Slightly Limited	19.0 (35.9)	19.0 (38)	38.0 (36.9)		
No Impairment	13.0 (24.5)	23.0 (46)	36.0 (34.9)		
Braden Scale - Moisture					

Risk assessment domain	**Cases (n=53)**	**Controls (n=50)**	**Total (n=103)**	**Parameter estimate (mean difference or odds ratio (95% CI))**	**p-value**
Median (Range)	3.0 (1 -4)	3.0 (1 -4)	3.0 (1-4)	-0.3 (-0.7; 0.01)	**0.06***
Constantly Moist	3.0 (5.7)	6.0 (12.0)	9.0 (8.7)		**0.002***
Very Moist	15.0 (28.3)	3.0 (6.0)	18.0 (17.5)		
Occasionally Moist:	23.0 (43.4)	17.0 (34.0)	40.0 (38.8)		
Rarely Moist	12.0 (22.6)	24.0 (48.0)	36.0 (35.0)		
Braden Scale- Activity					
Mean(sd) Median (Range)	2.0 (1-4)	3.0 (1 -4)	2.0 (1-4)	-1.2 (-1.4; -0.7)	**<0.0001***
Bedfast	26.0 (49.1)	5.0 (10.0)	31.0 (30.1)		**<0.0001***
Chairfast	15.0 (28.3)	14.0 (28.0)	29.0 (28.1)		

Risk assessment domain	**Cases (n=53)**	**Controls (n=50)**	**Total (n=103)**	**Parameter estimate (mean difference or odds ratio (95% CI))**	**p-value**
Walks Occasionally	10.0 (18.9)	14.0 (28.0)	24.0 (23.3)		
Walks Frequently	2.0 (3.7)	17.0 (34.0)	19.0 (18.5)		
Braden Scale -Mobility					
Median (Range)	2.0 (1 -4)	3.0 (1 -4)	3.0 (1 -4)	-0.9 (-1.2; -0.5)	**<0.0001***
Completely immobile	16.0 (39.2)	2.0 (2.0)	18.0 (17.5)		
Very limited	23.0 (43.4)	19.0 (38.0)	42.0 (40.8)		**<0.0001***
Slightly limited	11.0 (20.7)	11.0 (22.0)	22.0 (21.3)		
No limitation	3.0 (5.7)	18.0 (36.0)	21.0 (20.4)		
Braden Scale Nutrition					
Median (Range)	3.0 (1-4)	4.0 (1-4)	3.0 (1-4)	-0.6 (-0.9; -0.2)	**0.002***

Risk assessment domain	**Cases (n=53)**	**Controls (n=50)**	**Total (n=103)**	**Parameter estimate (mean difference or odds ratio (95% CI))**	**p-value**
Very poor	3.0 (5.7)	1.0 (2.0)	4.0 (3.9)		
Probably inadequate	19.0 (35.9)	5.0 (10.0)	24.0 (23.3)		**0.006***
adequate	13.0 (24.5)	16.0 (32.0)	29.0 (28.1)		
Excellent	18.0 (33.9)	28.0 (56.0)	46.0 (44.7)		
Braden Scale Friction and shear					
Mean(sd) Median (Range)	2.0 (1 -3)	2.0 (1 -3)	3.0 (1 -3)	-0.5 (-0.8; -0.2)	**0.0008***
Problem	20.0 (37.8)	10.0 (20)	30.0 (29.1)		**0.001***
Potential problem	27.0 (50.9)	19.0 (38.0)	46.0 (44.7)		

Risk assessment domain	**Cases (n=53)**	**Controls (n=50)**	**Total (n=103)**	**Parameter estimate (mean difference or odds ratio (95% CI))**	**p-value**
No apparent problem	6.0 (11.3)	21.0 (42.0)	27.0 (26.2)		

*variables with p-values <0.1 included in multivariable analysis.

6.3.5 Vascular assessments

All participants had vascular assessments except for five participants that either could not tolerate an assessment due to confusion or had limb amputation. Claudication, punched out ulcer and night pain (typical signs of underlying arterial disease) were observed in less than five participants for each of these variables. Over 30% of the participants were reported to have one or more cold/cool lower limbs on the day of assessment, cases (participants with HPU) were at least two times more likely to have a cold left limb compared to controls (p=0.02). Cases were at least two times likely to have pale limb(s) reported on the day of assessment and this difference was statistically significant with p-value=0.02. Pale limbs (right and left), cold left limb and capillary refill of less than 2 seconds had p-values less than 0.1 and were included in the modelling process. Table 6-6 provides further vascular assessment results of recruited patients by study group.

Table 6-6 Summary of vascular assessments by study population

Variable	**Cases (n=53)**	**Control (n=50)**	**Total (n=103)**	**Difference estimate (95% CI)**	**p-values**
Pale Limbs:					
Right Y (%)	25.0 (50.0)	14.0 (28.0)	39.0 (39.0)	2.6 (1.0; 6.4)	**0.02***
Left Y (%)	25.0 (47.2)	14.0 (28.0)	39.0 (39.8)	3.0 (0.91, 12.76)	**0.02***
Hairless limb:					
Right	40.0 (76.9)	36.0 (72.0)	76.0 (76.0)	1.6 (0.6, 4.4)	0.3
Left	38.0 (71.7)	36.0 (72.0)	74. 0 (75.5)	1.4 (1.4, 4.2)	0.4
Cold/cool limb:					
[m]*Right Y (%)*	22.0 (41.5)	15.0 (30.0)	37.0 (37.0)	1.8(0.7; 4.5)	0.2
[m]*Left Y (%)*	26.0 (49.1)	15.0 (30.0)	41.0 (41.8)	2.8(1.1; 6.9)	**0.02***
[a]HPU with a punched-out appearance:					

Variable	Cases (n=53)	Control (n=50)	Total (n=103)	Difference estimate (95% CI)	p-values
Right Y (%)	2.0 (3.8)	0.0 (0.0)	2.0 (2.0)	n/a	0.5
Left Y (%)	1.0 (1.9)	0.0 (0.0)	1.0 (1.0)	n/a	
[b]Claudication:					
Right Y (%)	1.0 (1.9)	1.0 (2.0)	2.0 (2.0)	n/a	1.0
Left Y (%)	0.0 (0.0)	1.0 (2.0)	1.0 (1.0)	n/a	1.0
Night leg pain:					
Right Y (%)	1.0 (1.9)	1.0 (2.0)	2.0 (2.0)	1.0 (0.01; 76.9)	1.0
Left Y (%)	1.0 (1.9)	1.0 (2.0)	2.0 (2.0)	1.0 (0.01; 80.1)	1.0
Capillary refill time less than 2s:					
Right Y (%)	28.0 (52.8)	36.0 (72.0)	64.0 (64.5)	1.9 (0.8; 4.9)	**0.1***
Left Y (%)	25.0 (47.2)	35.0 (70.0)	60.0 (61.2)	2.1 (0.9; 5.3)	**0.07***

m=missing data due to amputation or confusion (n≤5%), a=ulcer on legs only, b=only applicable to those that could walk, Fisher Exact significance reported as n<5 in applicable cells; *variables with p-values <0.1 included in multivariable analysis.

6.3.6 Venous Skin Changes Assessment

Table 6-7 describes the vascular changes observed in all study participants except for five participants who were too confused to undertake the assessment. The majority (over 60%) of participants were reported to have dry skin on at least one of their legs. Dry skin on the left leg was more likely to be observed in participants with HPU compared to those without, with an OR: 3.0 (0.91, 12.76), p=0.02. None of the recruited participants presented with right ankle flare and two cases (3.8%) were observed to have left ankle flare. Left scaly skin, dry left leg, and skin staining (both limbs) were included in multivariable analysis.

Table 6-7 Summary of venous skin changes assessment by study group

Variable	Cases (n=53)	Control (n=50)	Total (n=53)	Difference estimate (95% CI)	p-values
Dry skin:					
Right Y (%)	40.0 (80.0)	30.0 (60.0)	70.0 (70.0)	1.3(0.4; 4.1)	0.6
Left Y (%)	39.0 (73.6)	30.0 (60.0)	69.0 (70.4)	3.0(1.1; 8.2)	**0.02***
Scaly skin:					
Right Y (%)	9.0 (18.0)	5.0 (10.0)	14.0 (14.0)	2.0(0.5; 8.1)	0.2
Left Y (%)	11.0 (22.9)	4.0 (8.0)	15.0 (15.3)	3.4 (0.9; 15.8)	**0.05***
Ankle flare:					
Right Y (%)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	n/a	n/a
Left Y (%)	2.0 (3.8)	0.0 (0.0)	2.0 (2.0)	n/a	0.2
Skin Staining:					
Right Y (%)	13.0 (24.5)	7.0 (14.0)	20.0 (20.0)	2.2 (0.7; 7.1)	**0.1***
Left Y (%)	14.0 (29.2)	8.0 (16.0)	22..0 (22.5)	2.2 (0.7; 6.6)	**0.1***

*variables with p-values <0.1 included in multivariable analysis.

6.3.7 Doppler Ultrasound Assessment

Over half of both cases (62.3%) and controls (70.0%) agreed to complete a Doppler ultrasound (DUS) assessment as part of the study (full details are presented in Appendix 24). Of those who lacked the mental capacity to provide informed consent, 39.5% (17/43) of their nominated consultees agreed for them to complete a DUS assessment compared to 85% of those that had the mental capacity to provide study consent. All three pedal pulses, dorsalis pedis (DP), posterior tibial (PT), and peroneal were attempted to be assessed in all participants who could comply during assessment, including those that opted for toe and branchial assessment (TBPI) instead of ankle and brachial assessment (ABPI). All pedal pulse assessments (that is whether pedal pulses were palpable) for both feet (left and right) yielded significant associations with the presence of a HPU at p-value =0.1. The case group had a significantly lower number of palpable pedal pulses in both legs

compared to controls (full results presented in Table 6-8). Cases had a higher proportion of pedal pulses that were either not assessed as participants were not able to comply during assessment due to cognitive impairment, or pulses were not palpable compared with controls. Peroneal pulses in the case population were the least palpable and less cases had confirmed peroneal pulse waveforms for both limbs (full results presented in Table 6-8).

Table 6-8 Summary of pedal pulse palpation assessment by study group

Pedal Pulse	**Cases (n=53)**	**Controls (n=50)**	**Total (n=103)**	**Estimate Difference (95% CI)**	**p-values**
Dorsalis Pedis Pulse:					
Right N (%)	17.0 (48.6)	11.0 (23.9)	28.0 (34.6)	3.0 (1.1; 8.7)	**0.02***
Left N (%)	18.0 (53.0)	9.0 (20.0)	27.0 (34.2)	4.5 (1.5; 13.8)	**0.002***
Posterior Tibial Pulse:					
Right N (%)	16.0 (53.3)	15.0 (32.6)	31.0 (40.8)	2.4 (0.8; 6.8)	**0.07***
Left N (%)	20.0 (60.6)	15.0 (32.6)	35.0 (44.3)	3.2 (1.1; 9.0)	**0.01***
Peroneal Pulse:					
Right N (%)	28.0 (84.9)	27.0 (60.0)	55.0 (70.5)	3.7 (1.1; 14.5)	**0.02***
Left N (%)	26.0 (81.3)	28.0 (60.9)	54.0 (69.2)	2.8 (0.9; 9.8)	**0.08***

*variables with p-values <0.1 included in multivariable analysis.

Table 6-9 summarises the doppler ultrasound waveform assessment by study group. Pulse waveforms are classified into three categories, triphasic, biphasic and monophasic with tri- and bi-

phasic considered as normal waveforms while monophasic is considered abnormal. The number of participants that were able to complete each of the assessments varied for each pulse assessment as some participants were not able to fully comply with the assessment mainly because of their inability to comprehend instructions due to cognitive impairment. Left and right DP, and left PT waveforms (tri-and bi-phasic compared to monophasic) were observed less in the case group compared to the control group.

Table 6-9 Summary of Doppler ultrasound waveforms assessment by study group

Pedal Pulse waveform	**Cases (n=53)**	**Controls (n=50)**	**Total (n=103)**	**Estimate Difference (95% CI)**	**p-values**
Dorsalis Pedis:					
Right					
Triphasic	2.0 (3.8)	11.0 (22.0)	13.0 (12.6)	5.2 (1.0; 50.7) ^{W}P=0.03	**0.09***
Biphasic	17.0 (32.1)	20.0 (40.0)	37.0 (35.9)		
Monophasic	15.0 (28.3)	15.0 (30.0)	30.0 (29.1)		
Unable to assess	19.0 (35.9)	4.0 (8.0)	23.0 (22.3)		
Left					
Triphasic	1.0 (1.9)	9.0 (18.0)	10.0 (9.7)	8.0 (1.0; 362.2) ^{W}P=0.04	**0.005***
Biphasic	12.0 (22.6)	24.0 (48.0)	36.0 (35.0)		
Monophasic	21.0 (39.6)	13.0 (26.0)	34.0 (33.0)		
Unable to assess/locate	19.0 (35.9)	4.0 (8.0)	24.0 (23.3)		
PT					

Pedal Pulse waveform	**Cases (n=53)**	**Controls (n=50)**	**Total (n=103)**	**Estimate Difference (95% CI)**	**p-values**
Right					
Triphasic	1.0 (1.9)	8.0 (16.0)	9.0 (8.7)		
Biphasic	15.0 (28.3)	19.0 (38.0)	34.0 (33.0)	5.4 (0.6; 249.2)	
Monophasic	10.0 (18.9)	18.0 (36.0)	27.0 (27.2)	[W]P=0.1	0.2
Unable to assess/locate	27.0 (50.9)	5.0 (14.0)	32.0 (31.1)		
Left					
Triphasic	0.0 (0.0)	7.0 (14.0)	7.0 (6.8)		
Biphasic	11.0 (20.8)	23.0 (46.0)	34.0 (33.0)		
Monophasic	14.0 (26.4)	15.0 (30.0)	29.0 (27.2)	-	**0.04***
Unable to assess/locate	28.0 (52.8)	5.0 (10.0)	33.0 (32.0)		
Peroneal:					
Right					
Triphasic	0.0 (0.0)	4.0 (8.0)	4.0 (3.9)		
Biphasic	4.0 (7.6)	16.0 (32.0)	20.0 (19.4)	-	0.2
Monophasic	7.0 (13.2)	11.0 (22.0)	18.0 (17.5)		

Pedal Pulse waveform	**Cases (n=53)**	**Controls (n=50)**	**Total (n=103)**	**Estimate Difference (95% CI)**	**p-values**
Unable to assess/locate	42.0 (79.3)	19.0 (38.0)	61.0 (59.2)		
Left					
Triphasic	0.0 (0.0)	4.0 (8.0)	4.0 (3.9)	-	0.3
Biphasic	5.0 (9.4)	17.0 (34.0)	22.0 (21.4)		
Monophasic	6.0 (11.3)	9.0 (18.0)	15.0 (14.5)		
Unable to assess/locate	42.0 (79.3)	20.0 (40.0)	62.0 (60.2)		

w=p-value triphasic vs biphasic, monophasic, and unable to assess; *variables with p-values <0.1 included in multivariable analysis.

Table 6-10 provides a summary of the ankle brachial pressure index (ABPI) and toe brachial pressure index (TBPI) as assessed using a DUS machine for those that were statistically significant at p-value=0.1 and were further considered in multivariable analysis. Complete DUS assessment results including the statistically non-significant variables at p-value =0.1 are presented in Appendix 25. ABPI assessment was completed in 32.0% (33/103) of the participants, however, not every one of three pedal pulses (dorsalis, posterior tibial and peroneal) could be assessed in these individuals. Peroneal pulse was the least detectable pulse in both limbs when assessed manually and using the DUS machine. There were no significant differences between cases and controls for their brachial, DP, PT, and peroneal systolic pressures in both limbs. ABPI was calculated for each of the pedal arteries and only the right peroneal arteries had a significant mean difference of -0.2 (-0.3; -0.1) and a p-value 0.001.

One participant (1/17) in the case group had a value for left peroneal systolic pressure compared to ten (10/16) in the control group; this could possibly explain why the majority of the HPUs observed in this study were located on the left heel. Right peroneal ABPI was significantly higher in controls compared to cases however only 45.5% (15/33) participants had a detectable pulse. Left PT and right peroneal PAD severity (normal vs moderate) had a p-value ≤0.1 and were further considered for univariate and multivariable logistic regression. PAD severity was defined as normal 0.9> ABPI <1.3; mild 0.8≥ ABPI ≤0.9; moderate 0.5≥ ABPI <0.8; ABPI <0.5; TBPI-normal >0.7; mild 0.64-0.7; moderate 0.4 <TBPI ≤0.64; severe ≤0.4 (Foley et al., 2016; Vowden and Vowden, 2001). None of the participants in both case and control groups had severe PAD as diagnosed using a manual DUS machine. More participants with HPU were likely to be observed to have moderate PAD compared to controls for right DP, left PT, and right peroneal (p-value =0.1).

Thirty-four participants (cases n=16 vs controls n=18) had toe systolic pressures assessed due to either having a diagnosis of diabetes, lower limb oedema or unable to tolerate the BP cuff around their leg. For both lower limbs, none of the TBPI were significantly different between the case and control groups. However, when PAD severity was assessed the p-value for the left TBPI was p-value =0.1. Though, when included in the multivariable analysis it further reduced the sample size with complete data and therefore was excluded in the final analysis.

Table 6-10 Summary of ABPI/TBPI Doppler Ultrasound assessment by study group

Pulse location	**Cases (n=53)**	**Controls (n=50)**	**Total (n=103)**	**Parameter estimate mean difference/ odds ratio (95%CI)**	**p-values**
Peroneal systolic pressure (mmHg) Median (Range)					
Right	94.0 (92.0-96.0)	122.0 (90.0-160.0)	117.0 (90.0,160.0)	-25.8 (-52.5-0.08)	**0.06***
[h]PAD severity (Left leg)					
Normal	9.0 (64.3)	15.0 (93.8)	24.0 (80.0)	8.3 (0.7; 419.7)	**0.07***
Moderate	5.0 (35.7)	1.0 (66.3)	6.0 (20.0)		
ABPI summary by pedal artery					
PAD Severity (Right DP)					
Normal	8.0 (72.7)	16.0 (100.0)	24.0 (88.9)	-	**0.06***
Moderate	3.0 (27.3)	0.0 (0.0)	3.0 (11.1)		
PAD Severity (Left PT)					
Normal	5.0 (41.7)	13.0 (81.3)	18.0 (64.3)	6.1 (0.9; 48.2)	**0.05***
Moderate	7.0 (58.3)	3.0 (18.8)	10.0 (35.7)		

Pulse location	**Cases (n=53)**	**Controls (n=50)**	**Total (n=103)**	**Parameter estimate mean difference/ odds ratio (95%CI)**	**p-values**
Peroneal Right	0.7 (0.69-0.73)	0.9 (0.9-1.2)	0.9 (0.7- 1.2)	-0.2 (-0.3; -0.1)	**0.001***
PAD Severity (Right Peroneal)					
Normal	0.0	8.0 (72.7)	8.0 (57.1)		**0.01***
Moderate	3.0 (100.0)	2.0 (27.3)	6.0 (42.9)		
Toe Brachial Pressure Index (TBPI)					
PAD Severity (Left TBPI)					
Normal	7.0 (63.6)	14.0 (93.3)	21.0 (60.8)	8.0 (0.6; 421.3)	**0.1***
Moderate	3.0 (27.3)	0.0 (0.0)	3.0 (11.5)		
Severe	1.0 (9.1)	1.0 (6.7)	2.0 (7.7)		

h= *ABPI calculated based on high pedal pressure/ highest brachial pressure; TBPI calculated based on average mean toe pressure / highest brachial pressure; *variables with p-values <0.1 included in multivariable analysis.*

6.3.8 Heel Pressure Ulcer Characteristics

6.3.8.1 Cases HPU screening summaries

Of all the patients that were screened for a HPU, 42% (190/452) developed a HPU during their hospital stay, with 36.7% (166/452) having developed a HPU whilst living in their own home. However, none of the hospital acquired HPUs were classified as a category 4 (most severe HPU), most of the hospital acquired HPUs were classed as category 2 (superficial skin damage) (116/190, 61.1%), whereas those acquired at home were mostly more category 3 and above (95/166, 57.2%). Of those acquired at home, categories 1 and 2 were relatively fewer in numbers compared to the more severe HPUs (42.8% vs 57.2% respectively). This is likely because the case population was screened from the Datix database which only holds HPU data that have been reported by ward staff, and within the research site it is not mandatory to report category 1. Category 2 HPUs acquired outside the researcher's organisation do not require input from a Tissue Viability specialist, but clinical staff are required to record them on the Datix for prevalence monitoring. Six percent (6.0%, 30/482) of the screened patients were misdiagnosed on initial assessment by the clinical staff, therefore are not included in Figure *6-2*.

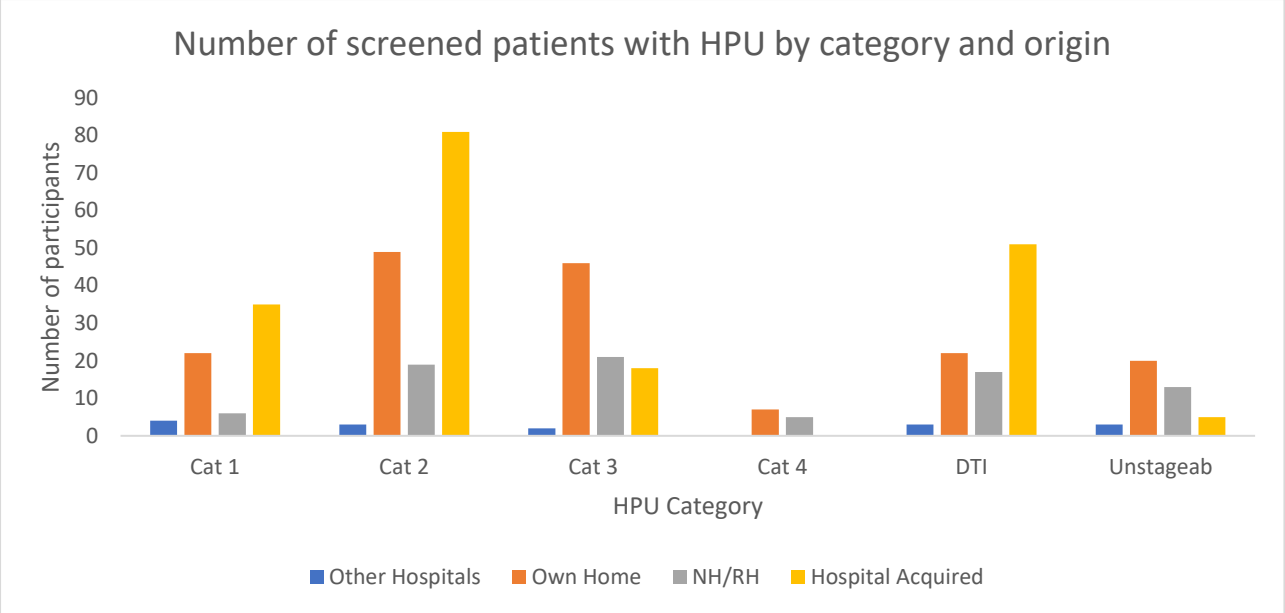


Figure 6-2 Histogram showing the percentage of HPU categories by origin of wounds for screened participants.

6.3.9 HPU Summaries for Recruited Cases.

6.3.9.1 Baseline Summaries

Results in this section are only for patients that were recruited into the study with a HPU(s), 88.4% (23/26) of the recruited cases that were admitted with a HPU from their own home had at least a category 3 and above compared to 59% (13/22) hospital acquired HPUs that were either a category 2 or 3. Figure *6-3* summarises the HPU severity by place of origin (participant's own home, current hospital admission, or nursing or residential care home).

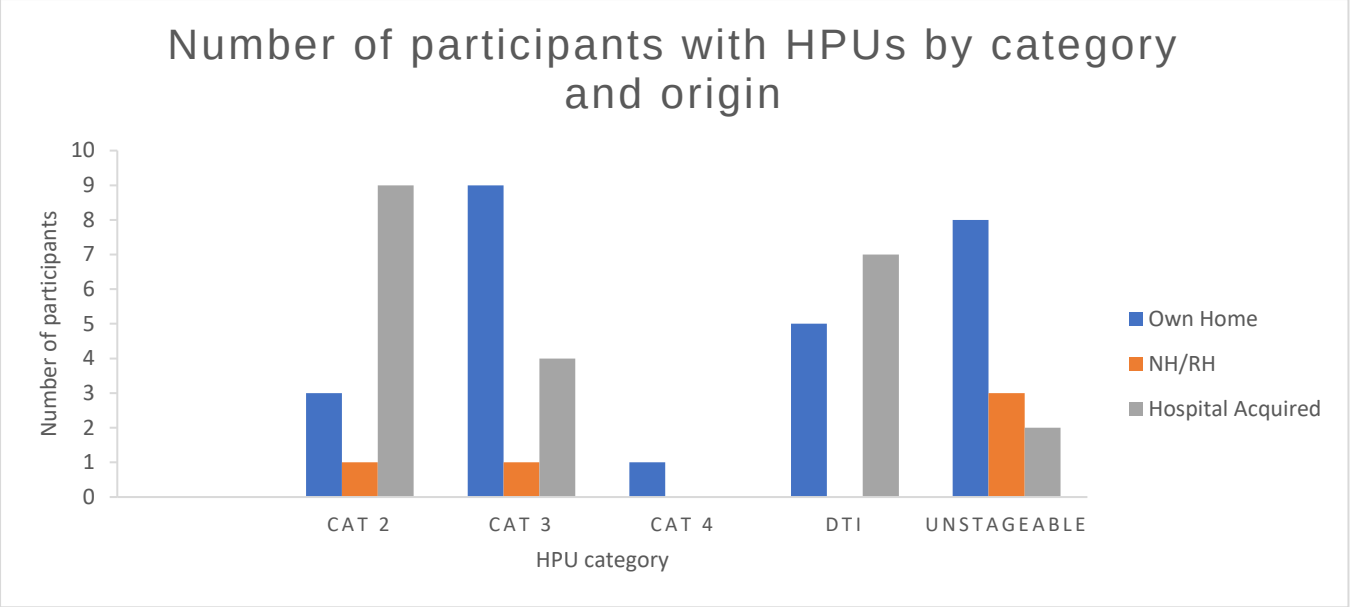


Figure 6-3 Histogram showing the number of HPU for recruited participants by categories and origin.

Table 6-11 provides descriptive summaries for HPU presentation as assessed by either hospital tissue viability nurses or the researcher on the day of recruitment. In total 53 patients with at least one HPU were recruited in the study duration; of these 26 (49.1%) had pressure ulcers on the left heel, 12 (22.6%) had pressure ulcers (PU) on the right heel, and 15 (28.3%) had PU on both heels (hospital acquired n=9 and own home or care home n=6); accounting for a total of 68 HPUs case study population. Most recruited patients either acquired a HPU during their hospital stay or whilst living in their own home, 43.5% (24/53) and 41.4% (21/53) respectively. This was similar to the screened patients HPU origin distribution (Figure 6-2). Over sixty percent (60%) of all recruited cases had category 3 HPU, unstageable or DTI. The majority of HPU did not require a dressing (34/68), because they were either fluid filled blisters or deep tissue injuries (DTIs). Of those that needed dressings, they either had a non-microbial or antimicrobial dressing applied.

Table 6-11 Summary of heel pressure ulcer characteristics for recruited patients.

Total recruited Cases (n=53)	**Left (n=41)**	**Right (n=27)**
Origin-N (%) (participants)	Hospital acquired n=25 (47.1) [O]; Care Homes n=6 (11.3); Own Home n=22 (41.5)	
Origin- N (%) (heels)		
Own Home	13.0 (31.7)	12.0 (44.4)
[o]Hospital acquired	24.0 (58.5)	10.0 (37.0)
Care Homes	4.0 (9.8)	5.0 (18.5)
HPU Severity (%)		
Cat2	11.0 (26.8)	3.0 (11.1)
Cat 3	4.0 (9.8)	5.0 (18.5)
Cat 4	1.0 (2.4)	0.0
DTI	15.0 (36.6)	8.0 (29.6)
Unstageable	11.0 (26.8)	11.0 (40.7)
Wound bed appearance:		
Cat2	clear/brown fluid filled/ reabsorbing blister	clear fluid filled/ reabsorbing blister
Cat 3	mostly granulation, <50% necrosis and/or slough	mixture of slough, necrosis and granulation

Total recruited Cases (n=53)	**Left (n=41)**	**Right (n=27)**
DTI	purple fluid blister or PNB areas	Purple fluid blister or PNB areas
unstageable	60-100% necrosis and/or slough	unstageable 60-100% necrosis and/or slough
Wound exudate Y (%)		
None	33.0 (80.5)	18.0 (66.7)
Low	7.0 (17.1)	6.0 (22.2)
Medium	1.0 (2.4)	3.0 (11.1)
Wound infection	1.0 (2.4)	3.0 (11.1)
Wound dressing applied to ulcer		
None	24.0 (58.5)	10.0 (37.0)
Aquacel foam, Attrauman, Duoderm Extra thin	8.0 (19.5)	5.0 (18.6)
Antimicrobial	9.0 (22.0)	12.0 (44.4)
Condition of surrounding skin:		
Normal	0.0	2.0 (7.4)

Total recruited Cases (n=53)	**Left (n=41)**	**Right (n=27)**
Red dry and blanching	32.0 (78.0)	20.0 (74.1)
Red dry and non-blanching	4.0 (9.8)	3.0 (11.1)
Callous	5.0 (12.2)	2.0 (7.4)

*Includes bilateral HPU participants, o= includes n=1 HPU from other hospital

6.3.9.2 Heel Pressure Ulcer Follow-up

All cases were followed up through telephone consultation or their medical records if they could not be reached via telephone. Four cases could not be contacted at 3 months follow-up; however, their follow-up was completed as appropriate using their medical records. At three months follow-up 66.0% (35/53) of the cases were still alive and 27.9% (19/68) of all HPUs were reported to have healed at 3 months follow-up and these were on 15 participants (n=5 had HPU on both heels). Of the HPU that had healed at 3 months follow-up, 78.9% (15/19) were either a category 2 or DTI. Eighteen participants (34.0; (18/53) had died at 3 months follow-up and none of their wound status could be ascertained and therefore were regarded as not healed at time of death. Two participants developed a new HPU at 3 months follow-up; one was from the case group (right heel, hospital acquired with unknown category) and one from the control group (left heel, unstageable acquired in a nursing home). No information could be identified in terms of their vascular assessment or whether they had a follow-up Doppler assessment at the time of diagnosis.

For two participants that could not be reached at 6 months follow-up, medical records were used to complete their assessments as appropriate. At six months follow-up 54.7% (29/53) cases were still alive; a further 9 HPUs had healed from a total of seven participants and 55.5% (5/9) were category 3 or unstageable at time of recruitment. A total of 38.2% (26/68) heels had healed at 6 months follow-up, with an average healing time of 187.6 (133.0) days (ranging 13.0 to 457.0 days). In total, 24 participants (45.3%) had died within the duration of the study and the wound status of 91.3% (21/24) could not be ascertained and therefore were regarded as not healed at the time of death. HPU follow-up summarises are provided in Table 6-12.

Table 6-12 Summary of HPU severity at 3- and 6-months study follow-up

Heel pressure ulcer categories	**3 months follow-up (n=34)**	**6 months follow-up (n=29)**
Number of HPU healed (left) (%)	11.0 (11/41; 26.8)	5.0 (5/31; 16.7)
Cat 2/ DTI	11.0	3.0
Cat 3	0.0	1.0
Unstageable	0.0	1.0
Number of HPU healed (right) (%)	8.0 (8/27; 29.6)	4.0 (4/20; 20.0)
Cat 2/ DTI	5.0	1.0
Cat 3	2.0	2.0
Unstageable	2.0	1.0

6.4 Phase 2: Risk factors associated with HPU Presence

6.4.1 Logistic Regression Analysis Results

Table 6-13 outlines summary results from the univariate and multivariable logistic regression analysis for the 32 variables that were found to be statistically significant at 10% level from association tests using t-test or chi-squared tests (section 6.3). These variables were further analysed using logistic regression univariate analysis, and variables with $p \leq 0.1$ were further analysed using multivariable logistic regression to identify potential independent variables. All Braden Scale subdomains were heavily correlated with each other, and associations were significant at 5% except for the nutrition subdomain, which had a weak correlation with coefficients of less than 0.4. Therefore, a decision was made to use the total Braden Scale score as a composite variable. Similarly, CKD and diabetes were moderately correlated with a significant association ($p<0.05$) thus a composite variable created by adding the two variables together was used to adjust for collinearity in the multivariable model.

A final model including variables with $p< 0.05$ was identified which included albumin blood tests results, AF, composite variables- for exposure to CKD and diabetes, total Braden Scale score, and total peripheral neuropathy assessment scores for left and right feet. Albumin and composite variables for total peripheral neuropathy assessment scores were observed to be highly significant with $p < 0.001$; a unit increase in albumin levels reduces the odds of having a HPU by 0.8 while a unit increase in left foot neuropathy total assessment score increases the odds of having a HPU by 7.7. However, a unit increase in the right foot neuropathy total assessment score decreases the odds of a HPU by 0.2. Exposure to CKD or Diabetes increases the odds of a HPU by 2.3. The final multivariable model (including albumin, AF, composite variables for CKD and diabetes, Braden Scale scores, and total neuropathy

assessment scores for left and right feet accounted for at least 40% variability observed within the study population (R^2-0.45; n=95; p-value <0.0001).

Table 6-13 Summary results from the univariate and multivariable logistic regression analysis

Variable	**Univariate**	**Multivariable**
	Odds Ratio (95%CI) p value	
Alcohol consumption (Y)	0.5 (0.2; 1.0) **0.06**	-
Hb	1.0 (0.9; 1.0) 0**.004**	-
Albumin	0.8 (0.7; 0.9) <**0.0001**	0.8 (0.7 - 0.9) **<0.0001**
Diabetes (Y)	4.5 (1.9; 10.3) **<0.0001**	-
CKD (Y)	3.9 (1.7; 9.0) **0.002**	-
Exposure to CKD and/or Diabetes	-	2.3 (1.1 - 4.7**) 0.02**
Asthma (Y)	0.3 (0.1; 1.1) **0.08**	-
AF (Y)	2.7 (1.0; 7.4) **0.05**	4.7 (1.2 - 18.4**) 0.03**
HF (Y)	4.4 (0.9; 21.7) **0.07**	-
Angina (Y)	5.2 (0.6; 46.3) **0.1**	-
Braden Scale Subdomains		
Sensory	*0.5 (0.3; 0.8)* ***0.003***	-
Moisture	*0.7 (0.4; 1.0) 0.6*	-
Activity	*0.3 (0.2; 0.5)* ***<0.0001***	-
Mobility	*0.4 (0.2; 0.6)* ***<0.0001***	-
Nutrition	*0.5 (0.3; 0.8)* ***0.003***	-

Variable	Univariate	Multivariable
	Odds Ratio (95%CI) p value	
Friction	*0.4 (0.2; 0.7)* ***0.001***	-
Total Braden Scale Score	*0.7 (0.7; 0.9)* ***<0.0001***	0.8 (0.7 - 1.0) **0.03**
Peripheral Neuropathy Assessment		
Left 1st toe	3.3 (1.4; 7.9) **0.006**	-
Left 3rd toe	3.5 (1.4; 8.2) **0.005**	-
Left 5th toe	4.3 (1.8; 10.1) **0.001**	-
Left total neuropathy score	1.7 (1.2; 2.3) **0.001**	7.7 (1.8 - 32.7) **0.006**
Left Heel	4.6 (1.9; 11.1) **0.001**	-
Right 1st toe	1.9 (0.9; 4.3) **0.1**	-
Right 3rd toe	4.0 (1.7; 9.4) **0.001**	-
Right 5th toe	3.2 (1.4; 7.3)**0.007**	-
Right total neuropathy score	1.4 (1.1; 2.0) **0.009**	0.2 (0.0 - 0.6) **0.007**
Right Heel	4.6(1.9 - 11.0) **0.001**	-
Vascular Assessments		
Pale limb (Y)		
Left	2.9 (1.3; 6.8) **0.01**	-
Right	2.7 (1.2; 6.2) **0.02**	-
Cold/cool limb (Y): Left	2.9 (1.3; 6.7) **0.01**	-
Capillary refill time less than 2s (Y): Left	0.4 (0.2; 1.0) **0.06**	-
Venous Skin Changes Assessment		
Dry skin (Y):		

Variable	Univariate	Multivariable
	Odds Ratio (95%CI) p value	
Left	2.8 (1.1; 7.1) **0.03**	-
Right	2.6 (1.1; 6.4) **0.04**	-
Scaly skin Left Limb (Y):	3.5 (1.0; 12.0) **0.04**	-
Skin Staining -Left Limb (Y):	2.2(0.8; 5.9) **0.1**	-

6.4.2 Logistic Regression Analysis using Doppler Ultrasound Data

Study participants were required to complete a Doppler ultrasound assessment (DUS) to assess for undiagnosed PAD. In total 68 (66.0%) participants consented to an either ankle or toe brachial assessment and 34% agreed to a foot assessment which included palpating foot pulses (DP, PT, and peroneal pulses) as well as pulse waveform assessment using a DUS machine. Data was collected and recorded for each of the activities however some participants could not complete all assessments hence data was recorded as 'unable to assess', and this impacted the overall sample size for each of the measured variables. Of all the DUS assessment variables reported in Table 6-6 to Table 6-10, 13 variables were observed to be significant at 10% level using either a t-test or chi-squared tests. These 13 variables were further considered in univariate and multivariable analysis, results are reported in Appendix 26. Participants with palpable pedal pulses had lower odds of having a HPU, for example, participants with a DP pulse that could not be palpated were at least four times more likely to have a HPU. The waveforms of each of the pulses were also assessed as either triphasic, bi-phasic or monophasic with triphasic being normal (no issues) and monophasic being abnormal showing signs of stenoses. For the left DP pulse, having a monophasic waveform increased the odds of a HPU by 14.5 (p value= 0.02).

PAD severity was calculated using ABPI measurements; these were categorised as follows: normal ABPI > 0.9; moderate ABPI ≤0.9 or ABPI ≤0.6; severe < 0.5. Only left PT PAD severity (normal vs moderate) was observed as statistically significant at p<0.5. In a univariate analysis, right DP and peroneal ORs and 95% CI could not be calculated as all participants in the control group that were assessed had a normal ABPI value for right DP and for right peroneal none of the case group participants that were assessed had a normal ABPI value. None of the DUS assessment variables were significant in a multivariable analysis at p-value =0.05.

6.5 Phase 3a: Health Related Quality of Life and Pain Assessments

Health related quality of life (HRQoL) assessed using EQ5D-5L and pain (numeric rating scale or Pain Assessment in Advanced Dementia) results were separated into two groups – those reported by study participants (cases n=30; controls n=30), and those reported by participants' proxy (consultee) (cases n=23; controls n=20) due to cognitive impairment and not being able to answer research questions appropriately. HRQoL baseline data and follow-up data was completed with either the participants or their proxies. At 3 and 6 months from recruitment, data was only collected if the participant was still alive at the time of the study follow-up. For the summaries presented below each of the five subdomains was further categorised into two levels – 'I have no problems' vs 'having a problem', regardless of severity. Also, an index score was calculated using the English (ENG) Devlin value set (Devlin et al., 2018) which converts the reported health states into a score based on the health state preferences of the population in England. The EQ-5D-5L index has an upper bound equal to 1 that indicates full health (indicated by "no problem" in all domains), whereas 0 represents death and any values below 0 indicate quality of life worse than death.

6.5.1 Baseline: Quality of Life and Pain Assessments

6.5.1.1 Baseline: Patient Reported Health Related Quality of Life and Pain Assessment

EQ5D-5L mobility, self-care and usual activities domains had statistically significant differences at 5% significance level, pain and anxiety at the 10% significance level; more cases compared to controls reported to have some form of a problem. Participants in control group on average reported a significantly better quality of life compared to cases [-0.03(-0.4; -0.1), p=0.0008]. However, their perception of their health measured on the day of recruitment using the EQ5D-5L visual analogue score was not statistically significant at p-value=0.05. Pain as measured using the numeric rating scale had an observed MD: of 1.6 (-0.1; 3.3) p-value=0.06. Table 6-14 presents the summary of the HRQoL at baseline as measured using EQ-5D-5L questionnaire.

Table 6-14 Summary of baseline HRQOL as measured using EQ-5D-5L by study group.

EQ-5D-5L Domains; Median (Range)	**Case (n=30)**	**Control (n=30)**	**Total (60)**	**Estimate Difference (95% CI)**	**p-values**
Mobility	5.0 (1-5)	3.0 (1-5)	3.5 (1-5)	1.4 (0.7; 2.1)	**0.0002^**
I have no problems in walking about	3.0 (10.0)	11.0 (36.7)	14.0 (23.3)		
I have slight problems in walking about	2.0 (6.7)	2.0 (6.7)	4.0 (6.7)		
I have moderate problems in walking about	3.0 (10.0)	9.0 (30.0)	12.0 (20.0)	5.2 (1.1; 32.1)	**0.03^**
I have severe problems in walking about	6.0 (20.0)	5.0 (16.7)	11.0 (18.3)		
I am unable to walk about	16.0 (53.3)	3.0 (10.0)	19.0 (31.7)		
Self-care	3.0 (1-5)	1.0 (1-5)	2.0 (1-5)	0.9 (0.2; 1.6)	**0.009^**

I have no problems washing or dressing myself	9.0 (30.0)	17.0 (56.6)	26.0 (43.3)		
I have slight problems washing or dressing myself	4.0 (13.3)	6.0 (20.0)	10.0 (16.7)		
I have moderate problems washing or dressing myself	7.0 (23.3)	3.0 (10.0)	10.0 (16.7)	3.1 (0.9; 10.2)	**0.04^**
I have severe problems washing or dressing myself	5.0 (16.7)	3.0 (10.0)	8.0 (13.3)		
I am unable to dress myself	5.0 (16.7)	1.0 (3.3)	6.0 (10.0)		
Usual Activities	3.5(1-5)	2.0 (1.0-5.0)	3.0 (1-5)	1.0 (0.2; 1.8)	**0.02^**
I have no problems doing my usual activities	4.0 (13.3)	12.0 (40.0)	-16.0 (26.7)	4.3 (1.1; 20.9)	**0.04^**

I have slight problems washing or dressing myself	4.0 (13.3)	4.0 (13.3)	8.0 (13.3)		
I have moderate problems doing my usual activities	7.0 (23.3)	5.0 (16.7)	12.0 (20.0)		
I have severe problems doing my usual activities	2.0 (6.7)	3.0 (10.0)	5.0 (8.3)		
I am unable to do my usual activities	13.0 (43.3)	6.0 (20.0)	19.0 (31.7)		
Pain/Discomfort	3.5 (1.0-5.0)	2.0 (1.0-5.0)	2.0 (1.0-5.0)	0.5 (-0.2; 1.2)	0.1
I have no pain or discomfort	7.0 (23.3)	11.0 (36.7)	18.0 (30.0)		
I have slight pain or discomfort	8.0 (26.7)	8.0 (26.7)	16.0 (26.7)		
have moderate pain or discomfort	6.0 (20.0)	6.0 (20.0)	12.0 (20.0)	1.9(0.5; 7.0)	0.3
I have severe pain or discomfort	5.0 (16.7)	4.0 (13.3)	9.0 (15.0)		
I have extreme pain or discomfort	4.0 (13.3)	1.0 (3.3)	5.0 (8.3)		

Anxiety/Depression	2.0 (1-5)	1.5 (1-3)	2.0 (1-5)	0.4 (-0.06; 0.9)	0.08
I am not anxious or depressed	9.0 (30.0)	15.0 (50.0)	24.0 (40.0)		
I am slightly anxious or depressed	7.0 (23.3)	6.0 (20.0)	13.0 (21.7)		
I am moderately anxious or depressed	13.0 (43.3)	9.0 (30.0)	22.0 (36.7)	2.3 (0.7; 7.0)	0.1
I am severely anxious or depressed	0.0	0.0	0.0		
I am extremely anxious or depressed	1.0 (3.3)	0.0	1.0 (1.7)		
Index score	0.4 (-0.1 – 1)	0.8 (0.006 – 1)	0.6 (-0.1- 1)	-0.03 (-0.4; -0.1)	**0.0008^**
Your health today scores	50.0 (22.0 – 100.0)	62.5 (30.0 - 100.0)	60.0 (22.0-100.0)	-2.7 (-13.7; 8.1)	0.6
Pain Numeric rating scale	5.5 (0.0-10.0)	4.5 (0.0-10.0)	5.0 (0.0-10.0)	1.6 (-0.1; 3.3)	0.06

6.5.1.2 Baseline: Proxy Completed Health Related Quality of Life

For participants that had some form of cognitive impairment and could not complete study questions, their data was collected with the help of personal or professional nominated consultees. Cases were reported to have at least moderate or more severe walking problems whereas 15% of cases were reported to have slight or no walking problems at baseline. Baseline data was completed on the day of recruitment, cases and controls had similar health states across all five domains. This is likely to show the impact cognitive impairment has on both the participant and their consultee's quality of life. The mean differences across all the five domains were not significant at p=0.05. The proportion of participants that were reported to have problems in each of the five domains were not significantly different between cases and controls (Table 6-15). Cases were reported to have a lower health score by their proxy compared to control participants (MD: -15.4 [95%CI: -31.0; 0.1] p-value 0.05).

Appendix 29 shows the proportion of participants with no problems vs those with problems, reported by group, and whether the health states were completed by patients themselves or their nominated consultee. For self-reported health states, there is visual difference whereas proxy completed no difference is observed, this is likely to be reflecting the impact that cognitive impairment has on those caring for them, regardless of whether they have a HPU.

Table 6-15 Summary of baseline HRQoL as measured using EQ-5D-5L completed by proxies (consultee)

EQ-5D-5L Domains; Median (Range)	**Cases (n=23)**	**Control (n=20)**	**Total (n=43)**	**Estimate Difference (95%)**	p-value
Mobility	5.0 (1-5)	4.0 (1-5)	5.0 (1-5)	1.0 (0.3; 1.7)	0.05
No problems in walking about	0.0	2.0 (10.0)	2.0 (4.7)	4.0 (0.2; 218.5)	0.3
Slight problems in walking about	0.0	3.0 (15.0)	3.0 (7.0)		
Moderate problems in walking about	2.0 (8.7)	3.0 (15.0)	5.0 (11.6)		
Severe problems in walking about	3.0 (13.0)	3.0 (15.0)	6.0 (14.0)		
Unable to walk about	18.0 (78.3)	9.0 (45.0)	27.0 (62.8)		
Self-care	5.0 (2-5)	5.0 (2-5)	5.0 (2-5)	0.4 (-0.2; 1.1)	0.2
No problems washing or dressing him/herself	0.0	0.0	0.0	1.1(0.01; 93.4)	1.0

EQ-5D-5L Domains; Median (Range)	**Cases (n=23)**	**Control (n=20)**	**Total (n=43)**	**Estimate Difference (95%)**	p-value
Slight problems washing or dressing him/herself	2.0 (8.7)	3.0 (15.0)	5.0 (11.6)		
Moderate problems washing or dressing him/herself	1.0 (4.4)	3.0 (15.0)	4.0 (9.3)		
Severe problems washing or dressing him/herself	3.0 (13.0)	3.0 (15.0)	6.0 (14.0)		
Unable to dress him/herself	17.0 (73.9)	11.0 (55.0)	28.0 (65.1)		
Usual Activities	5.0 (2.0-5.0)	5.0 (1.0-5.0)	5.0 (1.0-5.0)	0.6 (-0.02; 1.2)	0.06
No problems doing his/her usual activities	0.0	1.0 (5.0)	5.0 (2.3)	2.4 (0.1; 147.4)	0.6

EQ-5D-5L Domains; Median (Range)	**Cases (n=23)**	**Control (n=20)**	**Total (n=43)**	**Estimate Difference (95%)**	p-value
Slight problems his/her usual activities	1.0 (4.4)	2.0 (10.0)	3.0 (6.9)		
Moderate problems doing his/her usual activities	0.0	3.0 (15.0)	3.0 (7.0)		
Severe problems doing his/her usual activities	5.0 (21.7)	3.0 (15.0)	8.0 (18.6)		
I am unable to do his/her usual activities	17.0 (73.9)	11.0 (55.0)	28.0 (65.1)		
Pain/Discomfort	2.0 (1.0-5.0)	2.0 (1.0-5.0)	2.0 (1.0-5.0)	0.4 (-0.3; 1.1)	0.3
No pain or discomfort	7.0 (30.4)	9.0 (45.0)	16.0 (37.2)	2.0 (0.5; 8.3)	0.3
Slight pain or discomfort	7.0 (30.4)	5.0 (25.0)	12.0 (27.9)		

EQ-5D-5L Domains; Median (Range)	**Cases (n=23)**	**Control (n=20)**	**Total (n=43)**	**Estimate Difference (95%)**	p-value
Moderate pain or discomfort	5.0 (21.7)	5.0 (25.0)	10.0 (23.3)		
Severe pain or discomfort	2.0 (8.7)	0.0	2.0 (4.7)		
Extreme pain or discomfort	2.0 (8.7)	1.0 (5.0)	3.0 (7.0)		
Anxiety/depression	2.0 (1.0-5.0)	2.5 (1.0-5.0)	2.0 (1.0-5.0)	-0.3 (-1.1; 0.4)	0.4
Not anxious or depressed	8.0 (34.8)	4.0 (20.0)	12.0 (27.9)		
Slightly anxious or depressed	5.0 (21.7)	6.0 (30.0)	11.0 (25.6)		
Moderately anxious or depressed	7.0 (3.4)	5.0 (25.0)	12.0 (27.9)	0.6 (0.1; 2.6)	0.4
Severely anxious or depressed	1.0 (4.4)	3.0 (15.0)	4.0 (9.3)		
Extremely anxious or depressed	2.0 (8.7)	2.0 (10.0)	4.0 (9.3)		
Index scores	0.3 (-0.3 – 0.7)	0.3 (-0.3 – 0.8)	0.3 (0.3 – 0.8)	-0.1 (-0.3; 0.03)	0.1

EQ-5D-5L Domains; Median (Range)	**Cases (n=23)**	**Control (n=20)**	**Total (n=43)**	**Estimate Difference (95%)**	p-value
Subject's health today scores	30.0 (0.0-90.0)	60.0 (5.0; 99.0)	50.0 (0.0-99.0)	-15.4 (-31.0; 0.1)	0.05

^variables with p-values < 0.05

6.5.1.3 Baseline: Proxy Completed Pain Assessment

Pain Assessment in Advanced Dementia tool was used to assess pain for participants who were not able to report using a numeric rating scale; none of the 5 domains (Breathing independent of vocalisation, negative vocalisation, facial expression, body language, consolability) had a p-value < 0.1. Appendix 28 provides the overall pain assessment using PAINAD at baseline for participants who were not able to measure their pain using the NRS due to cognitive impairment.

6.5.2 Quality of Life and Pain Assessments at 3 months follow-up

6.5.2.1 Follow-up 3 months: Patient Reported Health Related Quality of Life and Pain Assessment.

A total of 42 participants (65.6%) completed their HRQoL assessment using the EQ5D-5L questionnaire at 3 months follow-up (summary results are presented in Table 6-16). Six participants were not contactable at 3 months follow-up (cases 4; controls 2) and withdrawal (n=1) imputed with baseline data. Two cases reported no problems at 3 months compared to zero at baseline, possibly because their pressure ulcer had healed. However, more cases continued to experience poor health states compared to controls at 3 months follow-up. Similar to baseline mobility, self-care and usual activities were statistically significant at 5% level and the mean index scores also remained the same as baseline including their health scores and pain as assessed using NRS. Table 6-16 presents a summary of the HRQoL at 3 months follow-up as measured using EQ-5D-5L and completed by participants.

Table 6-16 Summary of HRQoL as measured using EQ-5D-5L at 3 months follow-up as completed by participants.

EQ-5D-5L Domains; Median (Range)	**Case (n=19)**	**Control (n=22)**	**Total 42)**	**Parameter estimate mean difference / odds ratio (95% CI)**	**p-values**
Mobility	5.0 (1-5)	2.0 (1-5)	3.0 (1-5)	1.8 (1.4; 2.6)	**<0.0001^**
I have no problems in walking about	2.0 (3.3)	7.0 (33.3)	9.0 (22.0)	4.0 (0.6; 43.5)	**0.001^**
I have slight problems in walking about	0.0 (0.0)	5.0 (22.8)	5.0 (12.2)		
I have moderate problems in walking about	2.0 (10.5)	6.0 (27.6)	8.0 (19.5)		
I have severe problems in walking about	3.0 (15.8)	3.0 (13.6)	5.0 (14.6)		
I am unable to walk about	12.0 (63.2)	1.0 (4.8)	13.0 (31.7)		
Self-care	3.0 (1-5)	1.0 (1-4)	1.5 (1-5)	1.0 (0.2; 1.7)	**0.02^**

EQ-5D-5L Domains; Median (Range)	**Case (n=19)**	**Control (n=22)**	**Total 42)**	**Parameter estimate mean difference / odds ratio (95% CI)**	**p-values**
I have no problems washing or dressing myself	7.0 (36.8)	13.0 (51.1)	20.0 (48.8)	2.5 (0.6; 10.6)	**0.04^**
I have slight problems washing or dressing myself	0.0	3.0 (13.6)	3.0 (7.3)		
I have moderate problems washing or dressing myself	5.0 (26.3)	5.0 (22.7)	10.0 (24.9)		
I have severe problems washing or dressing myself	6.0 (31.6)	1.0 (4.8)	7.0 (17.1)		
I am unable to dress myself	1.0 (5.3)	0.0	1.0 (2.4)		

EQ-5D-5L Domains; Median (Range)	**Case (n=19)**	**Control (n=22)**	**Total 42)**	**Parameter estimate mean difference / odds ratio (95% CI)**	**p-values**
Usual Activities	4.0 (1.0-5.0)	2.0 (1.0-5.0)	3.0 (1.0-5.0)	1.2 (0.3; 2.2)	**0.01^**
I have no problems doing my usual activities	4.0 (21.1)	9.0 (40.9)	13.0 (31.7)	2.8 (0.6;15.4)	**0.04^**
I have slight problems washing or dressing myself	0.0	3.0 (13.4)	3.0 (7.3)		
I have moderate problems doing my usual activities	3.0 (15.8)	3.0 (13.4)	6.0 (14.6)		
I have severe problems doing my usual activities	3.0 (15.8)	5.0 (22.7)	8.0 (19.5)		

EQ-5D-5L Domains; Median (Range)	**Case (n=19)**	**Control (n=22)**	**Total 42)**	**Parameter estimate mean difference / odds ratio (95% CI)**	**p-values**
I am unable to do my usual activities	9.0 (47.4)	2.0 (9.5)	11.0 (26.8)		
Pain/Discomfort	3.0 (1.0-5.0)	2.0 (1.0-5.0)	3.0 (1.0-5.0)	0.4 (-0.4; 1.2)	0.3
I have no pain or discomfort	4.0 (21.1)	5.0 (22.7)	9.0 (22.0)		
I have slight pain or discomfort	3.0 (15.8)	7.0 (31.8)	10.0 (24.4)		
have moderate pain or discomfort	5.0 (26.3)	4.0 (18.2)	9.0 (22.0)	1.2 (0.2; 7.1)	0.8
I have severe pain or discomfort	6.0 (16.7)	5.0 (22.7)	10.0 (26.8)		
I have extreme pain or discomfort	1.0 (5.3)	1.0 (4.5)	2.0 (4.9)		
Anxiety/Depression	2.0 (1.0-5.0)	1.0 (1.0-4.0)	1.5 (1.0-5.0)	0.3 (-0.4; 1.0)	0.3

EQ-5D-5L Domains; Median (Range)	**Case (n=19)**	**Control (n=22)**	**Total 42)**	**Parameter estimate mean difference / odds ratio (95% CI)**	**p-values**
I am not anxious or depressed	9.0 (47.4)	11.0 (52.4)	20.0(50.0)	1.2 (0.3; 5.0)	0.9
I am slightly anxious or depressed	3.0 (15.8)	5.0 (22.7)	8.0 (20.0)		
I am moderately anxious or depressed	4.0 (21.1)	5.0 (22.7)	8.0 (20.0)		
I am severely anxious or depressed	2.0 (10.5)	1.0 (4.8)	3.0 (7.5)		
I am extremely anxious or depressed	1.0 (5.3)	0.0	1.0 (2.5)		
Index score	0.4 (-0.2- 1.0)	0.7 (0.3; 1.0)	0.5 (-0.2- 1.0)	-0.3 (-0.5; -0.1)	**0.002^**
Your health today scores	50.0 (22.0-100.0)	77.5 (50.0-100.0)	75.0 (22.0-100.0)	-10.3 (-22.9; 2.0)	0.1

EQ-5D-5L Domains; Median (Range)	**Case (n=19)**	**Control (n=22)**	**Total 42)**	**Parameter estimate mean difference / odds ratio (95% CI)**	**p-values**
Pain Numeric rating scale	6.0 (0.0-10.0)	5.0 (0.0 - 10.0)	5.0 (0.0-10.0)	0.8 (-1.3; 2.8)	0.5

^variables with p-values < 0.05

6.5.2.2 Follow-up 3 months: Proxy Completed Health Related Quality of Life Assessment

Two participants were not contactable through their consultee at 3 months follow-up, their missing data was imputed with baseline (controls n=2). Ten participants (cases n=5; control n=5) who had previously completed their questionnaire at baseline, their cognition had deteriorated at 3 months follow-up and therefore their QoL assessment was completed with the help of their consultee. Despite this, the overall sample size for this group of participants was reduced by 25.5% (11/43). Cases were reported to have at least moderate or severe problems with caring for themselves. On average, controls appear to have better health states at 3 months follow-up compared to baseline. The difference between mean scores for mobility, self-care, and usual activities significant at p=0.05. At 3 months follow-up, better HRQoL was reported for controls compared to cases and the difference in index score was significant [-0.2 (-0.4; -0.006), p=0.04] for a sample size of 32 participants (Table *6-17* provides further details).

Table 6-17 Summary of HRQoL measured using EQ-5D-5L completed by proxy (consultee) at 3 months follow-up.

EQ-5D-5L Domains; Median (Range)	**Cases (n=16)**	**Control (n=16)**	**Total (n=32)**	**Estimate Difference (95%)**	**p-value**
Mobility	5.0 (2-5)	4.0 (1-5)	5.0 (1-5)	1.3 (0.3; 2.2)	**0.01^**
I have no problems in walking about	0.0	3.0 (18.8)	3.0 (9.3)		
I have slight problems in walking about	1.0 (6.3)	3.0 (18.8)	4.0 (12.1)		
I have moderate problems in walking about	2.0 (12.5)	2.0 (12.5)	4.0 (12.1)	4.5 (0.4; 236.1)	0.07
I have severe problems in walking about	0.0	2.0 (12.5)	3.0 (9.1)		
I am unable to walk about	13.0 (81.3)	6.0 (37.5)	19.0 (57.6)		
Self-care	5.0 (3-5)	4.0 (1-5)	5.0 (1-5)	**1.1 (0.3; 18)**	**0.009^**
I have no problems washing or dressing myself	0.0	1.0(6.3)	1.0 (3.1)	2.1 (0.09; 132.6)	1.0

EQ-5D-5L Domains; Median (Range)	**Cases (n=16)**	**Control (n=16)**	**Total (n=32)**	**Estimate Difference (95%)**	**p-value**
I have slight problems washing or dressing myself	0.0	3.0 (18.8)	3.0 (9.3)		
I have moderate problems washing or dressing myself	2.0 (12.5)	3.0 (18.8)	5.0 (15.6)		
I have severe problems washing or dressing myself	1.0 (6.3)	3.0 (18.8)	4.0 (12.5)		
I am unable to dress myself	13.0 (81.3)	6.0 (37.5)	19.0 (59.4)		
Usual Activities	5.0 (2.0-5.0)	5.0 (1.0-5.0)	5.0 (1.0-5.0)	**0.9 (0.07; 1.8)**	**0.04^**
I have no problems doing my usual activities	0.0	1.0 (6.3)	1.0 (3.1)	2.0 (0.09; 124.8)	0.2
I have slight problems washing or dressing myself	1.0 (6.2)	3.0 (18.8)	4.0 (12.5)		

EQ-5D-5L Domains; Median (Range)	**Cases (n=16)**	**Control (n=16)**	**Total (n=32)**	**Estimate Difference (95%)**	**p-value**
I have moderate problems doing my usual activities	2.0 (12.5)	4.0 (25.0)	6.0 (18.8)		
I have severe problems doing my usual activities	0.0	1.0 (6.3)	1.0 (3.1)		
I am unable to do my usual activities	13.0 (81.3)	7.0 (43.8)	20.0 (60.6)		
Pain/Discomfort	2.0 (1.0-5.0)	2.0 (1.0-4.0)	2.0 (1.0-5.0)	0.5 (-0.4; 1.4)	0.3
I have no pain or discomfort	6.0 (37.5)	8.0 (50.0)	14.0 (43.8)		
I have slight pain or discomfort	3.0 (18.8)	2.0 (12.5)	5.0 (15.6)		
have moderate pain or discomfort	4.0 (25.0)	6.0 (37.5)	10.0 (31.3)	1.7 (0.3; 8.5)	0.4
I have severe pain or discomfort	1.0 (8.7)	0.0	1.0 (3.1)		
I have extreme pain or discomfort	2.0 (12.5)	0.0	2.0 (6.5)		

EQ-5D-5L Domains; Median (Range)	**Cases (n=16)**	**Control (n=16)**	**Total (n=32)**	**Estimate Difference (95%)**	**p-value**
Anxiety/Depression	2.0 (1.0-5.0)	3.0 (1.0-4.0)	2.0 (1.0-5.0)	-0.5 (-1.3; 0.3)	0.2
I am not anxious or depressed	7.0 (43.8)	2.0 (12.5)	9.0 (28.1)		
I am slightly anxious or depressed	4.0 (25.0)	5.0 (31.3)	9.0 (28.1)		
I am moderately anxious or depressed	2.0 (12.5)	5.0 (31.3)	8.0 (21.9)	0.2(0.2; 1.2)	1.0
I am severely anxious or depressed	1.0 (6.3)	4.0 (25.0)	5.0 (15.6)		
I am extremely anxious or depressed	2.0 (12.5)	0.0	2.0 (6.3)		
Index score	0.3 (-.3 - 0.7)	0.3 (-0.03 -0.8)	0.3 (-0.3 – 0.8)	**-0.2 (-0.4; -0.006)**	**0.04^**
Your health today scores	42.5 (10.0-90.0)	60.0 (20.0; 85.0)	50.0 (10.0-90.0)	-12.5 (-28.3; 3.3)	0.3

^variables with p-values < 0.05

6.5.2.3 Follow-up 3 months: Proxy Completed Pain Assessment.

Pain assessment for participants deemed to have cognitive impairment was measured using a PAINAD scale completed by their consultee with the support of the researcher at all study time points. There was no significant change in the pain score as measured by PAINAD scale [-0.4 (-2.1; 1.5) p=0.7] at 3 months follow-up (full results are presented in Table *6-18*).

Table 6-18 Summary of pain assessment using PAINAD tool at 3 months follow-up.

PAINAD subdomains; Median (Range)	**Cases (n=23)**	**Control (n=20)**	**Total (n=43)**	**Estimate Difference (95%)**	**p-value**
Breathing independent of vocalisation	0.0 (0.0 - 2.0)	0.0 (0.0 - 1.0)	0.0 (0.0 - 2.0)	0.1 (-0.3; 0.5)	0.8
Normal	11.0 (68.8)	11.0 (68.8)	22.0 (68.7)	-	1.0
Occasional laboured breathing. Short period of hyperventilation	4.0 (25.0)	5.0 (29.4)	9.0 (28.1)		
Noisy laboured breathing. Long period of hyperventilation. Cheyne-stokes respirations	1.0 (6.3)	0.0	1.0 (3.1)		
Negative vocalisation	0.0 (0.0 - 2.0)	0.0 (0.0 - 2.0)	0.0 (0.0 - 2.0)	-0.1 (-0.6; 0.5)	0.8

PAINAD subdomains; Median (Range)	**Cases (n=23)**	**Control (n=20)**	**Total (n=43)**	**Estimate Difference (95%)**	**p-value**
None	10.0 (62.5)	9.0 (56.3)	19.0 (59.4)	-	1.0
Occasional moan or groan. Low-level of speech with a negative or disapproving quality	4.0 (25.0)	5.0 (31.5)	9.0 (28.1)		
Repeated troubled calling out. Loud moaning or groaning. Crying.	2.0 (1.,5)	2.0 (12.5)	4.0 (12.5)		
Facial expression	0.0 (0.0-1.0)	0.0 (0.1.0)	0.0 (0.1.0)	0.0 (-0.3; 0.3)	1.0
Smiling or inexpressive	11.0 (68.8)	11.0 (68.8)	22.0 (68.8)	-	1.0
Sad, frightened, frown	5.0 (31.3)	5.0 (31.3)	10.0 (31.2)		
Facial grimacing	0.0	0.0	0.0		
Body language	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	-0.3 (-0.6; 0.1)	0.2
Relaxed	11.0 (68.8)	7.0 (43.7)	18.0 (56.3)	-	0.3
Tense, distressed pacing, fidgeting	5.0 (31.3)	9.0 (56.3)	17.0 (43.7)		

PAINAD subdomains; Median (Range)	**Cases (n=23)**	**Control (n=20)**	**Total (n=43)**	**Estimate Difference (95%)**	**p-value**
Rigid. Fists clenched. Knees pulled up. Pulling or pushing away. Striking out	0.0	0.0	0.0		
Consolability	0.0 (0.0-2.0)	1.0 (0.0-1.0)	0.0 (0.0-2.0)	0.2 (-0.6; 0.3)	0.4
No need to console	10.0 (62.5)	8.0 (50.0)	18.0 (56.3)	-	0.7
Distracted or reassured by voice or touch	5.0 (31.3)	8.0 (50.0)	13.0 (40.6)		
Unable to console, distract or reassure	1.0 (6.3)	0.0	1.0 (3.1)		
Total score	0.0 (0.0-6.0)	2.0 (0.0 – 6.0)	0.5 (0.0-6.0)	-0.4 (-2.1; 1.5)	0.7

6.5.3 Quality of Life and Pain Assessments at 6 months Follow-up

6.5.3.1 Follow-up 6 months: Patient Reported Health Related Quality of Life and Pain Assessment.

At 6 months follow-up, 47.1% (33/70) participants that were still alive were able to complete their own QoL assessment (full results are presented in Table 6-19). All the cases had at least slight or worse problems with mobility. On average controls continued to report better QoL compared to cases. Differences in mean index score

remain significant [-0.2 (-0.4; -0.05), p=0.02]. The control group reported better health scores by a mean difference of [-13.8 (--27.0; -0.6) p=0.04]. Table 6-19 summarises the HRQoL at 6 months follow-up as measured using EQ-5D-5L for participants deemed to be able to complete their own questionnaire. Average pain scores as measured using the NRS were not significantly different at 6 months follow-up.

Table 6-19 Summary of HRQoL as measured using EQ-5D-5L at 6 months follow-up.

EQ-5D-5L Domains; Median (Range)	**Case (n=14)**	**Control (n=19)**	**Total (n=33)**	**Estimate Difference (95% CI)**	**p-values**
Mobility	5.0 (1-5)	3.0 (1-5)	3.5 (1-5)	1.3 (0.4; 2.2)	**0.007^**
I have no problems in walking about	0.0	6.0 (31.5)	6.0 (18.2)	7.5 (0.8; 360.0)	**0.03^**
I have slight problems in walking about	3.0 (21.4)	4.0 (21.1)	7.0 (21.2)		
I have moderate problems in walking about	3.0 (21.4)	4.0 (21.1)	7.0 (21.2)		
I have severe problems in walking about	2.0 (14.3)	4.0 (21.2))	6.0 (18.2)		
I am unable to walk about	6.0 (42.9)	1.0 (5.3)	7.0 (21.2)		
Self-care	2.0 (1.0 – 4.0)	1.0 (1.0 – 4.0)	2.0 (1.0 – 4.0)	0.7 (-0.9; 1.6)	0.08
I have no problems washing or dressing myself	5.0 (35.7)	12.0 (63.2)	17.0 (51.2)	3.1 (0.6; 16.6)	0.2

EQ-5D-5L Domains; Median (Range)	**Case (n=14)**	**Control (n=19)**	**Total (n=33)**	**Estimate Difference (95% CI)**	**p-values**
I have slight problems washing or dressing myself	3.0 (21.4)	2.0 (10.5)	10.0 (16.7)		
I have moderate problems washing or dressing myself	1.0 (7.1)	4.0 (21.1)	10.0 (16.7)		
I have severe problems washing or dressing myself	5.0 (35.7)	1.0 (5.3)	8.0 (13.3)		
I am unable to dress myself	0.0	0.0	6.0 (10.0)		
Usual Activities	3.5 (1.0 - 5.0)	2.0 (1.0 – 5.0)	3.0 (1.0 – 5.0)	1.0 (-0.05; 2.1)	0.06
I have no problems doing my usual activities	3.0 (21.4)	8.0 (42.1)	11.0 (33.3)	2.7 (0.5; 19.3)	0.1

EQ-5D-5L Domains; Median (Range)	**Case (n=14)**	**Control (n=19)**	**Total (n=33)**	**Estimate Difference (95% CI)**	**p-values**
I have slight problems washing or dressing myself	2.0 (14.3)	3.0 (15.8)	5.0 (15.2)		
I have moderate problems doing my usual activities	2.0 (14.3)	5.0 (26.3)	7.0 (21.2)		
I have severe problems doing my usual activities	2.0 (14.3)	1.0 (5.3)	3.0 (9.1)		
I am unable to do my usual activities	5.0 (35.7)	2.0 (10.5)	7.0 (21.2)		
Pain/Discomfort	3.0 (1.0 – 5.0)	2.0 (1.0 – 5.0)	3.0 (1.0 – 5.0)	0.4 (-0.5; 1.3)	0.4
I have no pain or discomfort	4.0 (23.3)	6.0 (36.7)	10.0 (30.3)	0.4 (0.03; 3.4)	0.6
I have slight pain or discomfort	0.0	4.0 (21.1)	4.0 (12.1)		

EQ-5D-5L Domains; Median (Range)	**Case (n=14)**	**Control (n=19)**	**Total (n=33)**	**Estimate Difference (95% CI)**	**p-values**
have moderate pain or discomfort	6.0 (42.9)	6.0 (31.6)	12.0 (36.4)		
I have severe pain or discomfort	3.0 (16.7)	2.0 (13.3)	5.0 (15.2)		
I have extreme pain or discomfort	1.0 (7.4)	1.0 (5.3)	2.0 (6.1)		
Anxiety/Depression	2.0 (1.0 – 4.0)	1.0 (1.0 – 4.0)	1.0 (1.0 – 5.0)	0.4 (-0.3; 1.1)	0.2
I am not anxious or depressed	6.0 (42.8)	11.0 (57.9)	17.0 (51.5)		
I am slightly anxious or depressed	2.0 (14.2)	5.0 (26.3)	13.0 (21.7)		
I am moderately anxious or depressed	5.0 (35.7)	2.0 (10.5)	22.0 (36.7)	1.8 (0.4; 9.3)	0.4
I am severely anxious or depressed	1.0 (7.1)	1.0 (5.3)	0.0		
I am extremely anxious or depressed	0.0	0.0	1.0 (1.7)		
Index score	0.5 (-0.2 – 0.9)	0.8 (0.3 – 1.0)	0.7 (-0.2 – 1.0)	-0.2 (-0.4; -0.05)	**0.02^**

EQ-5D-5L Domains; Median (Range)	**Case (n=14)**	**Control (n=19)**	**Total (n=33)**	**Estimate Difference (95% CI)**	**p-values**
Your health today scores	55.0 (22.0 – 100.0)	75.0 (50.0 – 100.0)	60.0 (22.0 - 100.0)	-13.8 (--27.0; -0.6)	**0.04^**
Pain Numeric rating scale	5.0 (0.0-10.0)	5.0 (0.0-9.0)	5.0 (0.0-10.0)	0.6 (-1.8; 3.1)	0.6

6.5.3.2 Follow-up 6 months: Proxy Completed Health Related Quality of Life.

Nearly half of the remaining study population had some form of cognitive impairment at 6 months follow-up; eight participants' (cases n=5; controls n=3) cognition had deteriorated since their 3 months follow-up and they were no longer able to complete their own QoL assessment. Overall quality of life was similar between cases and control, both had index scores of less than 0.5 and p >0.05 (full results are presented in Table *6-20*).

Table 6-20 Summary of HRQoL as measured using EQ-5D-5L completed by proxy at 6 months study follow-up

EQ-5D-5L Domains; Median (Range)	**Cases (n=15)**	**Control (n=15)**	**Total (n=30)**	**Parameter estimate (95%)**	**p-value**
Mobility	5.0 (1.0 - 5.0)	4.0 (1.0 - 5.0)	5.0 (1.0 - 5.0)	1.0 (0.3; 1.7)	0.2
I have no problems in walking about	1.0 (6.7)	2.0 (13.3)	3.0 (10.0)	2.2 (0.1; 136.0)	0.4
I have slight problems in walking about	2.0 (13.3)	3.0 (20.0)	5.0 (16.7)		
I have moderate problems in walking about	0.0	2.0 (13.3)	2.0 (6.7)		

EQ-5D-5L Domains; Median (Range)	**Cases (n=15)**	**Control (n=15)**	**Total (n=30)**	**Parameter estimate (95%)**	**p-value**
I have severe problems in walking about	1.0 (6.7)	2.0 (13.3)	3.0 (10.0)		
I am unable to walk about	11.0 (73.3)	6.0 (40.0)	17.0 (56.7)		
Self-care	5.0 (1.0 – 5.0)	4.0 (2.0 – 5.0)	4.5 (1.0 -5.0)	0.1 (-0.9; 1.4)	0.8
I have no problems washing or dressing myself	2.0 (13.3)	0.0	2.0 (6.7)		
I have slight problems washing or dressing myself	1.0 (6.7)	2.0 (13.3)	3.0 (10.0)	3.1 (0.6; 16.6)	0.4
I have moderate problems washing or dressing myself	2.0 (13.3)	5.0 (33.3)	7.0 (23.3)		

EQ-5D-5L Domains; Median (Range)	**Cases (n=15)**	**Control (n=15)**	**Total (n=30)**	**Parameter estimate (95%)**	**p-value**
I have severe problems washing or dressing myself	1.0 (6.7)	2.0 (13.3)	3.0 (10.0)		
I am unable to dress myself	9.0 (60.0)	6.0 (40.0)	28.0 (65.1)		
Usual Activities	5.0 (1.0-5.0)	4.0 (1.0-5.0)	5.0 (1.0-5.0)	0.6 (-0.02; 1.4)	0.1
I have no problems doing my usual activities	1.0 (6.7)	0.0	1.0 (3.3)	0.5 (0.007; 10.1)	0.07
I have slight problems washing or dressing myself	0.0	1.0 (6.7)	1.0 (3.3)		
I have moderate problems doing my usual activities	1.0 (6.7)	6.0 (40.0)	7.0 (23.3)		

EQ-5D-5L Domains; Median (Range)	**Cases (n=15)**	**Control (n=15)**	**Total (n=30)**	**Parameter estimate (95%)**	**p-value**
I have severe problems doing my usual activities	1.0 (6.7)	1.0 (6.7)	2.0 (6.7)		
I am unable to do my usual activities	12.0 (80.0)	7.0 (46.7)	19.0 (63.3)		
Pain/Discomfort	2.0 (1.0 – 5.0)	2.0 (1.0 – 3.0)	2.0 (1.0 – 5.0)	0.2 (-0.6; 1.0)	0.6
I have no pain or discomfort	5.0 (33.3)	6. 0 (40.0)	11.0 (36.7)		
I have slight pain or discomfort	5.0 (33.3)	4.0 (26.7)	9.0 (30.0)		
have moderate pain or discomfort	4.0 (26.7)	5.0 (33.3)	9.0 (30.0)	1.6 (0.3; 8.4)	1.0
I have severe pain or discomfort	0.0	0.0	0.0		
I have extreme pain or discomfort	1.0 (6.7)	0.0	1.0 (3.3)		
Anxiety/Depression	2.0 (1.0-5.0)	3.0 (1.0-4.0)	2.0 (1.0-5.0)	-0.5 (-1.4; 0.3)	0.2

EQ-5D-5L Domains; Median (Range)	**Cases (n=15)**	**Control (n=15)**	**Total (n=30)**	**Parameter estimate (95%)**	**p-value**
I am not anxious or depressed	5.0 (33.3)	1.0 (6.7)	16.0 (37.2)		
I am slightly anxious or depressed	5.0 (33.3)	5.0 (33.3)	12.0 (27.9)		
I am moderately anxious or depressed	2.0 (13.3)	5.0 (33.3)	10.0 (23.3)	0.1 (0.002; 1.7)	0.2
I am severely anxious or depressed	2.0 (13.3)	4.0 (26.7)	2.0 (4.7)		
I am extremely anxious or depressed	1.0 (6.7)	0.0	3.0 (7.0)		
Index score	0.3 (-0.3 – 1.0)	0.3 (-0.03 – 0.8)	0.3 (-0.3 – 1.0)	-0.09 (-0.3; 0.1)	0.4
Your health today scores	50.0 (20.0 – 100.0)	60.0 (25.0 - 85.0)	57.5 (10.0 - 100.0)	0.0 (-15.9; 15.9)	1.0

6.5.3.3 Follow-up 6 months: Proxy Completed Pain Assessment.

Average pain scores for participants with cognitive impairment (proxy reported) at 6 months follow-up did not change significantly in both participant groups. Most of the scores reported at 6 months follow-up remained the same as those reported at 3 months follow-up (see Appendix 28). The observed pain score difference at 6 months follow-up was not statistically significant between the two study groups. Table *6-21* presents the PAINAD results at 6 months follow-up as completed by the consultees, with the support of the researcher, for participants deemed to lack the ability to complete study questionnaires due to living with cognitive impairment.

Table 6-21 Summary of pain assessment as measured using PAINAD at 6 months study follow-up

PAINAD subdomains; Median (Range)	**Cases (n=15)**	**Control (n=15)**	**Total (n=30)**	**Estimate Difference (95%)**	**p-value**
Breathing independent of vocalisation	0.0 (0.0 - 2.0)	0.0 (0.0 - 1.0)	0.0 (0.0 - 2.0)	0.3 (-0.1; 0.6)	0.2
Normal	10.0 (66.7)	13.0 (86.7)	23.0 (76.7)	-	0.3
Occasional laboured breathing. Short period of hyperventilation	4.0 (26.7)	2.0 (13.3)	6.0 (20.0)		
Noisy laboured breathing. Long period of hyperventilation. Cheyne-stokes respirations	1.0 (6.7)	0.0	1.0 (3.3)		

PAINAD subdomains; Median (Range)	**Cases (n=15)**	**Control (n=15)**	**Total (n=30)**	**Estimate Difference (95%)**	**p-value**
Negative vocalisation	1.0 (0.0-2.0)	0.0 (0.0-1.0)	0.0 (0.0 – 2.0)	0.2 (-0.2; 0.6)	0.3
None	6.0 (40.0)	8.0 (53.3)	14.0 (46.7)		
Occasional moan or groan. Low-level of speech with a negative or disapproving quality	8.0 (53.3)	7.0 (46.7)	15.0 (50.0)		0.7
Repeated troubled calling out. Loud moaning or groaning. Crying.	1.0 (6.7)	0.0	1.0 (3.3)		
Facial expression	0.0 (0.0-2.0)	0.0 (0.0-1.0)	0.0 (0.0-3.0)	0.2 (-0.2; 0.5)	0.3
Smiling or inexpressive	9.0(60.0)	11.0 (73.3)	20.0 (66.7)		
Sad, frightened, frown	6.0 (40.0)	4.0 (26.7)	10.0 (33.3)	-	0.4
Facial grimacing	0.0	0.0	0.0		
Body language	0.0 (0.0 - 1.0)	0.0 (0.0 - 2.0)	0.0 (0.0 - 2.0)	-0.1 (-0.6; 0.3)	0.6
Relaxed	9.0 (60.0)	9.0 (60.0)	18.0 (60.0)		
Tense, distressed pacing, fidgeting	6.0 (40.0)	4.0 (26.7)	10.0 (33.3)	-	0.5

PAINAD subdomains; Median (Range)	**Cases (n=15)**	**Control (n=15)**	**Total (n=30)**	**Estimate Difference (95%)**	**p-value**
Rigid. Fists clenched. Knees pulled up. Pulling or pushing away. Striking out	0.0	2.0 (13.3)	2.0 (6.7)		
Consolability	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.2 (-0.3; 0.6)	0.4
No need to console	12.0 (80.0)	10.0 (66.7)	22.0 (73.3)		
Distracted or reassured by voice or touch	3.0 (20.0)	5.0 (33.3)	8.0 (26.7)		0.7
Unable to console, distract or reassure	0.0	0.0	0.0		
Total score	2.0 (0.0-7.0)	1.0 (0.0-6.0)	1.5 (0.0-7.0)	0.3 (-1.2; 1.9)	0.7

6.5.4 Phase 3b: The Prognostic Value of HPUs in End of Life

This section presents the findings from a survival analysis using Cox Proportional Hazard aimed at investigating the predictive value of HPUs in EoL.

6.5.4.1 Survival Analysis at 3 months Follow-up

All 103 participants were followed up for survival using the SPINE NHS database at both 3- and 6-months post recruitment. Overall study mortality rate at 3 months follow-up was 29.1% (30/103) and at 6 months follow-up was 38.8% (40 /103) including three unmatched cases. The Kaplan Meier graph (Figure *6-4*) presents the survival estimates for each group at 3 months follow-up. Up to 40 days from recruitment, there was no difference in survival rates between cases and controls. At

both 3- and 6-months follow-up, none of the groups' survival rates decreased below 50%, therefore median survival rates could not be calculated using study data. At 3 months follow-up, 75% of the participants were still alive at 60 days compared to 75% still alive at 97 days for the control group (as shown in Figure 6-4), with a log rank p-value of 0.2. The observed difference in survival rate between the case and control groups were not statistically significant.

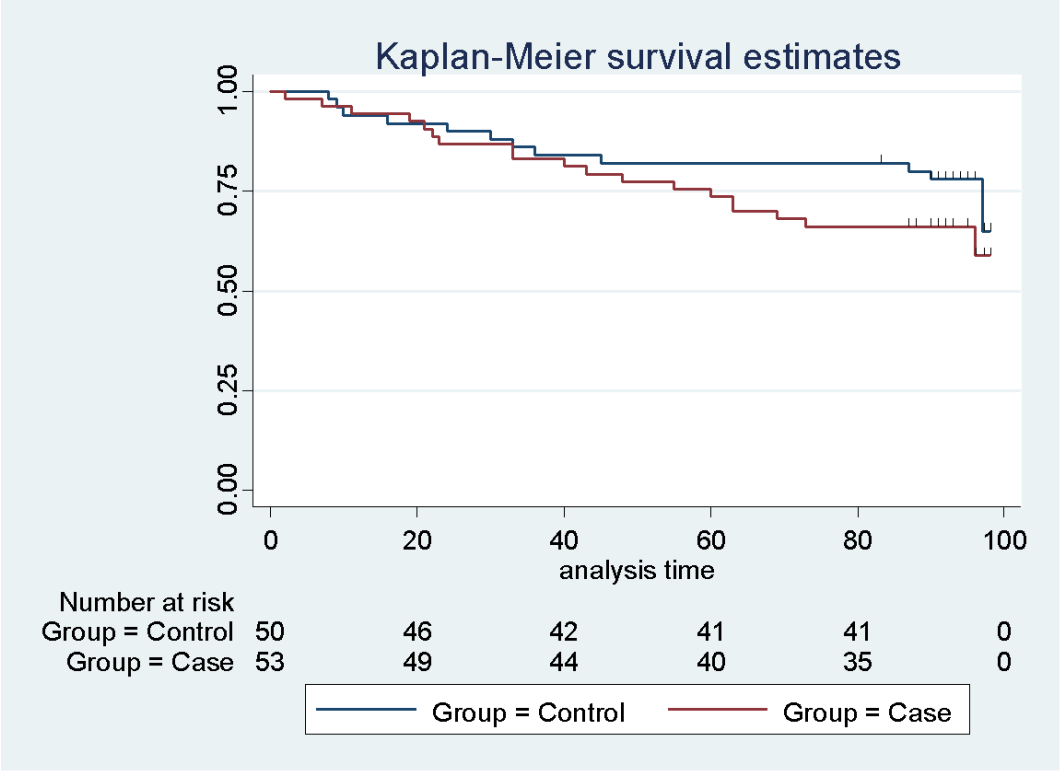


Figure 6-4 K-M survival estimates at 3 months follow-up by study group.

6.5.4.2 Survival Analysis at 6 months Follow-up

At 6 months follow-up, 45.3 % of cases had died compared to 32.0% of controls; 75.0% of cases were alive at 60 days compared to 75.0% still alive at 131 days in the control group with a log rank p-value of 0.2. Figure 6-5 presents the Kaplan Meier curve used to analyse the time to death (time to event). Although the gap between KM curves, which represents survival rate difference, appeared to widen beyond t=150, though there was no evidence to support the difference observed. Therefore, there were no significant differences detected between cases and control mortality rates at 6 months follow-up since date of recruitment. A Cox Hazard regression model adjusted for

participant group (cases vs control) reported a OR 1.5 (0.8; 2.9) p-value =0.2, which suggests that there is no evidence to support the difference in mortality rate between the two groups, therefore further modelling to adjust for potential confounders was deemed unnecessary.

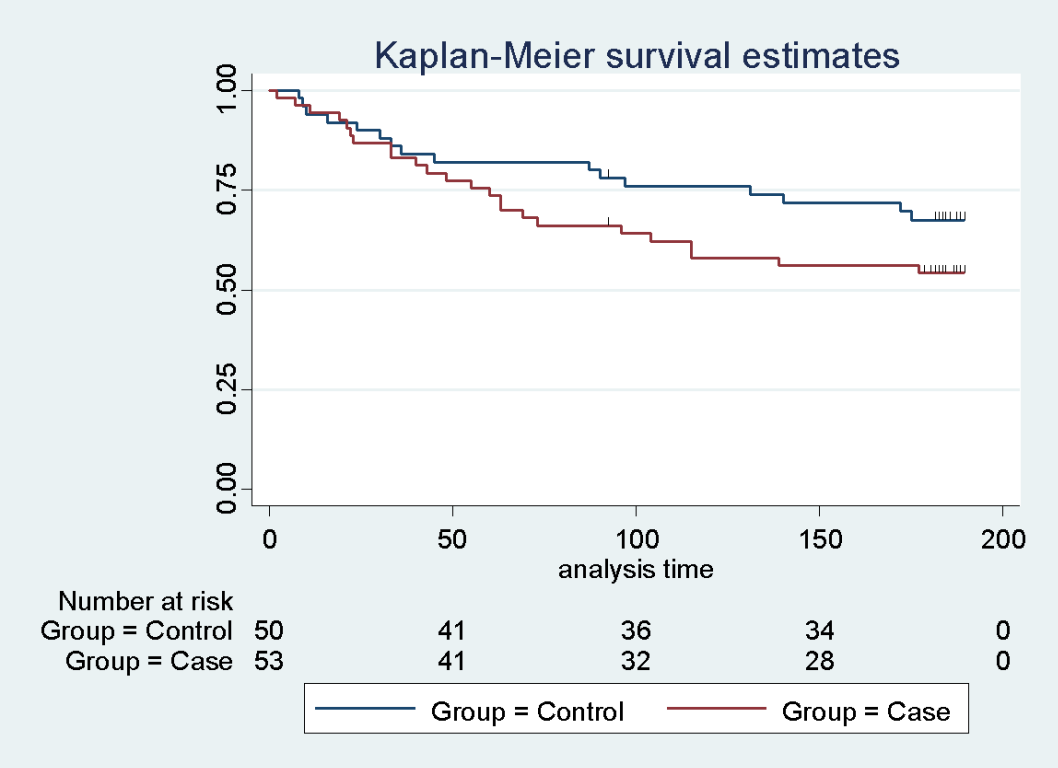


Figure 6-5 K-M survival estimates at 6 months follow-up by study group.

Table *6-22* summarises survival rates follow-up data at 3- and 6- months by study group. Summary details of cause of death are presented in Appendix 30 as reported in patients' medical records. For participants that died in hospital, the cause of death data was complete. However, for those that died either in their homes or community care settings, cause of death was not always available on the hospital databases. Attempts were made to obtain this data through patients' GPs; however, all attempts were unsuccessful. Therefore, nearly half of the data was reported as unknown (47.5%). Participants with known cause of death had at least three or more health conditions listed in their medical records as contributing to their death. Acute kidney injury (AKI), chronic kidney disease (CKD), and hypertension (HTN) were the most reported cause of death, despite being listed in less than ten separate participants' medical notes.

Table 6-22 Summary of survival rates follow-up data at 3- and 6- months by study group

Follow-up period	**Case (n=53)**	**Control (n=50)**	**Total (n=53)**
3 months follow-up			
Alive	31.0 (58.5)	34.0 (68.0)	64.0 (62.1)
Deceased	18.0 (34.0)	12.0(24.0)	30.0 (30.1)
[a]Lost to follow-up	4.0 (7.5)	4.0 (8.0)	8.0 (7.8)
6 months follows up			
Alive	27.0 (50.9)	31.0 (62.0)	58.0 (56.1)
Deceased	24.0 (45.3)	16.0 (32.0)	40.0 (38.8)
[a]Lost to follow-up	2.0 (3.8)	3.0 (6.0)	5.0 (4.9)

a=follow-up for survival using SPINE database (considered still alive)

6.6 Summary

In this study, a total of 103 participants were enrolled, with over 40% of them experiencing varying degrees of cognitive impairment that impacted their capacity to provide informed study consent. The case and control groups were comparable in terms of the four matching variables. The study explored numerous variables as potential risk factors for the development of HPUs, the following variables were statistically significant in a multivariable logistic analysis (AF, albumin, composite variables for total Braden Scale score, CKD and diabetes and peripheral neuropathy assessment scores). HPUs were observed to negatively affect health related quality of life for patient reported outcomes. However, there was no discernible evidence to suggest differential quality of life outcomes for participants living with cognitive impairment. Furthermore, although the mortality rate was observed to be higher among the cases compared to the control group, these differences did not reach statistical significance. Chapter 7 and 8 respectively, discuss these findings in the context

of the wider literature as well as discuss the contribution to knowledge based on the findings of this thesis.

Chapter 7 Discussion

7.1 Introduction

Pressure ulcers (PUs) remain a healthcare challenge due to their impact on quality of life, patient experience and outcomes, and continued financial demands on the NHS. Heel pressure ulcers (HPUs) are of interest in this study as they remain the second most common PU accounting for at least 30% of all PUs. Heels are anatomically disadvantaged as they have less tissue, less blood vessels, and sharp calcaneus bone thus increasing the risk of pressure damage in this area. Because of anatomical differences, heels require additional specialist equipment such as offloading and heel cushioning devices for elevation, however, there is unclear evidence to support the use of these specialist devices (Greenwood et al., 2022). There is also further evidence to suggest that risk factors for developing them might be different from those of other body sites, due to anatomical differences (Gefen, 2010). This thesis was therefore an exploratory study aimed at identifying factors associated with the presence or developing of HPUs in the adult population and quantifying their relationship, investigating the impact of HPUs on health-related quality of life (HRQoL) using EQ-5D-5L questionnaire, and investigating the prognostic value of HPUs in end of life (EoL).

To achieve the study aim, this thesis was underpinned by a pragmatic philosophy and used three distinct methodologies divided into three phases as outlined below.

- Phase 1 – was a systematic literature review conducted to identify and synthesise the evidence available in the literature on risk factors for developing HPUs in the adult population (published by (Dube et al., 2022)). The review identified several potential risk factors, however, most of them required further investigation as previously suggested by the EPUAP/NPUAP/PPPA (2019) in its PU definition. Therefore, the results of the systematic literature review were used to inform the design and data collection methods of a matched case control study, which formed the second component of this thesis (Phase 2).

- Phase 2 – was a matched case control study aimed at providing further evidence on already identified risk factors and potentially detect additional risk factors associated with HPU presence.
- Phase 3 - was a prospective cohort study which was designed to investigate a) the impact of HPUs on HRQoL and b) their prognostic value in EoL. This phase involved the study population that was recruited in Phase 2.

This chapter discusses the study findings within the wider context of available literature. Study limitations and strengths will be presented and discussed, and the chapter will conclude with a summary.

7.2 The HPU Risk Factors Framework

Risk assessment is an important aspect of PU prevention, and it is used to identify those at risk of developing PUs. PU guidelines and best practices recommend the use of a validated tool in conjunction with clinical judgement (European Pressure Ulcer Advisory Panel et al., 2019; NICE, 2014). However, the existing validated tools do not differentiate risk by anatomical site despite evidence suggesting variations in incidence and prevalence rates (Sardo et al., 2023). In addition, this assumes the existence of high-quality evidence to inform the risk assessment process. Phase 1 (Chapter 3) was the first systematic literature review to synthesise the existing evidence on factors associated with the presence of HPUs despite them being the second most common PUs after sacral PUs.

Most research classifies pressure ulcers (PUs) into a single, heterogeneous category, but evidence suggests that different anatomical sites have unique risk factors, as highlighted by Clark et al. (2017), Gefen (2010), Li et al. (2020), Sardo et al. (2023), and Stephenson et al. (2021). For example, the two most common sites for PUs are the heels, which have minimal subcutaneous tissue and are more prone to pressure and shear forces, and the sacrum, which is more affected by moisture and friction. Table 7-1 summarises some of the anatomical variances. Recognising these differences allows for tailored prevention and treatment strategies, such as using offloading

devices for heel ulcers and specialised mattresses for sacral ulcers. This approach can lead to more effective clinical practices and improved patient outcomes. Training programs for healthcare providers can be enhanced by incorporating site-specific risk factors and management strategies.

Table 7-1 Summary of similarities and dissimilarities between heel and sacral pressure ulcers.

Aspect	**Heel Pressure Ulcer**	**Sacral Pressure Ulcer**
Location	Heel, particularly the calcaneus (heel bone).	Sacrum, the lower back area near the tailbone.
Anatomy	Skin and bone with minimal muscle or fascia, little subcutaneous tissue.	Skin, subcutaneous tissue, and bone, with more muscle and fat compared to the heel.
Cause	Pressure, shear, friction	Pressure, shear, friction
Risk Factors	Immobility, diabetes, poor skin status, previous pressure ulcers or scar tissue, suboptimal tissue perfusion, orthopedic or vascular surgery.	Immobility, incontinence, poor nutrition, moisture, reduced sensation, advanced age.
Prevention strategies	Offloading devices to reduce pressure, regular repositioning, optimal moving and handling techniques monitoring skin status and early intervention.	Regular repositioning, use of pressure-relieving mattresses and cushions, skin care to manage moisture and prevent breakdown and nutritional support.
Complications	Pain, reduced mobility, osteomyelitis, potential for amputation, prolonged hospital length of stay.	Pain, risk of infection due to faecal contamination, potential for severe ulcers due to moisture and incontinence.

Sources: Nixon et al., 2007; Meaume and Faucher, 2008; Gefen, 2010; Tenenbaum et al., 2013; Beeckman et al., 2014; McGinnis et al., 2014, NICE, 2014; Yin et al., 2014; Davies, 2018; Gray and Giuliano, 2018; European Pressure Ulcer Advisory Panel et al., 2019; Manderlier et al., 2019; Dube et al., 2022.

Recent updates in terminology aim to standardise the definition, measurement, and reporting of pressure ulcers. However, the lifespan of pressure ulcer classification systems has shortened, with more frequent revisions and geographical variations, as noted by Kottner et al. (2020). Despite these changes, a consistent recommendation is the use of the appropriate PU/PI classification system in clinical practice. Clinicians are encouraged to apply the system adopted by their healthcare setting consistently and effectively. In England, the terms “avoidable” and “unavoidable” pressure ulcers are no longer used, which were previously used to describe whether proper care could have prevented an ulcer. This shift helps focus on learning from lapses in care, aligning with the management of other patient safety incidents (NHS England, 2018). Additionally, deep tissue injury and unstageable pressure ulcer categories have been consolidated into categories 2 and 3, respectively. This consolidation allows clinicians to concentrate on prevention strategies and quality improvement rather than resource-intensive categorisation. A Heel Pressure Ulcer Risk Factor Framework is proposed which provides an evidence-based approach to addressing lapses in care related to the prevention of all heel pressure ulcers, regardless of severity, and can inform training and robust preventative strategies. Integrating findings from this thesis into frameworks like PURPOSE T can significantly improve the prevention and management of pressure ulcers, particularly in high-risk areas like the heels.

HPUs have multifactorial contributory factors as evidenced in several studies synthesised by Dube et al. (2022). A systematic literature review by Dube et al, (2022) identified eight factors (age, Braden subscales (mobility and friction and shear), diabetes, mechanical ventilation, nutrition, perfusion issues, surgery, and vascular disease) associated with the presence of HPUs in the adult population. Six factors (albumin, atrial fibrillation (AF), and four separate composite variables representing the Braden Scale total score, CKD, and diabetes, and left and right feet neuropathy assessment scores) were identified in Phase 2 of this thesis. Diabetes and two Braden Scale domains (mobility and friction and shear) were previously identified in two high quality studies (Delmore et al., 2019; Manderlier et al., 2019) as presented by Dube et al. (2022).

To synthesise the combined evidence derived from the systematic literature review and the empirical findings from Phase 2 of this doctoral work, a HPU Risk Factors Framework is proposed as presented in Figure 7-1. The proposed framework could be used to identify individuals likely to develop HPUs (all categories or severity), inform clinical judgement and ensure those at risk receive appropriate HPU prevention interventions in a timely manner. Using the combined evidence from the systematic literature review and Phase 2 of this thesis (a matched case control study), the HPU Risk Factors Framework divides the risk factors related to HPU presence into four overarching domains: patient demographics; disease status; predisposing conditions; and risk assessments. Each domain lists risk factors that have been determined from the work of this thesis; however, this may not be exhaustive due to study limitations as outlined in section 7.8. This thesis is the first attempt to use quantifiably determined risk factors to model HPU development incorporating the wider body of literature and addressing some of the evidence shortcomings with new empirical data. The proposed HPU Risk Factors Framework further confirms the multifactorial complexity of HPUs and highlights the importance of responding to individual patient risk profiles.

Across England, there is a strong recommendation to embed the use of the newly developed evidence-based framework, PURPOSE T (Pressure Ulcer Risk Primary or Secondary Evaluation Tool). This framework optimises resource allocation by focusing comprehensive evaluations on those most in need, thereby reducing harm and enhancing patient outcomes. The PURPOSE T framework supports a systematic approach to risk assessment and management, ensuring that high-risk patients receive timely and appropriate interventions. Additionally, it promotes consistency in clinical practice and facilitates better communication among healthcare teams, leading to more effective prevention and treatment strategies. By integrating the research findings from this thesis into the PURPOSE T framework, NHS healthcare providers can further refine their strategies for preventing and managing pressure ulcers. This is particularly important for the heels, which remain the second most common site for pressure ulcers. This integration can enhance training and preventative measures, ultimately improving patient care quality. Each of the Risk Factors

Framework domains are discussed in the sections below, illustrating their relevance to clinical practice.

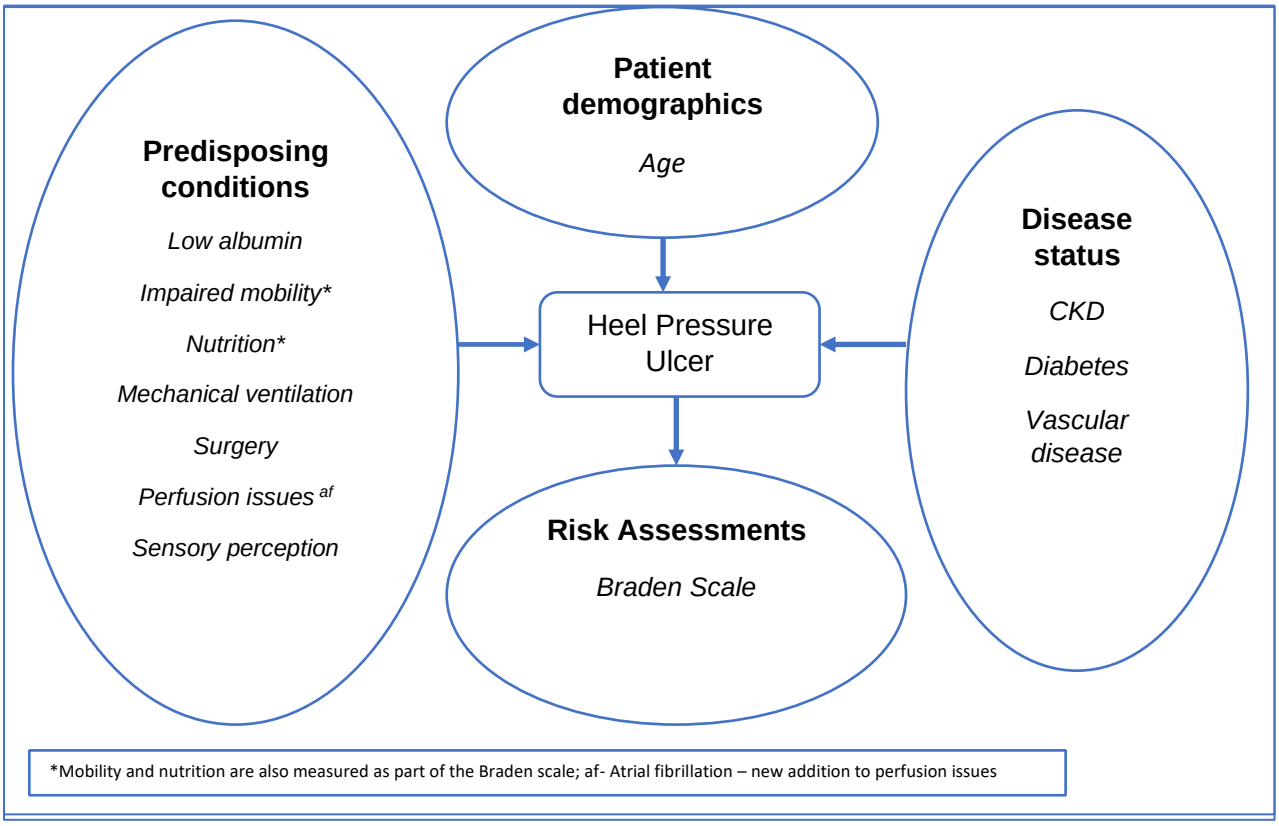


Figure 7-1 Heel Pressure Ulcer Risk Factors Framework.

As highlighted in Dube et al. (2022), there is limited evidence on risk factors for HPU, which is likely to have impacted the development and existence of validated heel-specific risk assessment tools, identification of those at risk and implementation of HPU-specific interventions. Furthermore, this could have contributed to the existence of unclear evidence on the effectiveness of HPU-specific interventions as highlighted by Clegg and Palfreyman, (2011) and Greenwood et al. (2022). The closest to a heel-specific assessment tool identified in the literature is a Heel Pressure Injury Prevention Enabler developed by Delmore et al. (2019) based on the findings of their two studies (Delmore et al., 2015; Delmore et al., 2019). Delmore et al. (2019) was a high-quality study whereas Delmore et al. (2015) was a moderate quality study as rated in a systematic literature review by Dube et al. (2022). Delmore et al. (2019) referred to this as an education enabler, and within the Heel Pressure Injury Prevention Enabler they listed seven risk factors (age >65; diabetes; impaired

nutrition; perfusion issues; vascular disease; mechanical ventilation and surgery) which had been found to be statistically significant and independent predictors of HPU within adult hospitalised patients.

The proposed HPU Risk Factors Framework is based on evidence from four studies as identified by Dube et al. (2022) which includes Delmore et al. (2019) in combination with the empirical evidence from Phase 2 of this thesis. Delmore et al. (2019) was a large case control study (total sample size of 1937), however, it only involved hospitalised patients and data was collected retrospectively using a New York statewide database. Limited data was found on mental status/cognitive impairment thus this data was not included in their analysis. The empirical evidence from the Phase 2 of this thesis (matched case control UK based study) involving both patients with community and hospital acquired HPUs suggests cognitive impairment (used as a matching variable) is an important factor to consider when investigating HPUs considering more than 40% of participants with a HPU were deemed to lack capacity. Delmore et al. (2019) included category 1 HPUs (intact skin but red and non-blanching), which accounted for 20-27% of the HPUs, however these were excluded in the Phase 2 of this thesis as they are less severe and tend to resolve within a few days to a week (Campbell et al., 2010a). Category 1 PUs are more likely to be misdiagnosed thus overrepresented (Nixon et al., 2005). Furthermore, the Delmore et al. (2019) study, due to its retrospective design, lacks a quality assurance for the diagnosis of HPUs whereas in the Phase 2 of this thesis, HPUs were initially diagnosed by ward nurses and confirmed by specialist tissue viability nurses.

Diabetes was the only factor to be found significant in both the Delmore et al. (2019) study and Phase 2 of this thesis. However, in Phase 2 of this thesis diabetes was found to be correlated to CKD (all stages), with an exposure to CKD and diabetes increasing the odds of a HPU by 4.6 times. Whereas diabetes alone, as identified in the Delmore et al. (2019) study, increased odds of HPU by 1.5. In Delmore et al. (2019), renal disease was not found to be significant, however the authors did not report on whether they investigated the link between renal disease and diabetes. In addition, the differences in study findings could have been related to age and the study populations. As alluded

to previously, there is a paucity of evidence on HPU risk factors, therefore the findings from this thesis construct a foundational base for HPU risk factors to inform HPU prevention and clinical judgement with additional research required to build on the evidence base and further improve patient outcomes.

Empirical evidence from Phase 2 of this thesis suggests that atrial fibrillation (AF), the Braden Scale (total score), low albumin, and peripheral neuropathy are significantly associated with HPU presence in adult populations. These factors were not found to be significant in the Delmore et al. (2019) study; they either did not collect this data, or it was missing. In their previous study (Delmore et al., 2015), a Braden Scale < 18 was predictive of HPU, however in the Delmore et al. (2019), Braden Scale data was not available. In addition, they specifically report on a lack of data on neuropathy; however, it's not clear whether this applies to atrial fibrillation and albumin variables. The following sections discuss the results of the Phase 2 study in combination with existing evidence as presented in the proposed HPU Risk Factors Framework (Figure 7-1).

7.2.1 Patient Demographics

Age was the only patient demographic found to be associated with the presence of HPUs in the adult population. Age is a well-known risk factor and confounder for many health conditions including PUs (Dhingra and Vasan, 2012). Older patients are more likely to develop HPUs; Delmore et al. (2019) found that those aged 65 years and above were three times more likely to develop a HPU compared to those aged 64 years and below. In other studies, (Campbell et al., 2010; Tourtual et al., 1997) both moderate quality studies) age did not emerge to be statistically significant. Differences in study populations may have contributed to variations in the findings from the three studies. Delmore et al. (2019) included data from various inpatient settings whereas Tourtual et al. (1997) and Campbell et al. (2010) included data from specific ward settings (high risk and orthopaedic patients respectively). Furthermore, Delmore et al. (2019) had a heterogenous population in terms of age compared with the other two studies (Tourtual et al.,1997 and Campbell et al., 2010). Nonetheless, in studies where age was used as a matching variable the average age

ranged between 70 and 87 years (Delmore et al., 2015; Meaume and Faucher, 2008b; Twilley and Jones, 2016) further suggesting a potential study relationship between age and HPUs.

The association between age and HPUs is consistent with the biological trajectory of the aging process. The skin serves to protect the internal organs from toxins, bacteria, and external forces, however, with increasing age, biological and biomechanical changes occur that affect the skin's ability to fulfil its role. As a result of these biological and biomechanical changes the skin becomes thinner, drier, and more fragile, thus reducing its ability to with stand external forces such as pressure and shear (Garcia-Martinez et al., 2020). This, consequently, increases the risk of pressure and/or shear damage in older people. Age has also been identified to be associated with PU development (González-Méndez et al., 2018; Nixon et al., 2006; Serpa and Santos, 2007; Strazzieri-Pulido et al., 2019)). Although age is a risk factor for all PUs, there is evidence to suggest that younger older adults (65 years and above) may be at more risk of developing HPUs as evidence from Delmore et al. (2019) study which involved a heterogenous age groups (mean age for cases 74.4 (15.4; 17.2); control-55.2 (18.4) and 55.8(21.5)). Whereas older adults (75 years and above) are more at risk for developing sacral PUs (Børsting et al., 2018; Delmore et al., 2019; Yin et al., 2024). Age alongside gender (mental capacity and EoL status) were used as matching variables in Phase 2 of this thesis (Chapter 6) to minimise their impact as confounding factors and reduce selection bias during recruitment of study participants. On average, participants with HPUs in Phase 2 (Chapter 6) were aged 77.9 years (standard deviation (sd)-12.3); this is comparable to other studies (Campbell et al., 2010a; Delmore et al., 2019; Garcia-Martinez et al., 2020; Tourtual, Dorothy May et al., 1997). Overall, the evidence suggests that older adults are more likely to develop HPUs (Delmore et al., 2019).

7.2.2 Disease Status

This section discusses the relationship between disease status and the presence of HPUs in the adult population as identified in literature and from findings of Phase 2 of this thesis (Chapter 6).

7.2.2.1 Chronic Kidney Disease (CKD) and Diabetes

A key finding of Phase 2 of this study (presented in Chapter 6) is the relationship between diabetes and chronic kidney disease (CKD) and the presence of HPUs. An exposure to CKD or diabetes was observed to increase the odds of HPU presence by 2.3 (1.1 - 4.7) with a p-value of 0.02. A disease status of diabetes has previously been investigated in four studies reported in the systematic literature review (Chapter 3; Dube et al., 2022). In two of these studies, an exposure to diabetes was found to be a predictor for HPU (Delmore et al., 2015; Delmore et al., 2019). In the Clegg et.al (2009) study, more than half of the study population had a diagnosis of diabetes, but the study did not have a control group for comparison. In contrast, the Gaubert-Dahan (2013) study of moderate quality found no evidence to support diabetes as a risk factor for HPUs. Gaubert-Dahan (2013) specifically excluded patients with a Mini Mental state Examination (MMSE) score less than 10 (severe cognitive impairment). Based on the findings of Phase 2 of this study presented in Chapter 6, at least 40% of those participants with a HPU were identified to have impaired cognitive function, thus excluding these patients it is likely to have biased Gaubert-Dahan's (2013) study findings.

Diabetes is a well reported risk factor for PUs and it is also highlighted as an important risk factor for HPU development in the prevention literature (Chung et al., 2022; Davies, 2018; Greenwood et al., 2022; Wei et al., 2017; Yin et al., 2024), which is consistent with the pathophysiology of diabetes. Diabetes occurs when the body cannot produce enough insulin, or the insulin it produces is not effective, resulting in chronic hyperglycaemia. The long-term effect of this is damage to blood vessels which can lead to problems with cardiovascular and kidney function as well as nerve damage (Beckman and Creager, 2016; Forbes and Cooper, 2013; Harding et al., 2019). For instance, poor blood circulation can result in drier and thinner skin around the heel, making them vulnerable areas to external forces. Type 2 was the most common category of diabetes amongst the study population in Phase 2 of this thesis, suggesting that it may be the main contributory factor associated with heel pressure damage. The disease status of CKD is yet to be fully investigated as a potential risk factor for developing HPU. Two studies (Clegg et al., 2009; Delmore et al., 2019) reported in the systematic literature review by Dube et al. (2022) investigated the relationship

between CKD and HPUs. Clegg et al. (2009) found that over a quarter of their HPU population had end-stage renal failure, however the study lacked a comparator group to estimate the impact of the condition. However, Clegg et al. (2009) involved participants that were under the care of Wound Ostomy Continence (WOC) nurses and had experienced HPU which suggests that their study population included high risk participants making their findings less generalisable. In the Delmore et al. (2019) study, diabetes emerged as a statistically significant factor, but renal disease did not. However, it is not clear if the authors considered potential correlation between CKD and renal disease. If correlation existed between diabetes and renal disease as observed in Phase 2 of this study, this would have reduced their statistical significance impacting on the observed p-value for renal disease in the Delmore et al. (2019) study. In other studies that have explored risk factors for PUs, patients with a CKD diagnosis have exclusively been excluded from taking part in the studies with no clear supporting evidence, suggesting selection bias (Feuchtinger et al., 2006; Goodridge et al., 1998; Serpa and Santos, 2007b), thus their results may be biased and equally not generalisable.

In the Phase 2 of this thesis presented in Chapter 6, 56.6% (30/53) of the case group participants reported to have a CKD diagnosis and more than 70% of these had no disease stage recorded in their medical records. CKD was observed to be correlated to diabetes; to reduce type I error due to collinearity, an additive composite variable representing a disease status of CKD and/or diabetes was found to be significantly associated with the presence of HPUs in the adult population. Phase 2 study of this thesis was the first study to consider the relationship between HPUs, CKD and diabetes. The empirical findings from the Phase 2 of this study suggests that participants with a disease status for both CKD and diabetes are at least four times likely to have a HPU compared to those without CKD or diabetes.

CKD can be caused by various factors including diabetes, in particular, type 2 diabetes is the leading cause of CKD. Persistent high blood sugar levels can damage the blood vessels in the kidneys leading to impaired renal function (Sugahara et al., 2021; Vallon, 2011). There is evidence to

suggest that patients with poorly controlled diabetes in combination with renal failure may experience ischemia even in heels with palpable DP pulse due to orphan heel syndrome (Taylor, 2013). Orphan heel syndrome is a condition that compartmentalises the heel circulation from the forefoot due to occlusive disease that disproportionately affects the posterior tibial and pedal arch vessels (Taylor, 2013). Furthermore, the imbalance of homeostasis functions due to CKD can increase the skin and underlying tissues' vulnerability to pressure and shear damage. Findings from the Phase 2 of this thesis as presented in Chapter 6 further suggests that the exposure to either CKD and or diabetes is a predictor for HPU presence. However, further research is required to fully investigate this area and inform future risk assessments and HPU prevention and management.

7.2.2.2 Vascular Disease

Pre-existing literature on predictors identifies vascular disease as a significant factor for developing HPUs (Clegg et al., 2009; Delmore et al., 2015; Delmore et al., 2019; Meaume and Faucher, 2008a; Twilley and Jones, 2016). Vascular disease is any abnormal condition of the blood vessels including peripheral arterial disease (PAD) resulting in poor blood supply to the skin and any underlying tissues. Individuals with a known diagnosis of vascular disease are at least two times more likely to develop a HPU (Delmore et al., 2019; Twilley and Jones, 2016). Four studies have been identified that investigated the relationship between vascular disease and HPU; all four studies found a statistically significant association (Clegg et al., 2009; Delmore et al., 2015; Delmore et al., 2019; Meaume and Faucher, 2008a; Twilley and Jones, 2016). Clegg et al. (2008) found that 40% of their participants had a history of PAD, however the study did not include a comparator group. Studies specifically investigating the relationship between PAD and HPU (Meaume and Faucher, 2008c; Twilley and Jones, 2016) found that patients diagnosed with evidence of atherosclerosis (PAD) were at least two times more likely to have a HPU. However, in a community setting, the odds of a HPU were as high as 11 times more in patients exposed to PAD compared to those without PAD (Twilley and Jones, 2016). Furthermore, PAD has been identified as a prognostic factor for healing of HPUs (McGinnis et al., 2014) An exposure to vascular disease is possibly linked to the presence of more severe HPUs; in four separate studies, 37% of the combined study participants were reported to

have a category 3 and above including unstageable wounds (Delmore et al., 2015; Delmore et al., 2019; Meaume & Faucher, 2008; Twilley & Jones, 2016).

Despite the evidence supporting vascular disease as a risk factor for HPUs, in Phase 2 of this thesis no evidence was found to support the relationship between HPU presence and peripheral vascular disease (PVD) or PAD. Only 7.8% of the study participants had an established diagnosis of PVD therefore the study sample did not have enough power to detect small differences as observed. There is evidence to suggest that at least 80% of people living with PAD are asymptomatic (NICE, 2020). It is possible that PAD is a risk factor for HPUs and those with HPUs may be living with undiagnosed PAD; Phase 2 was designed to test this hypothesis using Doppler ultrasound assessment to diagnose PAD. However, no evidence was found in support of the hypothesis. It is likely the study was not sufficiently powered to detect the difference. At least 40% of the study population (Phase 2, Chapter 6) had cognitive impairment affecting their ability to complete a Doppler ultrasound assessment, thus the total sample size was reduced to less than 30. Based on current evidence, vascular disease is an important risk factor for HPU and given the large proportion of people likely to be living with undiagnosed PAD, due regard should be given to those at risk of PAD to minimise their risk of HPUs. Doppler ultrasound may be used to diagnose PAD (NICE, 2020) in those at risk, however, this might not always be possible, particularly in patients with cognitive impairment and concordance issues. Whilst Doppler ultrasound is the gold standard for diagnosing PAD, arterial and vascular assessments need to be completed alongside (NICE, 2020). These can be useful in non-concordant patients; preliminary findings from Phase 2 suggests having a dry, scaly, stained skin, pale, cold or cool limb, poor capillary refill may be associated with the presence of HPUs particularly on the left heel.

7.2.3 Risk Assessments

Risk assessments are an important aspect of PU prevention and use of a validated tool supported with clinical judgement is highly recommended in literature (Chadwick, 2023; Mervis and Phillips,

2019; NICE, 2014). Whilst numerous validated risk assessment tools exist, Braden Scale was identified as the most used in HPU research.

7.2.3.1 Braden Scale

The Braden Scale has previously been investigated as a potential risk factor either as separate subdomains or as a total score (composite variable) (Clegg et al., 2009; Delmore et al., 2015; Manderlier et al., 2019; Tourtual et al., 1997). The separate subdomains include “sensory perception, mobility, activity, moisture, nutrition and friction and shear”. Activity, mobility and friction and shear emerged as significant risk factors associated with the presence of HPUs in one or more studies as highlighted in a review by Dube et al. (2022). Low activity and impaired mobility are well recognised risk factors as they are linked to sustained pressure over bony prominence areas resulting in PU development (Coleman et al., 2013; Gefen, 2010; National Pressure Ulcer Advisory Panel et al., 2014). Friction and shear are associated with development of category 2 PUs (Berlowitz and Brienza, 2007; Coleman et al., 2013; Kottner et al., 2009) which is consistent with results from Phase 2 of this thesis, as at least 20% (14/68) of the HPU were category two.

In Phase 2 of this thesis, the Braden Scale subdomains were all observed to be statistically significantly associated with the presence of HPUs. However, the subdomains were found to be highly correlated with each other and therefore an equal weighting composite variable (created by adding the all-subdomain scores together) was used to adjust for collinearity in the multivariable model. Evidence from Phase 2 of this study suggests that a total Braden Scale score is a predictor of HPU; an increase in the total Braden Scale score reduces the odds of HPU presence by 0.8 (p-value=0.03). This result is comparable to that reported by Delmore et al. (2015) (moderate quality), although they considered Braden Scale as a dichotomous variable (≤18 vs >18). Braden Scale and its subdomains are also most consistently indicated as a predictor for all PUs (Bergstrom et al., 1996; Schultz et al., 1999; Tschannen et al., 2012). In Tourtual et al. (1997) and Manderlier et al. (2019), the friction and shear subdomain were identified as a risk factor for HPUs. However, the mobility subdomain was identified in Manderlier et al. (2019) but not in Tourtual et al. (1997) study;

vice versa was true for the moisture subdomain in these studies. The difference between Manderlier et al. (2019) and Tourtual et al. (1997) findings could have been attributed to involving different study populations with different demographics that are age or gender related. Furthermore, Manderlier et al. (2019) only explored factors that they considered modifiable. Braden Scale subdomains have emerged separately as important in different populations except for impaired nutrition (Delmore et al., 2015; Manderlier et al., 2019; Tourtual et al., 1997). Nutrition defined by levels of malnutrition or cachexia has been identified as a risk factor in a study by Delmore et al (2019).

The evidence from Phase 2 study as presented in Chapter 6 suggests that using a Braden Scale is of clinical importance in identifying those at risk of HPU. The Braden Scale considers factors that can be modified using PU prevention interventions such as use of specialist mattresses and heel offloading devices for mobility and reduction of friction and shear forces, repositioning for activity and nutritional intake support with dietetics input where possible. Furthermore, findings from this thesis indicate the importance of other factors as listed in the HPU Risk Factors Framework, such as disease status, patient demographics and predisposing conditions that should be considered alongside the Braden Scale risk assessment tool as the Braden Scale within its subdomains does not consider vascular disease nor does it highlight important comorbidities to consider. This information would be particularly useful to less experienced clinicians to inform their clinical judgement; the proposed HPU Risk Factors Framework can be crucial in such instances.

At present within England there is a national drive to use PURPOSE T as a risk assessment of choice (National Wound Care Strategy Programme, 2023). PURPOSE T has similarities with the Braden Scale in that all six domains of the Braden Scale are also considered one way or the other as part of the PURPOSE T. However, like many other PU risk assessment tools, the PURPOSE T was developed based on data or evidence that included all PUs and does not distinguish between PUs at different anatomical sites despite HPUs remaining the second most common PU, the emerging evidence that risk factors might be location specific (Gefen, 2010), and that the incidence and prevalence rates of all PUs have barely reduced overtime (Li, Z. et al., 2020) there is need to

further explore the use of PURPOSE T and impact on HPU incidence rate. Using a validated tool such as the Braden Scale complimented with the proposed HPU Risk Factors Framework can assist clinicians to target at-risk patients by responding to their individual risk as identified by the tool.

7.2.4 Predisposing Conditions

In the context of this thesis, predisposing conditions are circumstances caused by or secondary to other medical conditions, for instance impaired mobility due to stroke or perfusion issues related to dehydration, hypovolemic shock, or myocardial infarction. Several predisposing conditions have been identified to be associated with HPU presence as discussed in this section.

7.2.4.1 Albumin Levels

Several haematological measures were considered as potential risk factors for developing HPUs and albumin levels were the only measure to emerge in a multivariable model in Phase 2 of this thesis as statistically significant. Albumin is a key protein synthesised by the liver and deviations from normal levels are indicative of pathophysiological processes. Albumin levels can serve as essential diagnostic markers for various medical conditions including malnutrition (Alcorta et al., 2018; Rozga et al., 2013). Albumin levels were previously investigated in two other studies as identified in the systematic literature review (Dube et al., 2022). In Tourtual et al. (1997) albumin levels were found to be lower in the case group compared to the control group however there was no statistically significant evidence to support the difference. Differences in study findings could be age-related as the Tourtual et al. (1997) study population were relatively younger compared to the population of this thesis study. Clegg et al. (2009) also found that the observed average albumin level was 2.4 (sd 0.8) amongst the HPU group, which is lower than the normal albumin range in the adult population. However, this study was of poor quality due to several reasons including lack of comparator and inadequate information on the selection criteria of study participants. Other studies in a systematic literature review of risk factors associated with PU (all anatomical sites including HPU) also found that lower levels of Albumin were associated with PU development (Reed et al., 2003) In this review, albumin levels emerged as significant in seven out of 11 studies, however only

one study (Reed et al., 2003) was of high quality and six were rated moderate to low quality. Findings from the study by Reed et al. (2003) suggests that low albumin levels increase the odds of PU (HPU included) presence. Given the empirical findings from Phase 2 of this thesis it is likely that the observed association between PU and albumin levels in the study by Reed et al. (2003) may have been influenced by the presence of HPU study population. The findings from this thesis suggest that albumin is a predictor for HPU presence within older patients, however, further research is required to confirm these results.

7.2.4.2 Impaired Mobility and Nutrition

Impaired mobility and nutrition have emerged as significant factors associated with the presence of HPUs in adult populations (Delmore et al., 2019; Manderlier et al., 2019). These conditions are both secondary to other health illnesses and within HPU research studies they have been measured in different ways. For these reasons, they are presented as separate factors within the predisposing conditions domain of the HPU Risk Factors Framework (section 7.2). By listing them separately it further emphasises the complexity of these factors as they are associated with numerous health conditions. In HPU studies, mobility and nutrition have both been defined either based on diagnosis that might affect mobility or nutritional intake such as stroke, plegia and shock states, or measured using risk assessment tools such as the Braden Scale. Furthermore, mobility is considered in all risk assessment tools as listed in Table *2-2*, however, the same cannot be guaranteed for nutritional status. Mobility and nutrition status have already been considered further under section 7.2.3.1 (Braden Scale) within the context of the Phase 2 results. However, for the purposes of emphasising their importance in HPU risk assessment they are also discussed separately in this section.

Impaired mobility is a well-known risk factor for PU development as it is associated with reduced ability for individuals to independently relieve pressure over bony prominence areas. Mobility can be measured using different scales including risk assessment tools. Despite using different measures, mobility status emerged as a significant factor for the presence of HPU in multiple studies (Delmore et al., 2015; Manderlier et al., 2019; Muntlin Athlin et al., 2016; Tourtual, et al., 1997).

These results are consistent with the pathophysiology of HPU. Using the Braden Scale, having a lower mobility score (no impairment) was associated with lower odds of having a HPU (Manderlier et al., 2019). These results were consistent with the findings in Phase 2 of this thesis, where mobility was measured as part of the Braden Scale using the mobility subdomain (discussed in section 7.2.3).

Nutritional status defined as either using a risk assessment tool or associated with conditions that affect nutritional intake, have emerged as factors significantly associated with HPU presence (Delmore et al., 2019). Individuals with nutritional status rated as impaired according to patient records using malnutritional or cachexia status were found to be at least six times more likely to have a HPU (Manderlier et al., 2019). Phase 2 (Chapter 6) also found nutritional status as measured using the Braden Scale as a significant factor associated with HPUs. In studies that have considered the relationship between PU (all anatomical sites) and nutrition, there is no clear evidence as nutritional status did not always emerge as statistically significant in studies of various quality as reported in the Coleman et al. (2013) review. Amongst the studies included in the Coleman et al. (2013) review, one study by Tourtual et al., (1997) explored the relationship of nutrition with HPUs amongst acute in-patients; however, nutrition did not emerge as significant. In Manderlier et al. (2019), nutrition as measured using the Braden Scale was not considered in their multivariable analysis, possibly because it would have been correlated to the mobility and friction shear subdomains (subdomains included in their final multivariable analysis). Instead, they used the Short Nutritional Assessment Questionnaire for Residential Care (SNAQ-RC) which emerged insignificant (Manderlier et al., 2019c). However, the SNAQ-RC is a tool that is yet to be fully validated. Nutrition is an important complex aspect that promotes skin integrity, despite numerous studies investigating its link with PU development, the evidence remains unclear (Coleman et al., 2013; Yap and Holloway, 2021). Evidence from Delmore et al. (2019) in combination with the findings from the Phase 2 of this thesis (Chapter 6), suggest that nutritional status is an important factor related to HPU presence. There are many ways of measuring nutritional status which are inconsistently used throughout literature and likely to contribute to variations in findings. Considering nutrition's role in

maintaining skin integrity it is worth focusing future research in identification of a standardised measuring tool that can be used in future research as well as in HPU prevention and clinical practice.

7.2.4.3 Mechanical Ventilation and Surgery

Mechanical ventilation and surgery have been identified within the literature as factors associated with HPU presence in hospitalised patients (Delmore et al., 2019). Mechanical ventilation and surgery are factors that mainly affect hospitalised patients. HPUs were seven times more likely to be observed in participants exposed to mechanical ventilation for more than 96 hours. HPUs were two times more likely to be observed in patients that had undergone surgery during their hospital admission (Delmore et al., 2019). These findings were consistent with other studies that have explored the link between PUs and mechanical ventilation or surgery (Cox and Roche, 2015; Cox et al., 2018; McEvoy et al., 2022). Associated with both, is the possible use of vasopressors which may increase the risk of PU development as they may alter skin tolerance to external forces. Vasopressors alongside mechanical ventilation have previously been linked to PU development (Cox and Roche, 2015; Cox et al., 2018)

There is limited evidence to support the link between HPU and surgery; Delmore et al., (2019) is one study that explored this relationship. The link between surgery and HPUs has also been explored in Clegg et al., (1997) and Campbell et al., (2010); however, both studies were at high risk of bias due to the nature of the study design employed. Furthermore, the Campbell et al. (2010) study included only orthopaedic patients. In the Delmore et al. (2019) study involving all hospitalised patients, vascular and cardiovascular surgery were the two most common types of surgical procedures reported amongst patients with HPUs. Orthopaedic, intestinal genitourinary and gynaecology were the other surgical procedures reported in the Delmore et al., (2019). This suggests that exposure to a surgical procedure is likely to increase the risk of developing a HPU, however vascular and cardiovascular surgical patients may be at a higher risk. In Phase 2 reported in Chapter 6 of this thesis, surgery during hospital stay was not linked to HPU presence and none of the participants were exposed to mechanical ventilation. However, based on the Delmore et al.

(2019) study, there is evidence to suggest that mechanical ventilation and surgery are significant factors for HPU development. Further research is required to support these findings, but current results can be used to inform clinical judgement.

7.2.4.4 Sensory Perception

Sensory perception has been investigated previously in relation with PUs as measured by the Braden Scale including in Phase 2 of this thesis. Sensory perception is the ability to detect, experience or sense stimuli. This can be affected by one's mental status or neuropathy. Neuropathy is characterised with thickening of and eventual loss of neurons leading to loss of protective sensation (Bril et al., 2018). It is a well-known risk factor for foot complications particularly in diabetic patients which is consistent with its pathophysiology (Bril et al., 2018; Shanmuga Raju et al., 2018). Peripheral neuropathy reduces the ability to respond to external forces thus increases the risk of pressure and/or shear damage over bony prominence areas. Similarly, an impaired mental status can reduce one's ability to respond appropriately to external stimuli thus increasing the risk of skin and tissue damage in those affected.

The Braden Scale sensory subdomain measures the ability of an individual to respond meaningfully to pressure related discomfort and this could be anywhere on the body, including the foot and or the heel. In studies that have investigated the association between sensory perception and PUs, there is conflicting evidence as it has not always emerged as a predictor (Delmore et al., 2015; Gaubert-Dahan et al., 2013; Tourtual, et al., 1997) however these studies have not always used the same tools to measure or classify sensory perception. Similarly mixed evidence also exists regarding the link between sensory perception and HPUs; the Gaubert-Dahan (2013) study found that neuropathy was a predictor for HPU as measured using the Neuropathy Symptom Score (NSS) and Neuropathy Deficit Score (NDS) (assessments normally used to diagnose diabetic neuropathy) however, the analysis performed in this study did not adjust for confounding factors. However, other studies have found no link between HPUs and neuropathy (Delmore et al., 2015; Tourtual, Dorothy May et al.,

1997). The lack of clear evidence to support sensory perception and HPUs could possibly be linked to the inconsistent use of measurement tools in these research studies.

A key finding of the Phase 2 of this study is that peripheral sensory perception on both legs (left and right) as assessed on the 1st, 3rd and 5th toe was a predictor for HPU presence. However, poor peripheral sensation (high sensory score) had opposite effects on the left and right foot. A unit increase in total neuropathy score increases the odds of a HPU by 7.7 on the left foot, however a unit increase in total neuropathy score on the right foot results in the opposite effect (that is decreases the odds of PU presence on the right heel by 0.8). Diabetic neuropathy and PAD are the two most common chronic complications of diabetes (American Diabetes Association, 2021). Diabetes and cognitive impairment were more prevalent in the case population, which could further explain the higher sensory scores (peripheral neuropathy) in the case population (Phase 2 study results presented in Chapter 6). It is not clear why an increase in neuropathy scores (sensory deficit) have different implications on the development of HPU. However, this is likely to explain why the majority of HPUs in this study were observed to be on the left heel. It is also possible that the left leg is less dominant in the study population thus is likely to experience higher pressure and or shear forces as it is less likely to be moved or more likely to be dragged along during self-repositioning.

7.2.4.5 Perfusion Issues

Perfusion issues are commonly highlighted as risk factors for HPU development. However, the term ‘perfusion issues’ encompasses a broad range of conditions that contribute to poor perfusion of organs or tissues. In the HPU literature, perfusion issues are associated with conditions such as anaemia, cardiovascular disease (stage IV), congestive heart failure, dehydration, myocardial infarction (MI), and pedal oedema, (this list is not exhaustive). In Tourtual et al. (1997), perfusion issues were not found to be independently associated with the presence of HPUs, however this study was rated moderate quality in Dube et al. (2022). In Clegg et al. (2019), a case series study, 26% (22/84) of their participants were observed to have pedal oedema, a condition that causes blood vessels to leak fluid into nearby tissues causing them to swell. This extra fluid in the skin can

cause it to become fragile and vulnerable to pressure and/ or shear. Conditions related to perfusion issues are not consistently investigated or reported in HPU literature with studies choosing to investigate specific conditions such as pedal oedema, congestive heart failure, respiratory diseases, or several of the conditions under one category. For instance, in Delmore et al. (2019), perfusion issues were defined as the presence of one or more conditions that affect tissue perfusion such as cardiovascular disease, dehydration, oedema of various origin, and MI. In the Delmore et al. (2019) study, perfusion issues were significantly associated with HPU development/ presence (Delmore et al., 2019). However, other perfusion related conditions may exist but could not be identified due to the retrospective nature of the study designs. Empirical evidence from this thesis suggests a link between HPUs and Atrial fibrillation (AF), the following section below discusses this evidence.

7.2.4.5.1 Atrial Fibrillation

Atrial fibrillation (AF) is another risk factor identified in phase 2 (Chapter 6); participants with a diagnosis of AF were observed to be at least four times more likely to have a HPU compared to those without an AF diagnosis. AF is a prevalent cardiac arrhythmia condition characterised by irregular and rapid electrical activity associated with significant morbidity and mortality (Kamel et al., 2016). It is a known risk factor for stroke and accounts for at least 30% of ischaemic strokes (Kamel et al., 2016; Lip et al., 2017). In other studies, AF has been linked to poor brain perfusion leading to cognitive decline in elderly patients (Alonso and Arenas de Larriva, 2016; Dietzel et al., 2018; Gardarsdottir et al., 2018; Kalantarian et al., 2013; Kamel et al., 2016; Lip et al., 2017; Tsiachris et al., 2015). Similar pathology could contribute to ischaemia over bony prominence areas exposed to external forces. Persistent AF has been found to reduce blood flow to the brain; in the same vein, irregularities associated with AF are likely to affect the circulation of oxygenated blood to the peripheral parts of the body, particularly the heel, which is located furthest away from the heart thereby affecting blood supply to the heel making it more susceptible to damage due to external forces. From the systematic literature review undertaken as part of this thesis (Dube et al., 2022), perfusion issues (defined as congestive heart failure, MI, anaemia, dehydration, and pedal oedema) were highlighted as a risk factor for HPU development in three out of 13 eligible studies. However,

of the three studies (Delmore et al., 2019 -high quality; Tourtual et al., 1997-moderate and Clegg et al., 2009- low quality), none investigated or reported AF as a risk factor for HPU development. Other studies investigating risk factors for PU (all anatomical sites including HPU) have explored the relationship between perfusion related factors and PU (Compton et al., 2008; Schultz et al., 1999; Serrano et al., 2017) but it is not clear if these studies included AF. Current evidence from this thesis suggests that AF is a factor to consider as part of risk assessment under perfusion issues, however as this is the first study to explore its relationship with HPU presence, further research is required to explore this relationship further.

7.2.4.6 Other potential risk factors for developing HPU in the adult population.

In Phase 2 (Chapter 6), the final model accounted for at least 40% of the study population's variation; however, it excluded many other potential risk factors. The systematic literature review (Dube et al., 2022) also identified 41 other potential risk factors, which included body mass index, smoking status, blood tests, systemic infection, vasopressor, corticosteroid use, haemoglobin, respiratory rate, length of surgery, and use of perioperative analgesia. These potential risk factors were identified in studies that were classed as moderate to low quality, therefore were further investigated in Phase 2 (matched case control) of this thesis. No evidence was found in Phase 2 (Chapter 6) to confirm their association with HPU presence. This could have been attributed to the sample size of 103 in total; a prior sample size calculation using an odds ratio of 2 had suggested a minimum sample size of at least 400 participants (200 cases and 200 controls). It is likely that the study did not have enough power to detect small differences associated with other potential risk factors as those reported in Chapter 6. Further research is warranted considering HPUs remain the second most common PU, more so there is limited research investigating HPU risk factors.

7.3 Ethnic Minority Population and HPUs

Ethnic minority individuals are disproportionately underrepresented in the study population of this thesis, particularly those with darker skin tone, for instance individuals of Asian or Black ethnic backgrounds. Phase 2 of this thesis (Chapter 6) was conducted in a large acute hospital which

provides over 800 000 episodes of care to patients per year across three hospital sites and serves over 500 000 people living in and around Coventry, Warwickshire and beyond (University Hospital Coventry and Warwickshire NHS Trust, 2023). At least 20% of the episodes of care are delivered as inpatient and day surgery. In the Phase 2 study only one participant of Asian ethnic background was recruited to this study representing less than two percent of the study population. This is despite at least 18% of the population being of Asian/Asian British ethnic background within the research site's catchment area (Office for National Statistics, 2021). The average age amongst the participants with HPUs in Phase 2 of this thesis was 77.5 years old and the lack of ethnic minority amongst this group might suggest that those admitted to the acute hospital were generally younger. Growth in ethnic minority population in the UK is on the rise and related to the labour market particularly in the NHS, although they more at risk of diabetes (a well-known risk factor for PUs) (Goff, 2019) they are more likely to be mobile and of working age and able-bodied thus less likely to have been at risk of developing HPUs.

Patients from ethnic minority groups are more likely to be cared for at home by their family members and therefore less likely to present in hospital or are more likely to present to hospital when they are very poorly and close to death. Such care arrangements are highly likely within ethnic minority communities due to the longstanding issues of mistrust and lack of access to healthcare services exacerbated by other issues such as language barrier (Kapadia et al., 2022; Lawrence et al., 2021). Mistrust has been cited as a barrier to seeking mental health support and vaccine hesitancy amongst ethnic minority groups which can be attributed to fear of being discriminated against and historical mistreatment in healthcare (Bailey and Tribe, 2021; Khan, 2022; Memon et al., 2016; Razai et al., 2021). This is likely to reflect the attitudes of adult ethnic minority populations at risk of HPUs as highlighted in Bailey and Tribe (2021) study involving Black Caribbean adults aged between 65 to 79 years. Reasons presented here are likely to have impacted on the overall number of ethnic minority individuals admitted to hospital with or developing HPUs during their hospital stay, thus resulting in an even smaller sample size eligible to take part in Phase 2 of this thesis.

Health inequalities exist between ethnic minority and white groups in the United Kingdom which were more recently amplified by the COVID-19 pandemic (Kapadia et al., 2022; Marmot, 2020). For instance, diabetes, a well-known risk factor for HPU, African and African Caribbean and South Asian descendants are at least three times more likely to have type 2 diabetes compared to their White counterparts (Meeks et al., 2016). In a study by Petersen et al. (2021) diabetes was found to be associated with higher admission rates amongst Black Caribbean group compared to the White group (Petersen et al., 2021). Furthermore, a diagnosis of diabetes in combination with other factors such as greater social deprivation contributed to higher COVID-19 related deaths amongst ethnic minority groups (Public Health England, 2020; Public Health England, 2020). In the Phase 2 of this thesis, participants with HPUs were at least three times more likely to have a diagnosis of diabetes compared to those without HPU. However, ethnic minority groups were disproportionately underrepresented despite such groups as Black Caribbeans being more likely to be admitted to hospital with diabetes related conditions compared to their White counterparts. As previously discussed, the underrepresentation of ethnic minority groups in this thesis may have been attributed to issues of mistrust. A recent rapid review by the NHS Race and Health Observatory has also highlighted the health inequalities experienced by ethnic minority individuals (Kapadia et al., 2022). The review found evidence of negative interactions, stereotyping, disrespect, discrimination, and cultural insensitivity, led to some women from ethnic minorities feeling “othered,” unwelcome, and poorly cared for within maternal health services (Kapadia et al., 2022); such behaviours from clinicians are likely to perpetuate the barriers for seeking help and sustain the existing health inequalities. These types of behaviours associated with poor health outcomes are not isolated to maternity care (Marmot, 2020).

In the field of tissue viability, darker skin tones present challenges in the identification of less severe PUs such as categories 1, 2 and DTIs which is likely to contribute to high prevalence of more severe PUs. The state of current guidance and/or training materials on the early detection of PUs focus on paler skin (Oozageer Gunowa et al., 2018) which impacts on quality of care and further extends the long-standing health inequalities amongst ethnic minority populations. Focusing on such skin colour

variations can result in patients with darker skin tones being missed when the damage first occurs thus missing the window to implement intervention to prevent further damage. In a recent study on PU, Black and Asian patients were more likely to present with severe ulcers compared to White patients (Kariwo et al., 2023). Furthermore, staff in the same study reported to be less confident in identifying early signs of tissue damage in patients with darker skin tones (Kariwo et al., 2023).

In Phase 2 (Chapter 6), 69.0% of screened patients with HPUs had either a category 1, 2 or deep tissue injury (DTI) which are harder to assess and identify, particularly in patients with darker skin tones thus can easily be missed. This is likely to have impacted on the total number of ethnic minority patients reported on the Datix incident management system with HPUs of lower severity, consequently reducing numbers eligible to take part in the study.

Emerging evidence suggests that patients with darker skin tone are more likely to present with more severe PUs (categories 3 and above) (Harms et al., 2014; Oozageer Gunowa et al., 2017); however, none of the categories 3 or above observed on study participants as part of Phase 2 (Chapter 6) were detected on darker skin tones or from ethnic minority groups. Ethnicity data is reported in a small number of studies investigating predictors for HPUs (Delmore et al., 2019; Demers, 2005; Tourtual et al., 1997); with participants being classed as White, other, and unknown. Moreso, none of these studies considered ethnicity as a potential predictor for HPU (Muntlin Athlin et al., 2016). Tourtual et al., (1997) and Delmore et al., (2019) used a retrospective study design, which relied on data as recorded in patient records which may highlight the quality of available data. In Demers (2005), 2.9% (3/103) had HPU and 10.7% of their study population were of Black ethnic background. However, the authors did not provide the HPU severity and the ethnic groups of those affected (Demers, 2005). In hindsight ethnicity screening data should have been collected in Phase 2 of this thesis (Chapter 6), however, the researcher does not remember seeing or discussing the study with patients or relatives of ethnic minority background except for the single patient of Asian origin that was recruited in the study. Given that the researcher is Black, she is more likely to have remembered if she had seen or observed ethnic minority patients with severe HPUs. Ethnicity data could have

been collected retrospectively using the hospital database systems in Phase 2 (Chapter 6), however, there are no guarantees that where data is available it would be accurate for non-white groups as evidence shows they are likely to be inaccurate or recorded as other (Grath-Lone et al., 2021; Mathur et al., 2014; Saunders et al., 2013). Ethnicity data is collected through self-assessment, or as assigned by an observer. The latter can be supported by available data or assigned based on visual inspection (Psoinos et al., 2011). In hospital settings ethnicity data tend to be collected in accident and emergency or outpatient settings, however these sources have been found to be unreliable, more so the data is rarely updated when necessary (Mathur et al., 2014)

Ethnicity is a complex multidimensional construct which is likely to change over time and context (Lam et al., 2023), making the later approach a less suitable method of data collection. Alongside race, ethnicity is a social construct encompassing characteristics such as language and cultural heritage, which are sometimes used to group individuals in a hierarchical ethnic order resulting in certain groups being minoritised or treated in a harmful manner because of their skin colour or religion. To reduce such impact, it is recommended to collect ethnicity data by asking the individuals (Bignall and Phillips, 2022; Lam et al., 2023; Race Disparity Unity, 2021). This should be practised at every opportunity to ensure all databases that contain health and social care data are as accurate as they can possibly be. For recruited study participants (Phase 2), the data was provided by the patient or their consultee. The continued disparities in health outcomes linked to different ethnic minority groups, and the lack of ethnicity data in HPU, this warrants further research/HPU studies to collect data on ethnicity and explore factors associated with the presence of HPU amongst ethnic minority populations.

7.4 Heel Pressure Ulcers: Their Impact on Health-Related Quality of Life (HRQoL) and Associated pain.

7.4.1 Impact of Heel Pressure Ulcers on HRQoL

Phase 3a of this thesis was the first to explore the impact of HPU on HRQoL of patients admitted to an acute hospital. Therefore, a systematic literature review on the impact of HPU on HRQoL could

not be completed as no studies have previously looked at this topic before this study. Other reviews exist that have been undertaken to determine the impact of wounds on lower limbs on HRQoL, including PUs and leg ulcers (Burston et al., 2023; Gorecki et al., 2009; Herber et al., 2007). A review by Gorecki et al. (2009) found that PUs alongside PU interventions have significant negative impact on HRQoL. However, previous research investigating the impact of PUs on HRQoL, similar to previous reviews on risk factors for PU development, do not distinguish the impact of PU by anatomical sites.

Phase 3a of this thesis measured HRQoL using EQ-5D-5L as self-reported by participants or by their proxy (nominated consultee) if the participant was not able to do so themself due to cognitive impairment. Using the EQ-5D-5L questionnaires allowed the researcher to explore the impact of HPUs in participants living with cognitive impairment and not able to complete HR-QoL questionnaires based on the responses provided by their nominated consultee. In this context, HRQoL measures one's ability to carry out predefined activities (mobility, self-care, usual activities) and the presence or absence of pain or discomfort and anxiety or depression in relation to their health at the time of assessment. Using such tools allows the identification of patients that may additionally require care and support outside of the hospital setting to facilitate successful hospital discharges. Empirical evidence from Phase 3a of this thesis confirms that HPUs significantly impact physical (limited mobility), social and psychological (such as depression and anxiety) aspects in participants that were able to self-complete the EQ-5D-5L questionnaire.

Findings from Phase 3a presented in Chapter 6 of this thesis suggest that HPUs have a negative impact on mobility with the case group reporting more severe mobility problems compared with the control group. This is expected as the PUs are situated on the aspects of the body that are designed to facilitate walking by absorbing the body weight. The negative impact from the HPUs was also experienced at follow-up (3-and 6- months follow-up from recruitment). These results are consistent with evidence that supports impaired mobility as an important risk factor for HPU development as discussed in section 7.2.3 and 7.2.4.2. Whilst impaired mobility is a risk factor for developing HPUs,

the presence of a HPU further reduces the ability to mobilise, thus those living with HPUs experience poorer HRQoL as observed in Phase 3a of this thesis. Furthermore, the presence of a HPU is sometimes accompanied by intervention(s) which are likely to increase patient burden in addition to that already caused by the presence of a HPU, as evidenced by findings from Phase 3a and other literature (Greenwood and McGinnis, 2016; Guest et al., 2018).

The presence of a HPU significantly affected participants' ability to complete everyday tasks such as washing or dressing themselves or their ability to do usual activities. For instance, participants with HPU were more likely to report having problems with washing or dressing themselves compared with others without HPUs. As reported in other studies, this can lead to social isolation and decline in mental health particularly where individuals have limited ability to engage in their usual activities (Gorecki et al., 2009; Roussou et al., 2023).These results are consistent with those reported in studies that have investigated the impact of PUs (PUs affecting all anatomical sites) on HRQoL, however these studies only assessed HRQoL at one time point, that is, they did not complete follow-up to assess the continued impact of having a HPU among their population. The evidence from this study suggests that the presence of HPU continues to significantly impact HRQoL for at least three months from initial study contact, making it an important consideration for discharge and home care planning to reduce premature placement breakdown and/ or hospital readmission rates.

Levels of anxiety or depression were observed to be similar amongst self-reported responses. Although patients with HPU reported poorer overall HRQoL sores, this was not reflected in their anxiety or depression levels in the study population. However, in other PU studies patients commonly reported emotions such as low mood, anger, frustration, anxiety, and depression (Galhardo et al., 2010). While this warrants further research to investigate the psychological impact of HPU, it is possible that the negative emotions reported by these patients are related to pain, wound infections, and dressings. In this study 50% of the HPU did not require a dressing and 13.5% had a known infection. Despite the lack of evidence to support association of HPU with higher levels of anxiety or depression, in Phase 3a of this thesis 70% of the participants with HPUs reported

experiencing slight anxiety or depression. These findings suggest that consideration of psychological impact of HPUs is a key concern in their management and treatment, particularly to enhance HRQoL of patients affected by HPUs.

This study included participants with cognitive impairment and their HRQoL questionnaires were completed by their proxies (nominated consultees). In contrast, the HRQoL as reported by participant proxies (nominated consultees) was on average lower in both study groups compared to the HRQoL reported by patients themselves. Previous studies investigating the impact of PU on HRQoL have not included individuals living with cognitive impairment and the impact it may have on both the patients and their carers (Gorecki et al., 2009; Herber et al., 2007). The results from Phase 3a of this study suggest that living with cognitive impairment is likely to have a negative impact on both the affected patient and their carers, as reflected by their lower HRQoL index scores. However, having a HPU did not make a difference in the presence of cognitive impairment. In this instance, HRQoL was reported by carers (professionals and non-professionals) thus the findings may reflect the perceived burden of looking after someone living with cognitive impairment. The proxies consistently reported lower/poorer HRQoL compared to those reported by patients themselves (patient deemed to have the mental ability to report their own HRQoL). It is hypothesised that proxies may have reported poorer HRQoL with the assumption that it might have influenced provision of extra support. Regardless of the reason, cognitive impairment has huge implications for clinical practice and research as those affected are usually underrepresented in research thus denying them evidence-based care and perpetuating health inequalities.

Longer hospital length of stay (LoS) is associated with poorer HRQOL outcomes and increased risk of infection, falls and resource utilisation (Rodziewicz and Hipskind, 2020). On average, hospital length of stay (LOS) amongst the case group was almost twice as long as those in the control group (mean difference (MD): -39.1 days [95% CI -74.3; -3.9) p-value =0.03). Phase 3a study participants were observed to be older and on average had five or more comorbidities. Evidence from this thesis suggests that having a HPU in this older patient population is likely to upsurge the disease burden

in already frail populations, resulting in the observed increase in LOS amongst the case group. Older patients with PUs (all anatomical sites included) have previously been reported to stay longer in hospital by at least 10 days compared to those without PUs (Theisen et al., 2012). However, the reported LOS mean difference for participants with a PU (all anatomical sites included) compared to those without PU was at least four times less compared to the mean difference observed between those with a HPU compared to those without HPU as reported in this study. This is a significant difference with huge implications for patients' HRQoL and healthcare experience, as well as clinical practice and the NHS.

A significant proportion (41.7%) of the population recruited in this study were living with some form of cognitive impairment, which further supports the need for future research on the effect of cognitive impairment in patients with or without a HPU and their carers. Enhancement of QoL has become an important aspect of healthcare service delivery and evaluations, therefore further research including interviews with participants and their careers are required to explore this further as the results will provide further insight that is likely to improve patient centred care and outcomes.

7.4.2 Pain Associated with Heel Pressure Ulcers

Pain is an inevitable symptom experienced by PU patients, which they can experience while resting as well as while performing activities of daily living and during PU related interventions (Briggs et al., 2013; McGinnis, Elizabeth, Briggs et al., 2014). In this thesis, pain was measured as part of the HRQoL as well as using two assessment tools targeted at pain assessment (PAINAD and NRS for participants with and without cognitive impairment, respectively). Participants with a HPU(s) on average reported higher pain scores compared to those without, however average pain scores across cases and controls were generally low at all three study time points (baseline, 3- and 6-months follow-up) and the differences between the two study groups were not statistically significant. On the contrary, other studies have previously found that participants with PUs reported to be constantly in pain and tended to report severe pain (García-Sánchez et al., 2019b; McGinnis et al., 2014). The findings from Phase 3a of this thesis may reflect the quality of pain management that

was available to all study participants. On another hand, it is possible that patients with HPU reported low pain scores due to experiencing peripheral neuropathy in the affected legs that tends to be characterised by numbness, tingling, and burning. This could suggest that the pain assessment tools used might not be suited to measuring pain associated with HPUs. This study was the first to specifically investigate pain associated with the presence of HPU, further studies are required to further investigate the type of pain associated with HPUs through exploring patient experiences.

7.5 Prognostic Value of Heel Pressure Ulcers in End of Life

This thesis is the first to investigate the prognostic value of HPUs in end of life (EoL) with the hypothesis that the skin, like any other organ, is likely to fail as individuals approach their end of life and HPUs might be a sign of skin failure as patients' approach EoL stages. Evidence from screening data of this study showed that at least 80% of all screened patients with HPUs had died approximately 18 months post screening date. In addition, a significant proportion (30.6%) of those excluded from the study (Phase 2) were identified as being in their last days of life (<72 hours) by their treating clinicians and a further 5.2% had died before they could be approached to take part in the study. Mortality rate in the case group was comparable to other similar studies (Berlowitz and Brienza, 2007; Brown, 2003), whilst that of the whole study population was similar to the average mortality rates as reported by the Office of National Statistics (2021). Observed time to death in the case group was similar to those reported in Jaul and Calderon-Margalit (2015), a study that included patients with PUs on different anatomical sites. However, patients with PUs had significantly lower median survival time than those without PUs (94 versus 414 days, respectively) (P = 0·005, log rank test) (Jaul and Calderon-Margalit, 2015). This suggests a possible link between PUs and EoL, however the authors do not report results by anatomical site thus its not clear what proportion of the PUs were observed on the heel. Although there were differences in mortality rates between those with HPUs and those without HPUs, this thesis did not find evidence to support the difference due to lack of study power to detect the small mortality rate differences observed in this study.

Overall study mortality rate was 38.8% (40 /103), however, 10.7% of the study participants were reported and documented in their medical or nursing records to be in their last year of life as defined

by the Supportive and Palliative Care Tool (SPICT). The SPICT is a clinical tool that was developed to support clinical judgement by helping identify patients at risk of deteriorating and dying. Previous research has shown that using the SPICT supports patients to receive EoL care and die in their place of choice (Lunardi et al., 2020). Effective use of the tool enables appropriate discussions and implementation of interventions to be done in a timely manner thereby enhancing patients' EoL care such as allowing patients to make informed decisions about their care, treatment and goals as well as voicing their preferences in terms of care provision setting (hospital, hospice, or patient's own home). This thesis shows that many the participants that died within the study duration are likely not to have benefited from the care and support associated with having a SPICT indicator in their nursing and medical records.

7.6 Cognitive Impairment and Healthcare Provision

A key finding of this thesis is that over 40% of the case population lived with some form of cognitive impairment on the day of assessment or had a diagnosis recorded in their medical records. This empirical evidence suggests that excluding this group of participants would likely have biased the results of the study. Therefore, future studies in HPU will need to give due consideration to patients' mental capacity as this is likely to impact the outcome of the study.

Cognitive impairment, whether due to chronic or acute illnesses, has huge implications for nursing care and research. Cognitive impairment describes a state when a person has problems with their memory or thinking; severity can range from mild to severe, short-term, or reversible, to long-term or permanent. One in six over 80s are reported to live with some form of dementia affecting their cognitive ability (Alzheimer's Society, 2024). In Phase 2 of this thesis, as reported in Chapter 6, 43.4%% of the case group (those with HPUs) were deemed to lack capacity or cognitive ability to complete study questionnaires as assessed by the researcher in conjunction with the treating clinicians. As mental status was used as a matching variable, case and control groups had comparable proportions of participants deemed to lack capacity. Excluding this group of patients would have resulted in poor recruitment rates, biased estimates, and reduced generalisability of the

findings of this thesis thus denying this group of patients' evidence-based care and maintaining health inequalities.

Persons that lack capacity are underrepresented in research, which impacts the quality of evidence and applicability of findings of interventions to this group of patients (Shepherd et al., 2019; Shepherd, 2020). Previous PU studies, including those investigating HPUs, either do not report on participant's cognitive status or they are largely excluded from research due to the complex nature of their (Gaubert-Dahan et al., 2013; McGinnis et al., 2014). Furthermore, the link between mental status and PUs is under researched; a systematic literature review by Coleman and colleagues found only 20.4% of their eligible studies considered mental status as a potential risk factor for PUs (Coleman et al., 2013).

Cognitive impairment increases the risk of complications, some of which are preventable, such as falls, injuries and poor nutritional intake, making it a safety and quality issue (Kupisz-Urbanska and Marcinowska-Suchowierska, 2022; Mustafa Khalid et al., 2022). HPUs have multifactorial risk factors as highlighted in the proposed Risk Factors Framework (section 7.2). Cognitive impairment is linked to some of the risk factors for HPUs, such as age, diabetes, impaired nutrition, mobility, peripheral neuropathy, and sensory perception (Kawamura et al., 2012; Lin et al., 2021; Moreira et al., 2015; Roman de Mettelinge et al., 2013). Diabetic neuropathy and dementia (cognitive impairment) might share similar pathophysiological aspects (Rose et al., 2015), whilst increasing age is a confounding factor for the listed HPU risk factors. This suggests cognitive impairment is an important factor to consider in relation to PU prevention.

HPU prevention, like all PU prevention, is complex and multifaceted. However, 24-hour access to healthcare professionals and use or access to the aSSKINg (assess risk; skin assessment and skin care; surface, keep moving; incontinence and moisture; nutrition and hydration; and giving information or getting help) framework is likely to reduce incidence and for those that develop heel pressure ulcers they are less likely to be severe or deteriorate (Young and Fletcher, 2019; Young, 2021). For instance, within the participating site where the aSSKINg bundle is implemented, hospital

acquired category four PUs are rare and within the 20 months study recruitment period there were no hospital acquired category four HPUs. However, in community settings, particularly for individuals living in their own homes, individuals have limited access to resources and healthcare professional input. More recently, there has been an increase in resources aimed at empowering patients to take ownership of preventing pressure damage, represented by the 'g' in the aSSKINg framework (Health Innovation Network, 2024; National Wound Care Strategy Programme, 2023). However, this assumes that patients can process and understand the information, or that they have access to 24-hour carers who are able to support them with implementing prevention strategies. A qualitative study by Fleeming (2015) involving patients and carers showed a general lack of awareness of the SSKIN care bundle was identified with some confusion surrounding its acronym. Despite this, participants were willing to be more involved in PU prevention (Flemming, 2015). Furthermore, recent research by Greenwood et al. (2022) into factors affecting the success of HPU prevention strategies highlighted patient concordance as one of the important factors. It is apparent from this study (Phase 2, Chapter 6) that at least 40% of heel pressure ulcers had impaired cognitive impairment, which underscores the importance of cognitive impairment in HPU prevention. Moreso, HPU prevention devices (offloading devices and heel-specific low-friction devices) may require patients' concordance. Whilst the aSSKINg framework might be a useful tool in combating PU prevention, there is need for further work to be done to support its implementation for the management of patients with cognitive impairment. This is further supported by the lack of clear evidence on the effectiveness of heel specific devices on reducing the incidence of HPUs (Clegg and Palfreyman, 2014; Greenwood et al., 2022).

Traditionally, PUs have been the problem for the nursing profession. However, more recently pressure ulcer prevention, management and treatment has become a multidisciplinary issue (Clarkson et al., 2019; Gould et al., 2019). Clinicians, such as dermatologists, can play a significant role in PU prevention by being aware of those at risk and implementing prevention strategies in a timely manner (Mervis and Phillips, 2019). Similarly, podiatrists working in the community have access to at risk populations (diabetic patients) in their own homes, thus their involvement may help

to reduce HPUs incidence rate within these settings. In Phase 2 of this study (reported in Chapter 6), 52.8% (28/53) patients had acquired more severe HPUs (categories 3 and 4) while living in their own homes. Moreover, cognitive impairment and HPUs are patient safety and quality concerns, which affect adults of all ages, thus making this a multidisciplinary concern. Therefore, educating and involving the multidisciplinary team in PU prevention and management is paramount to reduce both incidence and prevalence rates in all settings, including in patients' own homes.

Recognising the importance of interprofessional team working is crucial for effective heel pressure ulcer prevention. Collaboration with various specialists, such as the vascular team, is essential to address the complex factors contributing to pressure ulcer development. Findings from this thesis suggest that exposure to vascular disease significantly increases the risk of heel pressure ulcers. For instance, patients with peripheral arterial disease (PAD) are at a higher risk due to compromised blood flow to the heels. Vascular specialists can provide insights into circulatory issues that may affect heel health, while nurses, dietitians, and physiotherapists can contribute their expertise in skin care, nutrition, and mobility. This comprehensive, team-based approach ensures that all aspects of patient care are considered, leading to more effective prevention and management strategies, particularly in combating community-acquired heel pressure ulcers. By integrating these collaborative efforts into the PURPOSE T and the Heel Pressure Ulcer Risk Factors framework, healthcare providers can enhance training and preventative measures, ultimately improving patient care quality and reducing the financial burden on the NHS.

7.7 Impact of Public Involvement in Nursing Research

Public involvement in research has gained significant attention in recent years as it ensures that the research is relevant, ethical, and impactful (Domecq et al., 2014; Iliffe et al., 2013). In support of the growing momentum and importance, public involvement is a legal requirement as stipulated in the Health and Social Care Research Framework (Health and Social Care, 2018). As previously stated, public involvement in this context refers to research that is done with or by the public (patients, members of the public, service users and/or their families). In these cases, the public use their

relevant lived experience to contribute to how research is designed, conducted, and disseminated. This type of involvement is essential for ensuring that the research addresses the needs and concerns of the people it ultimately seeks to benefit. Moreso, it fosters empowerment, transparency and enhances the ethical conduct of the research, and thus increases participant recruitment and retention (Boote et al., 2015; INVOLVE, 2016; Rose, 2014; Swain et al., 1998).

This thesis intended to investigate factors associated with HPU presence within the adult population, understand their impact on health-related quality of life, and predictive value at the end of life. Evidence suggests that PUs are more likely to develop in older people (González-Méndez et al., 2018; Nixon et al., 2006; Serpa and Santos, 2007; Strazzieri-Pulido et al., 2019) and advanced age is aligned with different types of dementia such as Alzheimer's disease, vascular dementia, and other conditions such as Parkinson's disease. Unfortunately, these progressive conditions are associated with decline in brain functioning and affect at least one in six individuals aged over 80 years; this number will continue to rise with the ageing population in the UK (Alzheimer's Society, 2024). Individuals with cognitive impairment have previously been excluded from research investigating HPUs (Gaubert-Dahan et al., 2013) due to ethical concerns around vulnerability, lack of mental capacity and ability to provide informed consent. In studies where eligibility criteria included providing informed consent, the assumption is that patients living with cognitive impairment due to conditions such as dementia were excluded. On the contrary, evidence from this thesis underscores the importance of ensuring patients with cognitive impairment are involved in research, particularly studies on HPUs. In Phase 2 of this thesis, at least 40% of the study case group lived with some form of cognitive impairment, thus excluding this group of patients would have biased the study findings.

Public involvement played a significant role in the design of the research project presented in this thesis, particularly in the development and implementation of recruitment strategies and gaining NHS ethics approval. The researcher consulted four patients and two carers with experience of either living with or looking after a relative affected by a pressure ulcer who made up a public

involvement support group, to inform all aspects of this research (from study design, conduct, analysis, and dissemination) including whether individuals lacking mental capacity should be included in this research. The researcher also consulted with another public involvement group organised and managed by the research site which was larger and had wider representation. Both groups were in support of the research work and agreed that it was necessary to conduct research that was inclusive of all individuals, including those deemed to lack mental capacity, to ensure that the research would be generalisable and relevant to the NHS. Liffe et al (2011) adopted a similar public involvement strategy facilitated by the Dementia & Neurodegenerative Diseases Research Network (DeNDRoN), a group that works to support the involvement of lay representatives with mild cognitive impairment due to diagnosis of dementia and neurodegenerative diseases.

Inclusion of people without the mental capacity to provide informed consent was deemed important and acceptable by the public involvement contributors. In line with the Mental Capacity Act (2005), the researcher proposed to recruit eligible participants deemed to lack mental capacity with the support of personal consultees (that is patients' friends or family that maintained contact with the patient through hospital visits) (Mental Capacity Act, 2005). The support of the public involvement group on this proposal facilitated a good rapport with the Health Research Authority (HRA) and NHS Research Ethics Committee (REC) resulting in a favourable opinion. However, a silent exclusion criterion was imposed by the REC as the group only supported recruitment of patients that were deemed to lack capacity through face-to-face consultations with their personal consultees. Research ethics groups are tasked with assessing the ethical implications of research, including protecting the vulnerable, which sometimes overreaches to paternalism and overprotection minimising the potential benefit and thus further contributing to the exclusion and underrepresentation of adults who lack the capacity to provide informed consent in research (Biggs, 2009; Paddock et al., 2021). Additionally, the interpretation of the Mental Capacity Act 2005 is inconsistent amongst RECs and can contribute to further exclusion of already underrepresented groups (Dixon-Woods and Angell, 2009; Shepherd et al., 2019b; Shepherd et al., 2023).

Underrepresentation of such groups of people is a recognised ongoing problem in research due to several barriers such as restrictive eligibility criteria, roles of gatekeepers and methodological issues (Shepherd et al., 2023). Underrepresenting adults who lack capacity denies such groups evidence-based care and maintains health inequalities (Matsuda et al., 2016; Shepherd, 2020). This study experienced poor recruitment rates due to the inability of the researcher to meet on the hospital wards with friends and families of patients deemed to lack mental capacity to discuss the study as per criterion imposed by the REC. The researcher noted that at least 14.5% (30/206) of the identified personal consultees (family or friends) did not visit regularly or they visited out of hours, therefore making it difficult to meet with them within hospital settings to discuss the prospect of their relations taking part in the research study. Nurses on the wards acted as gatekeepers responsible for making the initial contact with patients' family and friends in the absence of the researcher. Nonetheless, the nurses were not able to facilitate the initial contact, likely because the nurses had competing commitments with their main priority focussed on delivering care to poorly patients thus leaving them with less or no time to support the research. Lack of consultees and the role of gatekeepers, amongst many other barriers, have been highlighted as challenges affecting the conduct of research with adults lacking the mental capacity to provide informed consent (Shepherd et al., 2023). Therefore, it was necessary to reconsider the research protocol and make amendments to address these challenges. It took the researcher approximately six months to gather supporting evidence for a substantial amendment; inevitably this contributed to the poor recruitment rates.

To address underrepresentation of adults lacking capacity and its impact on evidence-based practice and persisting health inequalities, the researcher proposes an advanced opt out consent process for research. Similar to the advanced decisions to refuse treatment, this would allow patients to make advanced decisions regarding taking part in research before decision-making capacity has been lost. The advance decisions would fall under the Mental Capacity Act 2005 accompanied by guidelines on their implementation. Advanced research opt out consent framework does not currently exist. This would require research by experts in the field to develop an evidence-based process informed by public involvement to ensure it is acceptable and feasible. Opt out consent has

been considered in observational studies and found to be beneficial; however, patients have raised concerns around privacy and data sharing (Cardillo et al., 2018; Henshall et al., 2021). In Henshall et al. (2021) an opt out consent was found to offer greater inclusivity for patients and dealt with the issue of gatekeepers. Furthermore, the study found that opt out consent might free up staff time as staff raised concerns about lack of time for clinical research. Clinical work takes priority over research; the advanced opt out provisions would need to take such issues into consideration as well as ethical factors.

Public involvement in this study played a fundamental role in the designing recruitment strategies and raising research awareness amongst gatekeepers (such as frontline nurses) thus facilitated an NHS research ethics committee (REC) approval of the study protocol including amendments. Public representatives were supportive of recruiting and involving patients deemed to lack capacity through consultation with either a personal or professional consultee. If an appropriate personal consultee could not be identified, the amendment proposed consulting a member of the treating team as a professional consultee for patients that were deemed to lack the mental capacity to provide informed consent and take part in the study. The professional consultees would also appoint appropriate healthcare professionals to complete study questionnaires on behalf of these patients. This arrangement facilitated the recruitment of at least a further 15% of the study population. Use of professional consultees has been reported in other studies and attributed to improved recruitment rates and representation of patients lacking the capacity to consent (McGinnis, et al., 2014; Shepherd et al., 2019b; Stanley and Nwosu, 2021). In addition, one member of the patient and public involvement group supported the researcher in raising research awareness amongst nurses by attending specific staff meetings and talking to the audience about why research was important to them as a patient and the need to empower other patients to take part in research.

Research involving vulnerable individuals has been challenging due to the sensitive nature, requiring a lot of involvement and support from both clinicians and researchers to engage eligible participants and their respective consultee (this can be next of kin, close friends, or relations, treating

clinicians) but it does not make it impossible. This can be overcome by educating and reassuring respective parties that all research conduct will be done in the patient's best interest and encouraging and supporting all involved parties to be part of the decision-making processes. In the context of this study, public involvement was crucial in ensuring the study processes were ethically acceptable and in raising research awareness amongst nurses in their role as gatekeepers. An important finding is that none of the HPU studies considered in this thesis report on the involvement of those with lived experience of having or looking after someone with a HPU.

7.8 Study Strengths and Limitations

This study utilised distinct designs in each of the three phases, which were appropriate for addressing specific research questions. Patient and Public Involvement played a fundamental role in the design and conduct of the study thus ensuring the study remained relevant to the patients and the NHS. In addition, this facilitated the study to be inclusive of underrepresented patient groups. The Phase 2 (a matched case control study) of this study was underpinned by evidence from a systematic literature review (Chapter 3). Key findings from this thesis are based on a 5% significance level which means there was evidence to support any observed relationships with a p-value less or equal to 0.05. Where p-values where greater than 0.05 further investigations are warranted as the study had limited evidence to support the observed associations.

This thesis was the first to conduct a systematic literature review on risk factors for HPUs in the adult population. A recent search identified no further research on risk factors for developing HPUs have been published since the publication of the literature review by Dube et al. (2022). This suggests more research is still required to address this important area.

The systematic literature review undertaken in Phase 1 of this thesis identified a lack of standard reporting, for instance, studies either used Braden scale, Norton, or Waterlow scores as risk assessment tools, which made it impossible to compare and quantitatively synthesise the results. In addition, the study populations were heterogeneous which impacted on the ability to conduct a meta-analysis; studies involved populations from acute, community settings, and other studies

included participants with specific conditions (for example orthopaedic patients or patients with diabetes).

This thesis involved a single centre, and several steps were taken in Phase 2 (matched case control study) to limit selection bias such as matching study participants based on age, gender, end of life status and mental capacity. Furthermore, all cases were screened from a Datix database which is used for recording and reporting all pressure ulcers including heel pressure ulcers, both hospital and non-hospital acquired. Another way of minimising selection bias was the use of a predefined eligibility criteria informed by literature and experts, for instance the study excluded patients in their last days of life 48-72 hours, as these would have overestimated mortality rates and would have been unethical as the study had no direct benefits to participants. The study was limited to a single acute hospital due to resources; this is likely to affect the generalisability of the study result especially for survival and quality of life as people are increasingly choosing to be cared for outside of formal hospital settings, that is, patients might choose to continue living in their own homes or care home settings whilst they receive end of life care. Also, 54.6% (247/452) of all screened patients of HPUs were acquired outside of the hospital setting, future studies would need to consider a multicentre design including community settings to increase generalisability of study findings.

To maximise the inclusion and participation of all potential participants the eligibility criteria was agile to the population characteristics, it divided into two: those eligible for DUS and those of contraindicated or did not want to complete a DUS. Through public involvement, the study incorporated the use of personal or professional (described in Chapter 5) consultees for those patients that lacked capacity to provide informed consent. This increased the inclusivity of the study and representation of patients deemed to lack capacity.

Measurement error is likely when participants complete self-reported questionnaires (such as ED5-5Q-5L) or recall bias when participants must rely on their memory for information. Questions requesting information from the past may be less well remembered than more recent events. In this study, HRQoL was measured using EQ5D-5L which asks participants to reflect on their HRQoL on

the day of assessment. Furthermore, the use of EQ5D-5L allowed patient representatives which could either be their family, carer or healthcare professional involved in their day-to-day care to provide data for those deemed to lack capacity and therefore not able to accurately complete the questionnaire. Thus, minimising missing EQ5D-5L data. Where applicable, medical records were used to confirm and supplement information provided by participants or their representative as appropriate. However, in some cases diagnosis dates and exposure history was not available for non-hospital acquired heel pressure ulcers, despite efforts being made to contact community-based healthcare professionals, an inherent limitation of retrospective data collection methods.

The SPINE database was accessed for mortality data; however, it does not include cause of death, therefore the main outcome for the survival data was 'all-cause mortality' which minimises any reporting bias. Questions relating to lifestyles maybe over-reported and / or medical history maybe under reported thus biasing study estimates. Another limitation of the study is the lack of preadmission quality of life to assess whether hospitalisation could have an impact on the HRQoL, however this affected both cases and control. The majority of the study data was collected retrospectively based on data availability within medical records and patient's or consultee memory. To minimise measurement error or reporting bias, where possible objective outcome measures were used, for instance PAD diagnosis was completed using doppler ultrasound by a trained researcher or healthcare professional.

Participants were followed for a 6-month period from recruitment for survival to investigate whether there was a link between HPU and time to death. For participants that died during hospital stay whilst admitted to the participating site, cause of death was readily available within the hospital database. However, those that died outside of the hospital setting or in another hospital were followed up using the SPINE database and cause of death data was not available for this group of participants. Attempts were made to retrieve data from their respective general practitioner (GP), however the researcher found it required several attempts to get the data which was time consuming for one researcher to complete. This may have affected the results as differential mortality by cause

of death was not possible due to the large percentage of missing data on the cause of death (47.5%; 19/40).

Confounding is a major issue when examining the relationship between exposure and or disease and outcome in non-randomised health-related study designs. To reduce the impact of confounding factors a matched case control design in Phase 2 was utilised and the same population was then followed up prospectively for survival and quality of life in Phase 3 of the study. The participants were matched based on their age, gender, mental capacity and EoL status. Furthermore, multivariable analysis was used to identify independent factors associated with the presence of HPUs in the adult population.

A pragmatic 6-month follow-up period informed by literature and experts in the field was chosen to fit in with the PhD project timeline for the research study being completed. This is likely to have affected the mortality rate differences observed in this study (Phase 3b). Future studies may want to consider a 12-month follow-up period based on the Kaplan-Meier curves (section 6.5.4), which show a potential difference in mortality rates between those with a HPU and those without beyond the 6 months follow-up. Retrospective evidence from the study screening data showed that at least 80% of all those with a HPU had died at 18 months post screening.

7.9 Summary

This is the first study to synthesise risk factors for developing HPU in the adult population and investigate the impact of HPU on health-related quality of life (HRQoL) and their prognostic value at the end of life. A HPU Risk Factors Framework is proposed based on combined key findings from the wider literature and empirical study both conducted as part of this thesis. The proposed HPU Risk Factors Framework can be used to inform future clinical practice and research. HPUs have a negative impact on patient's HRQoL, however in patients living with cognitive impairment clinicians would need to consider the impact it might have on their carers. Further research is required to investigate the predictive value of HPUs in EoL. Chapter 8 presents contributions to knowledge and recommendations for clinical practice and future research.

Chapter 8 Conclusions and Recommendations

8.1 Introduction

Pressure ulcer (PU) prevention relies on risk assessment and implementation of prevention strategies based on individual risk profile (European Pressure Ulcer Advisory Panel et al., 2019). Prevention of heel PUs (HPUs) requires additional specialist equipment such as heel offloading devices, specific constant low-pressure devices, and heel-specific low-friction devices (NICE, 2014). Clinicians use risk assessment tools and their clinical judgement to identify those at risk; this thesis proposes a HPU Risk Factors Framework, which can be used to support clinical judgement in prioritising patients that might require additional heel specific equipment.

PU prevention remains a challenge within all healthcare settings as evidenced by the persisting high incidence and prevalence rates (Clark et al., 2017; Stephenson et al., 2021). Despite sacral and heel PUs being the two most common types of PUs; the majority of research classes PUs into a single but heterogenous group despite evidence suggesting anatomical sites may have different risk factors (Clark et al., 2017; Gefen, 2010; Li, Z. et al., 2020; Sardo et al., 2023; Stephenson et al., 2021). There appears to be more research on sacral PUs compared to heel PUs and a lack of clear evidence to support the use of different HPU specific equipment (Clegg and Palfreyman, 2014; Greenwood et al., 2022). Furthermore, there is a lack of published evidence on national HPU incidence and prevalence rates within the UK. Effective PU prevention relies on risk assessment using validated tools to identify individuals' risk profile which in turn is used to inform implementation of PU strategies. To improve HPU prevention, quality of care and patient safety, this research intended to identify and quantify the relationship between risk factors and heel pressure ulcers (HPUs) presence and investigate their impact on health-related quality of life (HRQoL) and prognostic value in end of life (EoL). In doing so, this research has:

1. Developed a conceptual framework comprising evidence from the wider literature and new empirical data from this thesis describing risk factors for heel pressure ulcer presence and quantified these associations.

2. Identified the negative impact of HPUs on patients with mental capacity and identified that for patients without capacity, any compromise to quality of life is overshadowed by the impact of living without capacity on their caregivers.
3. Been unable to provide further evidence that HPUs can predict end of life, however, this could be because the time to end of life measured in this study was limited up to 6 months post recruitment.
4. Determined the importance of including ethnic minority populations and people without capacity to consent in research studies investigating HPUs.

This chapter, therefore, summarises the contribution to knowledge and outlines recommendations for clinical practice and future research based on the findings of this thesis.

8.2 Contribution to Knowledge

This study has made important contributions to the knowledge of HPUs in the adult population. It is the first study to synthesise the existing evidence on risk factors for developing HPUs in the adult population. There is a paucity of evidence regarding risk factors for HPUs as identified by the Dube et al., (2022) systematic literature review. The review identified only 13 eligible articles, of these 23.1% (3/13) were rated as high quality (Delmore et al., 2019; Manderlier et al., 2019; Twilley and Jones, 2016) and less than 20% of the eligible studies were conducted in the UK (2/13) (Duncan et al., 2003; Twilley and Jones, 2016). Eight risk factors associated with HPU development in the adult population were identified from the three high quality studies: age, Braden subscales (mobility and friction and shear), diabetes, mechanical ventilation, nutrition, perfusion issues, surgery, and vascular disease. In addition, Phase 2 (empirical study) was able to replicate findings from previous studies as highlighted in the systematic literature review, in terms of the Braden Scale, and diabetes. This thesis also found evidence to support relationships between the presence of HPUs and AF, albumin level, disease status of diabetes and/ or CKD and impaired sensory perception. Other potential risk factors do exist as discussed in section 7.2.5 which require further investigation.

Risk assessment completed using a validated tool is an important aspect of PU prevention as it helps identify those at risk and inform implementation of prevention strategies such as the use of pressure relieving mattresses and repositioning regimes. Prevention of HPUs requires the use of additional specialist equipment such as offloading devices, however there is a lack of clear evidence to support the use of such equipment (Clegg and Palfreyman, 2014; Greenwood et al., 2022). The lack of evidence-based HPU risk profiling processes might have contributed to the absence of clear evidence to support the use of HPU prevention devices. This thesis is the first attempt to use quantifiably determined risk factors to model HPU presence while incorporating the wider body of literature and addressing some of the evidence shortcomings with new empirical data. A HPU Risk Factors Framework is proposed which synthesises the combined evidence derived from the systematic literature review and the empirical findings from Phase 2. The framework can be used to support risk assessment and clinical judgement in practice thus can enhance patient outcomes and reduce harm. The proposed framework provides a foundational base to build on as other risk factors may exist and require further investigation.

Alongside patient experience, quality of life indirectly is considered a marker for quality of care (Mosadeghrad, 2012). This study is also the first to independently consider the impact of HPUs on HRQoL and explore their prognostic value in EoL. PUs in general are known to negatively impact on quality of life (Gorecki et al., 2009; Roussou et al., 2023); this was consistent with the Phase 3a findings for participants able to self-complete the EQ5D-5L questionnaire. However, for participants deemed to lack capacity, the presence of a HPU was not linked to poor HRQoL, that is participants with or without a HPU had similar HRQoL as reported by their proxy (personal or professional consultee). These findings are likely to reflect the impact of cognitive impairment on caregivers; clinicians will need to consider the impact of cognitive impairment during discharge planning to help reduce failed discharges and the negative impact of readmission on the affected. In addition, this research underscores the importance of inclusive research, excluding patients without capacity in

research, denies them evidenced based care and can have huge implications for the provision of nursing care and resource management.

In addition to addressing the originally proposed research aim and objectives, this study has been able to organically derive other important contributions to knowledge, specifically in relation to the involvement of ethnic minority populations and people without capacity to consent. Ethnic minority populations are underrepresented in HPU studies, thus their contribution to evidenced based practice is less compared to their White counterparts. Such underrepresentation is likely to further prolong long standing health inequalities and poor outcomes. Individuals or patients deemed to lack capacity are another group that is underrepresented in research making interventions less applicable to this group of patients. This study also underscores the importance of cognitive impairment in relation to HPU prevention and management. Public involvement played a fundamental role in ensuring the study participants included this underrepresented group (patients deemed to lack capacity) thus making the study findings more generalisable. Given the longstanding health inequalities amongst ethnic minority groups and those deemed to lack capacity to consent to research, future HPU research will need to consider ethnicity and mental capacity as important factors.

Public involvement has played a crucial role in this thesis; patients and members of the public contributed to the design of the study using their lived experience. Public involvement includes the patient voice, and this is important in making sure the research remains relevant to those it is intended for. In this study public involvement was fundamental in acquiring NHS research ethics committee (REC) approval and the recruitment of patients with cognitive impairment. In addition, lay representatives were involved in raising research awareness among patients and nurses. Patients deemed to lack the capacity to provide consent are underrepresented in HPU research which denies this group of patient's evidence-based care and continues to perpetuate health inequalities. This study contributes to the field by demonstrating that public involvement in research with this focus is

feasible and relevant. It is possible to include patients who are deemed to lack capacity through their family, friends, and carers as consultees.

8.3 Recommendations

There is a paucity of high-quality evidence on HPU risk factors to inform risk assessment and clinical judgement. HPUs remain the second most common PU in most healthcare settings. This thesis proposed an evidence based HPU Risk Factors Framework enlisting risk factors as identified in literature and identified in Phase 2 (Chapter 6). The HPU Risk Factors Framework can be used to inform risk assessments, clinical judgement, and implementation of HPU interventions.

Several other potential risk factors have been identified; further research is required to investigate their relationship with HPUs. Future studies are to give due consideration to the relationship between ethnicity and HPUs with a particular focus on skin tones. Current emerging evidence suggests that nurses are not well equipped to deal with PU prevention in darker skin tone populations (Kariwo et al., 2023). Consequently, this group of patients is likely to present late with more severe PUs which take longer to heal. Furthermore, future studies have to be inclusive to increase the generalisability of their findings to underrepresented groups such as those living with cognitive impairment and individuals from ethnic minority groups with darker skin tones.

Patient involvement played an important role in the recruitment of patients deemed to lack capacity, who are regularly underrepresented in research studies. Future studies would need to involve those with lived experience of HPUs to ensure the studies benefit the at-risk populations and ensure the study population is representative of the affected population. In addition, mixed methods studies on the impact of HPU on both the patients and their carers would help inform discharge processes and reduce hospital readmission rates.

Ethnic minority groups were disproportionately underrepresented in this thesis and ethnicity is not commonly reported in other HPU studies. Research of interest to the researcher is to conduct a study involving individuals of ethnic minority backgrounds to understand HPU incidence and prevalence rates, risk factors and impact on quality of life. In addition, the research would explore

the lived experiences of those living with HPUs to understand their experience of the diagnosis and treatment of their HPUs.

Patients lacking capacity are underrepresented in research, including studies investigating HPUs, due to ethical concerns around vulnerability, lack of mental capacity and ability to provide informed consent. In this study a salient exclusion criterion was imposed by the REC by only allowing this group of patients to be recruited through face-to-face consultations with personal consultees only. As previously alluded to, this condition contributed to the poor recruitment rates in Phase 2 of this study. Furthermore, evidence from this thesis suggests that consultees may be more protective than one would be if they were to make decisions for themselves, thus impacting how or what patients deemed to lack capacity can take part in. Of those who lacked the mental capacity to provide informed consent, 39.5% (17/43) of their nominated consultees agreed for them to complete a DUS assessment compared to 85% of those that had the mental ability to provide study consent. Whilst the decisions may have been made in the best interest of the patients at the time, it continues to perpetuate underrepresentation of this patient group, consequently impacting their care. To combat such issues in future research and empower patients to consider research as an important part of their healthcare, the researcher recommends use of an 'advanced opt out research consent'. Such provisions do not currently exist within research; however, a similar framework is available for treatment under the Mental Capacity Act 2005 – advanced decisions. The advanced opt out consent framework would need to be co-produced with key stakeholders including patients and members of the public. The researcher acknowledges that this is not their area of expertise and therefore, would recommend those with expertise and experience to undertake such work.

Another study of interest is to explore the prevalence of HPUs in community settings such as nursing and residential care homes and hospices in England; to further explore their prognostic value in EoL. HPUs acquired outside of the hospital setting accounted for at least 54.6% (247/452) of all screened patients, too large a statistic to ignore. Particularly, given that this study was the first to explore this research question, however, this thesis was limited to a single acute hospital setting.

8.4 Conclusion

This thesis has produced a novel contribution to knowledge investigating a population of patients often excluded from research due to their vulnerability and the complexity of their involvement, which often means they are resource intensive. Including people with cognitive impairment in studies where a large proportion of the potential participants would have a cognitive impairment is critical to improving both the quality and safety of their care. Exclusion from these studies would be discriminatory and deny them access to better care. Similarly, ethnic minority populations need to be considered and potentially purposely sought for inclusion in studies to ensure that HPU risk assessment and prevention processes using approaches or care bundles such as the Risk Factor Framework presented here are relevant to their care.

HPUs negatively impact quality of life and significantly increase healthcare resource use in the acute setting. Use of tools such as the HPU Risk Factors Framework can provide support to aid in their prevention by identifying people who display these risk factors and implementing prevention strategies accordingly.

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Appendices

Appendix 1: International NPUAP/EUPUAP (2014) Pressure ulcer classification system

Stage 1	Non-blanchable erythema of intact skin: Intact skin with a localized area of non-blanchable erythema, which may appear differently in darkly pigmented skin. Presence of blanchable erythema or changes in sensation, temperature, or firmness may precede visual changes. Colour changes do not include purple or maroon discoloration; these may indicate deep tissue pressure injury.
Stage 2	Partial-thickness skin loss with exposed dermis: Partial-thickness loss of skin with exposed dermis. The wound bed is viable, pink or red, moist, and may also present as an intact or ruptured serum-filled blister. Adipose (fat) is not visible and deeper tissues are not visible. Granulation tissue, slough and eschar are not present. These injuries commonly result from adverse microclimate and shear in the skin over the pelvis and shear in the heel. This stage should not be used to describe moisture associated skin damage (MASD) including incontinence associated dermatitis (IAD), intertriginous dermatitis (ITD), medical adhesive related skin injury (MARSI), or traumatic wounds (skin tears, burns, abrasions).
Stage 3	Full-thickness skin loss: Full-thickness loss of skin, in which adipose (fat) is visible in the ulcer and granulation tissue and epibole (rolled wound edges) are often present. Slough and/or eschar may be visible. The depth of tissue damage varies by anatomical location; areas of significant adiposity can develop deep wounds. Undermining and tunnelling may occur. Fascia, muscle, tendon, ligament, cartilage and/or bone are not exposed. If slough or eschar obscures the extent of tissue loss this is an Unstageable Pressure Injury.
Stage 4	Full-thickness skin and tissue loss: Full-thickness skin and tissue loss with exposed or directly palpable fascia, muscle, tendon, ligament, cartilage or bone in the ulcer. Slough and/or eschar may be visible. Epibole (rolled edges), undermining and/or tunnelling often occur. Depth varies by anatomical location. If slough or eschar obscures the extent of tissue loss this is an Unstageable Pressure Injury.
Extra categories recently added	
*Unstageable	Obscured full-thickness skin and tissue loss: Full-thickness skin and tissue loss in which the extent of tissue damage within the ulcer cannot be confirmed because it is obscured by slough or eschar. If slough or eschar is removed, a Stage 3 or Stage 4 pressure injury will be revealed. Stable eschar (i.e. dry, adherent, intact without erythema or fluctuance) on the heel or ischemic limb should not be softened or removed.
SDTI	Persistent non-blanchable deep red, maroon or purple discoloration: Intact or non-intact skin with localized area of persistent non-blanchable deep red, maroon, purple discoloration or epidermal separation revealing a dark wound bed or blood filled blister. Pain and temperature change often precede skin colour changes. Discoloration may appear differently in darkly pigmented skin. This injury results from intense and/or prolonged pressure and shear forces at the bone-muscle interface. The wound may evolve rapidly to reveal the actual extent of tissue injury, or may resolve without tissue loss. If necrotic tissue,

	subcutaneous tissue, granulation tissue, fascia, muscle or other underlying structures are visible, this indicates a full thickness pressure injury (Unstageable, Stage 3 or Stage 4). Do not use DTPI to describe vascular, traumatic, neuropathic, or dermatologic conditions.

Appendix 2: Risk Factors Associated with Heel Pressure Ulcer Development in Adult population: A systematic literature review (Dube et al., 2022)

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Risk factors associated with heel pressure ulcer development in adult population: A systematic literature review

Alisen Dube [a,b,c,*], Viola Sidambe [c], Amy Verdon [c], Eloise Phillips [d], Sarahjane Jones [b], Maxine Lintern [e], Mark Radford [a,f,g]

[a] Faculty of Health, Education and Life Sciences, Birmingham City University, Birmingham, UK
[b] School of Health, Science, and Wellbeing, Staffordshire University, Staffordshire, UK
[c] University Hospital Coventry and Warwickshire NHS Trust, Coventry, UK
[d] School of Pharmacy, Aston University, Birmingham, UK
[e] Faculty of Business, Law and Social Sciences, Birmingham City University, Birmingham, UK
[f] Health Education England, Birmingham, UK
[g] NHS England and NHS Improvement, Birmingham, UK

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ABSTRACT

Aims: The main aim of this systematic literature review was to identify risk factors for development of heel pressure ulcers and quantify their effect.
Background: Pressure ulcers remain one of the key patient safety challenges across all health care settings and heels are the second most common site for developing pressure ulcers after the sacrum.
Design: Quantitative systematic review.
Methods: Data sources: Electronic databases were searched for studies published between 1809 to March 2020 using keywords, Medical Subject Headings, and other index terms, as well as combinations of these terms and appropriate synonyms. Study eligibility criteria: Previous systematic literature reviews, cohort, case control and cross-sectional studies investigating risk factors for developing heel pressure ulcers. Only articles published in English were reviewed with no restrictions on date of publication. Participants: patients aged 18 years and above in any care setting. Study selection, data extraction, risk of bias and quality assessment were completed by two independent reviewers. Disagreements were resolved by discussion.
Results: Thirteen studies met the eligibility criteria and several potential risk factors were identified. However, eligible studies were mainly moderate to low quality except for three high quality studies.
Conclusions: There is a paucity of high quality evidence to identify risk factors associated with heel pressure ulcer development. Immobility, diabetes, vascular disease, impaired nutrition, perfusion issues, mechanical ventilation, surgery, and Braden subscales were identified as potential risk factors for developing heel pressure ulcers however, further well-designed studies are required to elucidate these factors. Other risk factors may also exist and require further investigation.
Prospero id: PROSPERO International prospective register of systematic reviews: CRD42017071459.

1. Introduction

Pressure ulcers (PUs) remain one of the key patient safety challenges across all health care settings alongside falls, urinary tract infections (UTIs) in patients with a catheter and new venous thromboembolisms (VTEs) [1].They affect mainly those with mobility problems, the acutely ill and the elderly. At least 200,000 people in the United Kingdom (UK) are estimated to develop a new PU each year. On average, PU treatment costs £1.45 million per day [2] and these costs are expected to rise with the aging population.

PUs, also commonly known as bedsores, pressure sores, decubitus or pressure injuries, are localised damage to the skin and/or underlying soft tissues caused by sustained pressure or shear at the weight bearing, bony prominence areas such as buttocks, hips, heels, sacrum, spine and elbows, of immobilised individuals (or related to medical devices) [3,4]. The skin damage can range from non-blanching redness to the skin

* Corresponding author. Staffordshire University, Centre of Excellence in Healthcare Education, Room BL132 Black Heath Lane, Stafford ST18 OYB, UK.
E-mail address: alisen.dube@staffs.ac.uk (A. Dube).

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Appendix 3: Accompanying Email Outlining Publishing Agreement and Scholarly Communication Rights

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Appendix 4.1: Systematic Literature Review Database Search Strategies Examples

Table 1: CINAHL Database

Search performed using Boolean/Phrase

Search	Search Terms	Results
S1.	(MH "Heel Ulcer/EP/ET/PC")	84
S2.	(MH "Heel Ulcer")	180
S3.	TI heel ulcer* OR AB heel ulcer*	303
S4.	S1 OR S2 OR S3	385
S5.	(MH "Pressure Ulcer/EP/ET/PC")	8, 267
S6.	TI pressure ulcer* OR AB pressure ulcer*	9, 489
S7.	TI pressure sore* OR AB pressure sore*	1, 916
S8.	TI bed sore* OR AB bed sore*	226
S9.	TI pressure injur* OR AB pressure injur*	1, 586
S10.	TI decubitus ulcer* OR AB decubitus ulcer*	203
S11.	TI decubitus OR AB decubitus	1, 252
S12.	S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11	16, 114
S13.	S4 AND S12	249
S14.	TI (risk factors or contributing factors or predisposing factors) OR AB (risk factors or contributing factors or predisposing factors)	189, 968
S15.	MH risk factors or contributing factors or predisposing factors	137, 784
S16.	S14 OR S15	311, 610
S17.	S13 AND S16	39

Table 2. Cochrane Library

Search	Search criteria	Results
#1	MeSH descriptor: [Heel] explode all trees	217
#2	MeSH descriptor: [Pressure Ulcer] explode all trees	728
#3	pressure sore	1, 034
#4	pressure injury	6, 785
#5	bedsore	84
#6	decubitus	1, 274
#7	MeSH descriptor: [Risk Factors] explode all trees	23, 627
#8	risk*	229, 041

#9	heel	2, 071
#10	pressure sore*	1, 892
#11	pressure ulcer*	3, 105
#12	pressure injur*	7, 970
#13	bedsore*	126
#14	#2 or #3 or #4 or 5 or #6 or 10 or #11 or #12 or #13	1 187 208
#15	#1 or #9	2071
#16	#7 or #8	229, 041
#17	#14 and #15 and #16	419

Table 3. EMBASE Database

Search	Search criteria	Results
1.	heel.sh. or heel*.ab. or heel*.ti.	18, 355
2.	pressure ulcer.sh. or pressure ulcer*.ab. or pressure ulcer*.ti.	9, 415
3.	pressure injury.sh. or pressure injur*.ab. or pressure injur*.ti.	972
4.	pressure sore.sh. or pressure sore*.ab. or pressure sore*.ti.	3, 630
5.	bedsore.sh. or bedsore*.ab. or bedsore*.ti.	711
6.	decubitus ulcer.sh. or decubitus ulcer*.ab. or decubitus ulcer*.ti.	1, 983
7.	decubitus.sh. or decubitus.ab. or decubitus.ti.	24,143
8.	risk.sh. or risk*.ab. or risk*.ti.	3 188 575
9.	bed sore.sh. or bed sore*.ab. or bed sore*.ti.	308
10.	2 or 3 or 4 or 5 or 6 or 7 or 9	27, 499
11.	1 and 8 and 10	284
12.	limit 11 to (human and (adult <18 to 64 years> or aged <65+ years>))	180

Table 5. MEDLINE Database

Search performed using Boolean/Phrase

Search	Search Criteria	Results
S1.	MH heel	3, 240
S2.	TI heel OR AB heel	12,927
S3.	S1 OR S2	12,848
S4.	MH pressure ulcer	12,149

S5.	(MH "Skin Ulcer/EP/PC/ET") OR (MH "Foot Ulcer/EP/ET/PC") OR (MH "Pressure Ulcer/EP/ET/PC")	11,616
S6.	TI pressure ulcer OR AB pressure ulcer	7,516
S7.	AB bedsore* OR TI bedsore*	480
S8.	AB decubitus OR TI decubitus	4,972
S9.	AB pressure injur* OR TI pressure injur*	2, 418
S10.	S4 OR S5 OR S6 OR S7 OR S8 OR S9	23,962
S11.	S3 AND S10	612
S12.	MH risk factors or contributing factors or predisposing factors	807, 768
S13.	AB (risk factors or contributing factors or predisposing factors) OR TI (risk factors or contributing factors or predisposing factors)	610, 451
S14.	S12 OR S13	1,132,958
S15.	S11 AND S14	126

Table 6. NICE/ NHS Evidence

Search	Search Criteria	Results
1.	Heel pressure ulcer	150

Table 7. PROQUEST Database

Search	Search Criteria	Results
1.	(su(pressure ulcer*) OR ti(pressure ulcer*) OR ab(pressure ulcer*) OR su(bedsore*) OR ti(bedsore*) OR ab(bedsore*) OR su(pressure injur*) OR ti(pressure injur*) OR ab(pressure injur*) OR su(decubitus) OR ti (decubitus) OR ab (decubitus)) AND (su(heel*) OR ti(heel*) OR ab(heel*)) AND (su(risk*) OR ti(risk*) OR ab(risk*))	585

Table 8. PubMed Database

Search	**Search Criteria**	**Results**
#7	(((pressure injur*[Title/Abstract]) AND heel[Title/Abstract])) OR (((((((pressure ulcer*[MeSH Terms]) AND heel[MeSH Terms])) OR ((pressure ulcer*[Title/Abstract]) AND heel[Title/Abstract])) OR	392

	((bedsore*[Title/Abstract]) AND heel[Title/Abstract])) OR ((decubitus ulcer[MeSH Terms]) AND heel[MeSH Terms])) OR ((decubitus ulcer[Title/Abstract]) AND heel[Title/Abstract]))	
#6	(decubitus ulcer[Title/Abstract]) AND heel[Title/Abstract]	20
#5	(decubitus ulcer[MeSH Terms]) AND heel[MeSH Terms]	212
#4	(bedsore*[Title/Abstract]) AND heel[Title/Abstract]	8
#3	(pressure injur*[Title/Abstract]) AND heel[Title/Abstract]	42
#2	(pressure ulcer*[Title/Abstract]) AND heel[Title/Abstract]	261
#1	(pressure ulcer*[MeSH Terms]) AND heel[MeSH Terms]	212

Table 9. Scopus Database

Search	Search Criteria	Results
1.	(TITLE-ABS-KEY ("heel pressure ulcer") OR TITLE-ABS-KEY ("heel pressure sore") OR TITLE-ABS-KEY ("heel pressure injury") OR TITLE-ABS-KEY (heel W/3 bedsore) OR TITLE-ABS-KEY (heel W/3 decubitus) AND TITLE-ABS-KEY (risk AND factors))	42

Table 10. Trip PRO Database

Search	Search Criteria	Results
#8	#6 and #7	498
#7	(risk factor*)	321, 228
#6	#1 or #2 or #3 or #4 or #5	956
#5	Pressure injur* heel	599
#4	(decubitus heel)	660
#3	(bed sore heel)	660
#2	(pressure sore heel)	148
#1	(pressure ulcer heel)	395

Table 11. Web of Science Database

Search	Search Criteria	Search Results
#1	TOPIC: (heel) *OR* TITLE: (heel) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*	15, 786
#2	TITLE: (pressure ulcer*) *OR* TOPIC: (pressure ulcer*) *OR* TOPIC: (pressure injur*) *OR* TITLE: (pressure injur*) *OR* TOPIC: (bedsore*) *OR* TITLE: (bedsore*) *OR* TOPIC: (pressure sore*) *OR* TITLE: (pressure sore*) *OR* TOPIC: (decubitus) *OR* TITLE: (decubitus) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*	70, 094
#3	#2 AND #1 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*	581

Appendix 4.2: Systematic Literature Review- Summary of Study Characteristics

Study Authors (year) and country	Study population (No. recruited, setting and speciality)	Eligibility criteria	Design and analysis method	Study aims and objectives	Population characteristics (Age, %Female, Ethnicity)	Prevalence and incidence rate % developing HPU and by Category	Risk factors investigated (no, list of risk factors)	p-value	Measure of association (OR, RR, MD (SD), correlation, frequencies)	95% Confidence intervals
Tourtual et al (1997)	Main analysis: n=209 patients	**Inclusion criteria**: All patients who gave informed consent and were admitted to four nursing units participating in the study.	Two Prospective cohort studies	The purpose of this research was to determine the predictors of hospital acquired HPU.	Mean age: 67.6 yrs. (18.2)	HPU incidence rate 26.8% (56/209)	**Main analysis** Age	0.0001	MD: 13.7	9.7; 17.8
							LOS	0.0001	MD: 12.9	6.8; 18.9
USA			Chi-square, t-test, logistic regression		Female: 56.5% (118/209)	Category	Height	0.002	MD: -2.1	-3.4; -0.8
	Validation analysis: n=291 patients					1: 94.6% (53/56)	Weight Initial	0.0001	MD -26.4	-40.3; -12.4
						2: 5.4% (3/56)	Weight Final	0.04	MD: -18.9	-36.7; -1.1
					Ethnicity (white): 96.2%	3: -	Albumin Initial	0.0001	MD: -0.4	-0.6; -0.2
						4: -	Albumin Final	0.002	MD: -0.4	-0.7; 0.2
							Protein-Initial	0.04	MD: -0.4	-0.7; -0.02
							Haemoglobin-(g/L) Initial	0.009	MD: -0.9	-1.6; -0.2
	Setting: Wilson Memorial Regional Medical Center, part of United	Exclusion criteria not specified.					Highest pulse	0.05	MD: 5.9	-0.005; 11.9
							No. of diagnosis	0.0001	MD: 3.5	2.5; 4.6
							Admitted with PU	0.005	RR: 2.3	1.4; 3.7
							Incontinence	0.00001	RR: 2.7	1.7; 4.3
							Limb weakness Left	0.02	RR: 1.7	1.1; 2.7

Study Authors (year) and country	Study population (No. recruited, setting and speciality)	Eligibility criteria	Design and analysis method	Study aims and objectives	Population characteristics (Age, %Female, Ethnicity)	Prevalence and incidence rate % developing HPU and by Category	Risk factors investigated (no, list of risk factors)	p-value	Measure of association (OR, RR, MD (SD), correlation, frequencies)	95% Confidence intervals
	Health Services Hospitals in the Broome County Metropolitan area of Johnson City, New York. **Population:** Acute inpatients admitted to units that experienced high HPU prevalence based on						Right Both Preventative ointment on heels on admission Had a diagnosis of neoplasm Circulatory problems of lower limb CHF Respiratory disease Any 3-consecutive worsening of appetite Nutrition services documented Sheets tightly tucked in before	0.07 0.4 0.04 0.004 0.004 0.01 0.002 0.0004 0.000001 0.009	RR: 1.5 RR: 1.6 RR: 2.0 RR: 2.0 RR: 1.0 RR:1.8 RR: 2.2 RR: 2.4 RR: 5.8 RR: 1.9	1.0; 2.4 1.0; 2.6 1.2; 3.4 1.3; 3.0 1.0; 3.2 1.2, 2.8 1.4; 3.4 1.4; 3.7 2.8; 12.3 1.1; 3.3

Study Authors (year) and country	Study population (No. recruited, setting and speciality)	Eligibility criteria	Design and analysis method	Study aims and objectives	Population characteristics (Age, %Female, Ethnicity)	Prevalence and incidence rate % developing HPU and by Category	Risk factors investigated (no, list of risk factors)	p-value	Measure of association (OR, RR, MD (SD), correlation, frequencies)	95% Confidence intervals
	their previous survey.						development of HPU			
							Braden Scale			
							Sensory perception	0.0001	MD: -0.4	-0.6; -0.2
							Moisture	0.03	MD: -0.2	-0.4; 0.02
							Activity	0.02	MD: -0.3	-0.06; -0.05
							Mobility	0.0001	MD: -0.5	-0.7; -0.3
							Nutrition	0.03	MD: -0.3	-0.5; -0.02
							Friction and shear	0.0001	MD: -0.5	-0.7, -0.4
							Total Braden Score	0.0001	MD: -2.3	-3.2, -1.4
							Validation Analysis			
					Mean age: 67.8 yrs (17.0)	HPU incidence 21.7% (63/291)	Age	0.0001	MD: 7.6	3.8; 11.4
							LOS	0.0001	MD: 8.4	4.5; 12.2
							Admitted with PU	0.02	RR: 2.5	1.4; 4.7
					Female:58.1% (169/291)	Category†	Incontinence (any)	0.0003	RR: 1.3	1.1; 1.5
						1: 92% (58/63)	Limb weakness- Left, Right, Both	0.03	RR: 1.6	1.0; 2.5
						2: 6.3% (4/63)				

Study Authors (year) and country	Study population (No. recruited, setting and speciality)	Eligibility criteria	Design and analysis method	Study aims and objectives	Population characteristics (Age, %Female, Ethnicity)	Prevalence and incidence rate % developing HPU and by Category	Risk factors investigated (no, list of risk factors)	p-value	Measure of association (OR, RR, MD (SD), correlation, frequencies)	95% Confidence intervals
					Ethnicity (white): 98.3% (286/291) Mean age: 67.6 yrs. (18.2)	3: 1.6% (1/63) 4: - **Overall incidence rate: 23.8% (119/500)**	Pulses (not palpable on one or the other extremity):			
							Popliteal	0.005	RR: 1.9	1.2; 3.1
							Posterior Tibial	0.01	RR: 1.8	1.1; 2.9
							Current diagnosis of circulatory problems of lower limb	0.08	RR: 1.5	1.0; 2.3
							Told has a diagnosis of:			
							CHF	0.005	RR: 1.9	1.2; 3.0
							Circulatory problems of lower limb	0.06	RR: 1.5	1.0; 2.4
							Braden Scale			
							Sensory perception	0.03	MD: -0.2	-0.4; -0.03
							Moisture	0.002	MD: -0.3	-0.5; -0.1

Study Authors (year) and country	Study population (No. recruited, setting and speciality)	Eligibility criteria	Design and analysis method	Study aims and objectives	Population characteristics (Age, %Female, Ethnicity)	Prevalence and incidence rate % developing HPU and by Category	Risk factors investigated (no, list of risk factors)	p-value	Measure of association (OR, RR, MD (SD), correlation, frequencies)	95% Confidence intervals
							Activity	0.0001	MD: -0.5	-0.8; -0.3
							Mobility	0.0001	MD: -0.4	-0.7; -0.2
							Nutrition	not significant	MD: -0.1	-0.3; 0.1
							Friction and shear	0.0001	MD: -0.4	-0.6; -0.2
							Total Braden score	0.0001	MD: -2.2	-3.1; -1.3
							Logistic regression results			
							Braden moisture	0.00001	Not reported	Not reported
							Braden Friction and Shear	0.01		

Study Authors (year) and country	Study population (No. recruited, setting and speciality)	Eligibility criteria	Design and analysis method	Study aims and objectives	Population characteristics (Age, %Female, Ethnicity)	Prevalence and incidence rate % developing HPU and by Category	Risk factors investigated (no, list of risk factors)	p-value	Measure of association (OR, RR, MD (SD), correlation, frequencies)	95% Confidence intervals
Duncan et al (2003) **UK**	n=53 patients **Setting:** large district general hospital **Population:** Major abdominal surgery patients	**Inclusion criteria:** Age of 20 years who had major abdominal surgery. use of epidural as pain relief during the peri-operative period No specified exclusion criteria	Prospective study Correlation analysis	The objective of this study was to investigate the relationship between post-operative epidural analgesia and incidence of heel pressure sores	Mean age†: 69 years Gender and Ethnicity not reported	Cases: 20.8% (11/53) Category 1: 72.7% (8/11) 2: 27.3% (3/11) 3: - 4: -	Level of epidural Pre-operative risk assessment Post-operative risk assessment Concentration of local anaesthesia Hypotension	Not reported Not reported 0.002 0.003 Not reported	Not reported Not reported Reports statistically significant correlation with no values. Reports negative correlation (no actual values) Not reported	Not reported
Meaume and Faucher (2008)	**n=82 patients**	Cases-Patients with established	Cross sectional non interventional	Explore for lower limb atherosclerosis	Mean age†: 86.2 years	Cases 48.8% (40/82) **Category**	Evidence of atherosclerosis (PAD)	States difference statistically	†OR: 2.1	0.8; 5.7

Study Authors (year) and country	Study population (No. recruited, setting and speciality)	Eligibility criteria	Design and analysis method	Study aims and objectives	Population characteristics (Age, %Female, Ethnicity)	Prevalence and incidence rate % developing HPU and by Category	Risk factors investigated (no, list of risk factors)	p-value	Measure of association (OR, RR, MD (SD), correlation, frequencies)	95% Confidence intervals
	Setting: 3	heel pressure	matched case	with the goal of	Female: 69.5%	1: 10% (4/40)		significant		
France	hospitals in a Paris region	ulcers Controls-patients without heel	control Parametric and non-parametric tests	attempting to associate the presence of blood	(57/82)	2: 50% (20/40) 3: 30% (12/40)	Evidence of severe vs moderate atherosclerosis	at p-value no actual p value reported	†OR: 15	1.7; 132.9
	Population: all hospital inpatients	pressure ulcer matched on age and gender No exclusion criteria specified			Ethnicity-not specified	4: 10% (4/40)				
Clegg et al (2009)	n=84 patients	The sample included patients	Retrospective cross-sectional	The purpose of the multisite research project	Mean age 73.1 (16.2) (Range:	Cases 100% (84)	Height (in) Mean (SD)		65.7 (5.9)	
	Setting: 8	18 years or	study	was to describe	18-98)	Category	Weight (lb) Mean (SD)		164.04(47.2)	
USA	health care system in North Carolina and Virginia	older, who were under the care of a participating WOC nurse and who experienced a HPU	Descriptive statistics (no control group)	the physical characteristics and medical history of patients	Female: 58% (49/84)	1: 12% (10/84) 2: 25% (21/84) 3: 4% (3/84) 4: 10% (8/84) Unstageable: 31% (26/84)	BMI Mean (SD) Braden scale score Mean (SD) Serum albumin (g/L), Mean (SD)	N/A	27.4 (11.3) 13.4 (3.3) 2.4 (0.8)	N/A

Study Authors (year) and country	Study population (No. recruited, setting and speciality)	Eligibility criteria	Design and analysis method	Study aims and objectives	Population characteristics (Age, %Female, Ethnicity)	Prevalence and incidence rate % developing HPU and by Category	Risk factors investigated (no, list of risk factors)	p-value	Measure of association (OR, RR, MD (SD), correlation, frequencies)	95% Confidence intervals
	Population: Patients under Wound Ostomy Continence nurses and experienced HPU	**Exclusion** No under 18 years old		experiencing HPU	Ethnicity not specified	SDTI: 19% (16/84)	Pre-albumin(g/dL) Mean (SD)		13.8 (5.7)	
							Pulse oximetry (%) Mean (SD)		96.2 (2.9)	
							Blood urea nitrogen(mg/dL) Mean (SD)		28.9 (21.9)	
							Creatinine(mg/dL) Mean (SD)		1.7 (1.3)	
							Time in surgery (minutes), mean (SD)		125.5 (36.8)	
							Palpable pedal pulse, (Y) n (%)		53 (63)	
							Pedal oedema, (Y) n (%)		22 (26)	
							Diabetes, (Y) n (%)		47 (56)	
							Smoker, (Y) n (%)		7 (8)	

Study Authors (year) and country	Study population (No. recruited, setting and speciality)	Eligibility criteria	Design and analysis method	Study aims and objectives	Population characteristics (Age, %Female, Ethnicity)	Prevalence and incidence rate % developing HPU and by Category	Risk factors investigated (no, list of risk factors)	p-value	Measure of association (OR, RR, MD (SD), correlation, frequencies)	95% Confidence intervals
							Vasopressor use, (Y) n (%)		7 (8)	
							Corticosteroid use, (Y) n (%)		7(8)	
							Systemic infection, (Y) n (%)		24(29)	
							End-stage renal Disease, (Y) n (%)		22(26)	
							Surgery this admission, (Y) n (%)		7(8)	
							History of peripheral arterial disease, (Y) n (%)		33 (40)	
							History of venous stasis disease, (Y) n (%)		5(6)	
							Hip patients			

Study Authors (year) and country	Study population (No. recruited, setting and speciality)	Eligibility criteria	Design and analysis method	Study aims and objectives	Population characteristics (Age, %Female, Ethnicity)	Prevalence and incidence rate % developing HPU and by Category	Risk factors investigated (no, list of risk factors)	p-value	Measure of association (OR, RR, MD (SD), correlation, frequencies)	95% Confidence intervals
Campbell et al (2010)	n=150 patients	**Inclusion criteria:**	Prospective study	1.The incidence of HPU in an orthopaedic	Mean age: 70.6yrs (12.9)	Incident rate: 16% (8/50)	Haemoglobin (g/L) mean (SD)	0.9	†MD: -1.7 (13.4)	-28.5; 25.2
							Age (years)	0.6	†MD: 3 (5.8)	-8.6; 14.6
Canada	**Setting:** 850 academic bed, tertiary care facility London Health Centre, University Hospital, located in a small urban canter in south-western Ontario Canada.	if they or their substitute decision-maker provided written informed consent to participate in the research study; were older than 18 years; had an orthopaedic condition of the pelvis, hip, or lower extremity; and were ulcer-free on both	Descriptive Chi-squared tests and student t-test	population of an acute care hospital in Canada. 2. Demographic, procedural, and prevention practices and medical risk factors associated with increased risk of developing a HPU.	Female: 69.3% (104/150) Ethnicity not specified		Pulse (per minutes) mean (sd)	1	†MD: 0 (5.8)	-11.6; 11.6
							HP relief measures used (n)	0.016	†OR: 7.5	0.87; 64.4
							Respiratory disease (n)	0.96	†OR: 1.24	0.13; 11.2
							Altered mental status (n)	0.41	†OR: 0.69	0.15; 3.2
							LOS mean (SD)	0.51	†MD: 3 (4.2)	-5.5; 11.5
							Elective patients			

Study Authors (year) and country	Study population (No. recruited, setting and speciality)	Eligibility criteria	Design and analysis method	Study aims and objectives	Population characteristics (Age, %Female, Ethnicity)	Prevalence and incidence rate % developing HPU and by Category	Risk factors investigated (no, list of risk factors)	p-value	Measure of association (OR, RR, MD (SD), correlation, frequencies)	95% Confidence intervals
		heels on admission.				Incidence rate: 13% (13/100)	Haemoglobin (g/L) (SD)	0.01	†MD: 16.2 (6.0)	4.3; 28.1
	Population: Patients admitted for elective orthopaedic surgery or treatment of a fracture	**Exclusion criteria:** Participants were excluded if they were actively dying or if it was impossible to view both heels for any reason (e.g. excessive pain or cast in place)		3. The natural history/sequelae of Category 1 heel PU			Age (years)	0.79	†MD: -3 (3.4)	-9.7; 3.7
							Pulse (per minutes)	0.05	†MD:10 (6.6)	-3.0; 23.0
							HP relief measures used (n)	0.55	†OR:0.95	0.1; 9.4
							Respiratory disease (n)	0.011	†OR: 5.8	1.4; 23.9
							Altered mental status (n)	0.029	†OR: 3.9	1.1; 14.0
							LOS mean (SD)	0.217	†MD: 2 (3.6)	-5.1; 9.10
							Combined patients			
						Overall incidence rate: 14% (21/ 150)	Haemoglobin (g/L) mean (SD)	0.056	†MD: 10 (6.1)	-2.1; 22.1
							Age (years) mean (SD)	0.602	†MD: -1.7 (3.1)	-7.8; 4.5
						Category: 1: 81%(17/21) 2: 19% (4/21)	Pulse (per minutes) mean (SD)	0.279	†MD: 5 (3.6)	-2.1; 12.1

Study Authors (year) and country	Study population (No. recruited, setting and speciality)	Eligibility criteria	Design and analysis method	Study aims and objectives	Population characteristics (Age, %Female, Ethnicity)	Prevalence and incidence rate % developing HPU and by Category	Risk factors investigated (no, list of risk factors)	p-value	Measure of association (OR, RR, MD (SD), correlation, frequencies)	95% Confidence intervals
						3:- 4:-	HP relief measures used (n)	0.133	†OR: 3.5	1.1; 11.5
							Respiratory disease (n)	0.016	†OR: 1.7	0.6; 4.7
							Altered mental status (n)	0.216	†OR: 0.6	0.2; 1.6
							LOS mean (SD)	0.161	†MD: 3.0 (2.1)	-1.2; 7.2
Gaubert-Dahan (2013) **France**	n=210 patients **Setting:** two French university hospitals. **Population:** Individuals admitted to a geriatric rehabilitation	**Inclusion criteria:** Individuals admitted to a geriatric rehabilitation center in two French university hospitals from March 2009 to June 2010.	Cross-sectional study Chi-squared and t-tests	To identify associated factors in older hospitalized adults	Mean age: 85 (72-101) Female: 74.8% (157/53) Ethnicity not specified.	HPU prevalence rate: 12.4% (26/210) Category 1: 50% (13/26) 2: 26.9% (7/26) 3: 15.4% (4/26) 4: 7.7% (2/26)	Sensory Peripheral Neuropathy (Light vs Moderate& Severe)	0.07	†OR: 3.8	†0.9; 16.6
							NSS	0.009	†MD: 1.3(0.5)	0.3; 2.3
							NDS	0.011	†MD: 3.0 (1.2)	0.6; 5.4
							HPU Category and NSS	0.02	r=0.45	Not reported
							HPU Category and activity limitation	0.02	r=0.44	

Study Authors (year) and country	Study population (No. recruited, setting and speciality)	Eligibility criteria	Design and analysis method	Study aims and objectives	Population characteristics (Age, %Female, Ethnicity)	Prevalence and incidence rate % developing HPU and by Category	Risk factors investigated (no, list of risk factors)	p-value	Measure of association (OR, RR, MD (SD), correlation, frequencies)	95% Confidence intervals
	centre from March 2009 to June 2010	**Exclusion criteria:** Individuals with a MMSE score of less than 10 were not included. Individuals with central or medullar nervous system disease (hemiplegic and paraplegic patients) were also not included.					HPU Category and Hip fracture, cancer, diabetes mellitus and nutritional status HPU severity vs Neuropathy severity	not significant correlation observed 0.04	no measure of association reported no measure of association reported	

Study Authors (year) and country	Study population (No. recruited, setting and speciality)	Eligibility criteria	Design and analysis method	Study aims and objectives	Population characteristics (Age, %Female, Ethnicity)	Prevalence and incidence rate % developing HPU and by Category	Risk factors investigated (no, list of risk factors)	p-value	Measure of association (OR, RR, MD (SD), correlation, frequencies)	95% Confidence intervals
Delmore et al (2015) **USA**	**Main analysis** n=337 patients Validation analysis n= 80 patients **Setting:** NYC based urban tertiary medical centre (discharged patients) **Population:** all	**Inclusion criteria:** Admitted with HPU or developed a HPU between 2009 and 2011. Aged 8 or over At least a 3 day stay. Control-without heel pressure ulcers patients matched on age.	Retrospective case control (reviewing of medical records) Stepwise Logistic regression	To develop and validate a method of predicting whether patients will develop a heel pressure ulcer during their hospital stay.	**Main analysis** Mean: age 73yrs (20) Gender and ethnicity not reported **Validation analysis** Age, gender and ethnicity not reported.	**Main analysis** Prevalence rate: 11% (37/337) **Validation analysis** Prevalence rate: 15% (12/80) HPU severity not reported for both analyses. **Overall prevalence rate:** 11.8% (49/417)	**Univariate analysis** Age (mean, SD) Braden scale score (mean, SD) Diabetes (%) Vascular disease Neuropathy Immobility Perfusion issues Morbid obesity Cachexia Surgery > 3h (%) ICU > 3 days (%) LOS in days (median, range) **Multivariable modelling** Diabetes	0.02 0.02 <0.001 0.03 <0.001 0.03 <0.001 0.007 0.3 0.7 0.7 <0.001 <0.001 0.02	no measure of association reported for all variables. OR: 2.9	Not reported for all variables 1.2; 1.7

Study Authors (year) and country	Study population (No. recruited, setting and speciality)	Eligibility criteria	Design and analysis method	Study aims and objectives	Population characteristics (Age, %Female, Ethnicity)	Prevalence and incidence rate % developing HPU and by Category	Risk factors investigated (no, list of risk factors)	p-value	Measure of association (OR, RR, MD (SD), correlation, frequencies)	95% Confidence intervals
	discharged patients						Vascular disease Immobility Braden scale score </=18	0.01 0.003 <0.001	OR: 3.8 OR: 4.7 OR: 21.8	1.3; 11.1 1.7; 12.9 6.3; 76.1
Muntlin-Athlin et al (2016) **Sweden**	n=183 patients **Setting:** Five ambulance stations, two EDs and 16 wards at 2 hospitals across two county councils in Sweden.	**Inclusion criteria:** older adults 70+Neurological symptoms or reduced general condition according to medical directives at the medical call centre No heel pressure ulcer	Prospective cohort study Descriptive Chi-squared test, Mann-Whitney U-test and t-test	1.Describe heel pressure ulcer prevalence and nursing actions in relation to pressure ulcer prevention during the care delivery chain (i.e. pre-hospital and emergency care level, and further at the hospital ward),	Mean age: 86.3 yrs (7.2) Female: 62.3% (114/183) †6 with unspecified gender Ethnicity-not specified.	ED incidence rate: 8% (15/183) Category 1-3 not specified distribution. **Overall Incidence rate: 21% (39/183)** Category 1-4 not specified distribution	**Ambulance and ED vitals:** Respiratory rate Heart rate Reaction Level Scale Pulse oximetry (%) Blood pressure (systolic) mmHg Blood pressure (diastolic) mmHg	Reported as not significant with no actual p-values	No mean differences presented however unable to calculate due to lack of data (n) **Day 1** MNS	

Study Authors (year) and country	Study population (No. recruited, setting and speciality)	Eligibility criteria	Design and analysis method	Study aims and objectives	Population characteristics (Age, %Female, Ethnicity)	Prevalence and incidence rate % developing HPU and by Category	Risk factors investigated (no, list of risk factors)	p-value	Measure of association (OR, RR, MD (SD), correlation, frequencies)	95% Confidence intervals
	Population: older patients (70+) with "neurological symptoms" or "reduced general conditions, according to medical directives without HPU	Admitted to one of the participating wards Able to sign consent form. **Exclusion criteria:** patients requiring life-threatening support and discharged from ED Unable to provide signed informed		for older patients with neurological symptoms or reduced general condition. 2.Investigate early predictors for the development of heel pressure ulcer during the care delivery chain			Mental condition Physical activity Mobility Incontinence Total risk score	0.01 0.001 <0.0001 0.002 0.002	MR: 55.8 vs 76.5 MR: 49.7 vs 78.0 MR:48.6 vs 78.2 MR:51.0 vs 77.7 MR:50.3 vs 76.	Not reported Not reported

Study Authors (year) and country	Study population (No. recruited, setting and speciality)	Eligibility criteria	Design and analysis method	Study aims and objectives	Population characteristics (Age, %Female, Ethnicity)	Prevalence and incidence rate % developing HPU and by Category	Risk factors investigated (no, list of risk factors)	p-value	Measure of association (OR, RR, MD (SD), correlation, frequencies)	95% Confidence intervals
		consent or did not have family member to sign.								
Twilley and Jones (2016) **UK**	n=30 patients **Setting:** community hospital providing stepdown care for acute hospitals **Population**: all inpatients	**Inclusion criteria:** Inpatients aged 18 and over with a Category 2, 3 or 4 pressure ulcers of the heel. **Exclusion criteria:** All inpatients without a pressure ulcer of the heel and matching the case group based on age,	Matched case-control (age, gender, and ethnicity) Odds Ratio	1. Explore the relationship between pressure ulcers of the heel and PAD. 2. Investigate the feasibility of conducting a statistically powered matched case control study that could further investigate aim (1)	Mean age: 86.5(77-94) Female: 26.7% (8/30) Ethnicity not specified	HPU: 50% (15/30) Category: 2: 33.3% (5/15) 3: 47.7% (7/15) 4: 20% (3/15)	PAD	0.01†	OR: 11	2.0: 60.6

Study Authors (year) and country	Study population (No. recruited, setting and speciality)	Eligibility criteria	Design and analysis method	Study aims and objectives	Population characteristics (Age, %Female, Ethnicity)	Prevalence and incidence rate % developing HPU and by Category	Risk factors investigated (no, list of risk factors)	p-value	Measure of association (OR, RR, MD (SD), correlation, frequencies)	95% Confidence intervals
		gender and ethnicity were eligible								
Delmore et al 2019 **USA**	Main analysis: n=1.637 patients Validation analysis: n= 240 Setting: New York state-wide hospitals Population: Hospitalised adult patients aged 18	**Inclusion criteria:** All hospitalised adults aged 18 years or above. **Exclusion criteria:** Patients with heel vascular wounds as designated by the associated International Classification of Disease (ICD-9).	Retrospective Case control study Univariate and multiple regression analysis	1.To replicate previous research that found that found four independent and significant predictors of HPUs in hospitalised patients using a larger and more diverse patient population. 2.To create a clinical enabler for assessing	Mean age: 59.3 (21.7) Female: 59.7% (1,013/1,697) Ethnicity Spanish/Hispanic origin: 0.2 (3/1697) Other: 94.3% (1600/1697) Unknown: 5.5% (94/1697 Validation analysis	Prevalence rate:19.9% (323/1637) Categories: 1: 21.4% (69/323) 2:30.7% (99/323) 3: 5.0% (16/323) 4: 4.0% (13/323) Unstageable: 28.5% (92/323) Unspecified: 10.5% (34/323) Validation analysis Prevalence rate:33.3% (80/240)	Main analysis Age> 65years Diabetes Vascular disease Perfusion issues Impaired nutrition Mechanical ventilation Surgery	<0.001 0.03 0.001 <0.001 <0.001 <0.001 <0.001	OR: 3.3 OR: 1.4 OR: 3.1 OR: 2.8 OR: 6.9 OR: 7.7 OR: 1.8	2.4; 4.6 1.0; 1.9 1.8; 5.2 2.1; 3.8 4.1; 11.5 4.2; 14.3 1.3; 2.5

Study Authors (year) and country	Study population (No. recruited, setting and speciality)	Eligibility criteria	Design and analysis method	Study aims and objectives	Population characteristics (Age, %Female, Ethnicity)	Prevalence and incidence rate % developing HPU and by Category	Risk factors investigated (no, list of risk factors)	p-value	Measure of association (OR, RR, MD (SD), correlation, frequencies)	95% Confidence intervals
	years or above	Obstetric and psychiatric patients. Children younger than 18 years old.		patients at risk of HPUs.	Mean age: 60.1yrs (20.6) Female: 57.5% (138/240) Ethnicity Spanish/Hispanic origin: 0.4% (1/240) Other: 97.1% (233/240) Unknown: 2.5% (6/240)	Categories 1: 27.5% (22/80) 2:26.3% (21/80) 3: 5.0% (4/80) 4: 5.0% (4/80) Unstageable: 31.3% (25/80) Unspecified: 5.0% (4/80) **Overall prevalence rate:** 20.8% (403/1937)				
Manderlier et al (2019) **Netherlands**	n= 4,842 patients **Setting:** nursing homes and community	**Inclusion criteria:** Participants had to be 18 years or older, reside in a nursing home or have received	Cross-sectional, secondary Single and multiple binary logistic regression	1.The primary aim of this study was to explore which modifiable patient-related factors are associated with	Mean age: 82.7 yrs (9.9) Female: 70.2% (3,398/4,842)	Prevalence rate: 1.5% (75/4,842) Category: 1: 50.7% (38/75) 2: 16% (12/75) 3: 16%	**Category 1-4** Malnutrition Braden mobility Braden moisture	 0.5 0.001 1 <0.001	 OR: 1.2 OR: 0.6 OR: 1 OR: 0.3	 0.7; 2.0 0.4; 0.8 0.8; 1.3 0.2; 0.5

Study Authors (year) and country	Study population (No. recruited, setting and speciality)	Eligibility criteria	Design and analysis method	Study aims and objectives	Population characteristics (Age, %Female, Ethnicity)	Prevalence and incidence rate % developing HPU and by Category	Risk factors investigated (no, list of risk factors)	p-value	Measure of association (OR, RR, MD (SD), correlation, frequencies)	95% Confidence intervals
	care facilities across Netherlands **Population**: all patients	community care in the Netherlands and approve receiving skin inspection. No exclusion specified.		the presence of category I–IV PUs on the body sites most vulnerable to PU development, the sacrum, and heels.	Ethnicity not specified.	(12/75) 4: 1.7% (8/75) Unstageable: 2.7% (2/75) DTI: 4% (3/75)	Braden friction and shear	**Category 3-4**		

Study Authors (year) and country	Study population (No. recruited, setting and speciality)	Eligibility criteria	Design and analysis method	Study aims and objectives	Population characteristics (Age, %Female, Ethnicity)	Prevalence and incidence rate % developing HPU and by Category	Risk factors investigated (no, list of risk factors)	p-value	Measure of association (OR, RR, MD (SD), correlation, frequencies)	95% Confidence intervals
				2.A secondary aim of this study was to explore which modifiable patient-related factors are associated with deep PUs (category III–IV).			Braden friction and shear	Not reported	OR 0.32	0.17; 0.62

Appendix 4.3: Systematic Literature Review- Summary of Quality Appraisal for Eligible Studies

Study Name	1.Selection Bias	2.Attrition Bias	3.Risk Factors measurement bias	4.Outcome measurement bias	5.Bias due to Confounders	6.Analysis and Reporting Bias	Overall study quality	Details of Concerns
Author(s) (year)	Clear eligibility criteria, method used to identify population, adequate study participation, Recruitment period, Presence of control group, baseline characteristics of participants,	Response rate, attempts to collect information on dropouts, Reasons for loss to follow-up provided,	Clear RF definition, method and setting of measurement, proportion of risk factor data available for analysis	Clear outcome measure definition, valid and reliable measurement of outcome, method and setting of outcome measurement, proportion of outcome measurement data available for analysis	Clear definition of confounding factors, valid and reliable measurement of confounding factors, method and setting of confounding factors, Method used for missing data, appropriate accounting of confounding factors	Use appropriate statistical analysis, pooled or individual reporting. Selective reporting, accuracy of reporting.	High/ moderate/ low	

Study Name	1.Selection Bias	2.Attrition Bias	3.Risk Factors measurement bias	4.Outcome measurement bias	5.Bias due to Confounders	6.Analysis and Reporting Bias	Overall study quality	Details of Concerns
Tourtual et al (1997)	Low	Low	Moderate	Moderate	Moderate	Moderate	Moderate	1. Do not specify missing data 2. Lack of quality assurance processes for outcome measurement based on skin assessment 3. Collect data on numerous factors however only used multivariable logistic regression in their validation study 2 to adjust for confounding factors 4. Lack of full information in statistical analysis plan 5. Authors only report significant results from their multivariate analysis in study 2 6. Insufficient number of events- logistic regression analysis

Study Name	1.Selection Bias	2.Attrition Bias	3.Risk Factors measurement bias	4.Outcome measurement bias	5.Bias due to Confounders	6.Analysis and Reporting Bias	Overall study quality	Details of Concerns
Duncan et al (2003)	Moderate	Moderate	Moderate	Moderate	Moderate	High	Moderate	1. No clear sampling frame and recruitment processes reported 2. Not specify number eligible or withdrawals 3. Subjective nature of staging tool and lack of quality assurance processes for outcome measurement 4. Only provide overall mean age for study population 5. Lack of reporting on missing data and reasons 6. High levels of missing data on reported risk factors also do not report for 2 other risk factors 7. Not specified statistical tests used
Meaume and Faucher (2008)	Moderate	Low	Low	Low	Moderate	Moderate	Moderate	1. Lack of reporting do not specify population details, no exclusion criteria 2. Recruitment summary not provided to assess generalizability of studies 3. No confounders considered however authors acknowledges in limitations 4. Partial reporting of statistical analysis used 5. No effect size, confidence interval reported

Study Name	1.Selection Bias	2.Attrition Bias	3.Risk Factors measurement bias	4.Outcome measurement bias	5.Bias due to Confounders	6.Analysis and Reporting Bias	Overall study quality	Details of Concerns
Clegg et al (2009)	Moderate	Low	Low	Moderate	High	High	Low	1. No adequate information on how subjects were recruited or exclusion criteria 2. Unable to ascertain generalisability of study 3. Subjective ascertainment of outcome measure as based on clinical staff assessment of skin assessment 4. Lacks comparator group 5. Descriptive analysis
Campbell et al (2010)	Moderate	Low	Low	Moderate	Moderate	Moderate	Moderate	1. Does not specify total number of patients screened and excluded for generalisability purposes 2. Subjective nature of outcome measurement (skin assessment and staging criteria) 3. Lack of clear definition and how these were measured 4. Partial reporting only p-values with no estimate of measure of association or differences

Study Name	1.Selection Bias	2.Attrition Bias	3.Risk Factors measurement bias	4.Outcome measurement bias	5.Bias due to Confounders	6.Analysis and Reporting Bias	Overall study quality	Details of Concerns
Gaubert-Dahan (2014)	Moderate	Low	Low	Moderate	Moderate	High	Moderate	1. Partial reporting study participation unable to fully assess representation 2. Subjective nature of outcome measurement (skin assessment and staging criteria) 3. Descriptive analysis no adjusting for confounders 4. Conclusions are not based on reported results or research question 5. Selective reporting making conclusion on unreported results 6. Authors' state that they used benferroni adjustment however do not provide full details.

Study Name	1.Selection Bias	2.Attrition Bias	3.Risk Factors measurement bias	4.Outcome measurement bias	5.Bias due to Confounders	6.Analysis and Reporting Bias	Overall study quality	Details of Concerns
Delmore et al (2015)	High	High	Moderate	Moderate	Moderate	Moderate	moderate	1. Poor reporting 2. Retrospective Medical record review of discharged patients 3. No specific exclusion criteria besides age for control group mentioned 4. Confusing eligibility criteria (exclude community acquired contradicts inclusion criteria) 5. High risk of selection bias as authors don't report final no. of reviewed records especially controls 6. Lack of reporting missing data and methods of imputation 7. No clear prespecified sample size calculation 8. Insufficient number of events- logistic regression analysis

Study Name	1.Selection Bias	2.Attrition Bias	3.Risk Factors measurement bias	4.Outcome measurement bias	5.Bias due to Confounders	6.Analysis and Reporting Bias	Overall study quality	Details of Concerns
Muntlin-Athlin et al (2016)	Moderate	High	Moderate	Moderate	Moderate	Moderate	Moderate	1. Partial reporting on key characteristics however reported in RCT paper 2. Unable to assess risk of attrition bias due to lack of reporting 3. Unable to ascertain level of RF data collection due to inconsistencies in reporting (not clear how many patients had complete data for each RF. 4. Outcome measurement used is very subjective and performed by several nurses with no quality assurance checks 5. Lack of reporting for confounders (pre-specifying RF vs confounders) at each follow-up time point 6. Selective reporting of significant data only 7. Do not report risk estimate or mean differences and confidence intervals
Twilley and Jones (2016)	Low	Low	Low	Low	Moderate	Moderate	High	1. No cofounding factors investigated or reported however authors acknowledge as limitation of study 2. No p-values reported

Study Name	1.Selection Bias	2.Attrition Bias	3.Risk Factors measurement bias	4.Outcome measurement bias	5.Bias due to Confounders	6.Analysis and Reporting Bias	Overall study quality	Details of Concerns
Delmore et al (2019)	Low	Low	Low	Low	Low	Low	High	Lack of validation of outcome measure
Manderlier et al (2019)	Low	Low	Low	Low	Low	Low	High	Lack of validation of outcome measure

Appendix 4.4: Systematic Literature Review- Summary of Risk Factors

Risk factor	High quality studies	Moderate quality studies	Low quality studies
Patient Characteristics			
Age	Delmore et al (2019)	Tourtual et al (1997); Campbell et al (2010)	
Height		Tourtual et al (1997)	Clegg et al (2009)
Weight (initial, final)		Tourtual et al (1997)	Clegg et al (2009)
BMI			Clegg et al (2009)
Smoker			Clegg et al (2009)
Vital signs			
Heart rate (highest)		Tourtual et al (1997); Campbell et al (2010); Muntlin-Athlin et al (2016)	Clegg et al (2009)
Pulse oximetry		Muntlin-Athlin et al (2016)	Clegg et al (2009)
Respiratory rate		Muntlin-Athlin et al (2016)	
Blood pressure (systolic, diastolic)		Muntlin-Athlin et al (2016) Duncan et al (2003)	
Hypotension		Duncan et al (2003)	
Reaction level scale		Muntlin-Athlin et al (2016)	
Haematological measures			
Albumin (initial; final)		Tourtual et al (1997)	Clegg et al (2009)
Pre-albumin			Clegg et al (2009)
Blood Urea			Clegg et al (2009)
Creatinine			Clegg et al (2009)
Protein- Initial		Tourtual et al (1997)	
Haemoglobin (g/L) (initial)		Tourtual et al (1997)	

Risk factor	High quality studies	Moderate quality studies	Low quality studies
Skin Status			
Admitted with PU		Tourtual et al (1997)	
Moisture/ incontinence			
Incontinence; Braden subscale-Moisture; MNS subscale Incontinence	Manderlier et al (2019)	Tourtual et al (1997); Muntlin-Athlin et al (2016)	
Preventive measures for HPU			
Preventative ointment on heels on admission		Tourtual et al (1997)	
Sheets tightly tucked in before development of HPU		Tourtual et al (1997)	
HPU relief measures used		Tourtual et al (1997)	
Disease or physical conditions			
Total number of diagnosis		Tourtual et al (1997)	
Had a diagnosis of neoplasm		Tourtual et al (1997); Gaubert-Dahan et al (2013)	
Systemic infection			Clegg et al (2009)
Limb weakness (left/ right/ both)		Tourtual et al (1997)	
Diabetes	Delmore et al (2019)	Gaubert-Dahan (2013); Delmore et al (2015)	Clegg et al (2009)
Perfusion issues defined congestive heart failure, MI, anaemia, dehydration, pedal oedema	Delmore et al (2019)	Tourtual et al (1997)	Clegg et al (2009)
Circulatory problems of lower limb		Tourtual et al (1997)	Clegg et al (2009)
peripheral arterial disease/vascular disease	Twilley and Jones (2016); Delmore et al (2019)	Meaume and Faucher (2007); Delmore et al (2015);	Clegg et al (2009)
venous stasis disease			Clegg et al (2009)

Risk factor	High quality studies	Moderate quality studies	Low quality studies
Pulses (not palpable on one or the other extremity):			
Popliteal/Posterior Tibia		Tourtual et al (1997)	Clegg et al (2009)
Respiratory disease		Tourtual et al (1997); Campbell et al (2010)	
End-stage renal Disease			Clegg et al (2009)
Nutritional Status			
Any 3-consecutive worsening of appetite/ Nutrition services documented		Tourtual et al (1997)	
Nutrition-Braden subscale/ Malnutrition/impaired nutrition	Delmore et al (2019); Manderlier et al (2019)		
Length of stay (LOS)		Tourtual et al (1997); Campbell et al (2010)	
Sensory perception			
Braden subscale-Sensory perception;		Tourtual et al (1997)	
Sensory peripheral neuropathy (NSS, NDS)		Gaubert-Dahan et al (2013); Delmore et al (2019)	
Friction and shear			
Braden subscale-Friction and shear	Manderlier et al (2019)	Tourtual et al (1997);	
Mobility /Physical activity			
Activity- Braden subscale/MNS subscale		Tourtual et al (1997); Delmore et al (2015); Muntlin-Athlin et al (2016)	
Mobility- Braden subscale/ MNS subscale/ Immobility	Manderlier et al (2019)	Tourtual et al (1997); Delmore et al (2015); Muntlin-Athlin et al (2016)	
Risk Assessment tools			

Risk factor	High quality studies	Moderate quality studies	Low quality studies
Braden Scale total risk score		Tourtual et al (1997); Delmore et al (2015)	
MNS total risk score		Muntlin-Athlin et al (2016)	
Pre and post-operative risk assessments		Duncan et al (2003)	
Medication			
Vasopressor use			Clegg et al (2009);
Corticosteroid use			Clegg et al (2009);
Epidural (level of epidural, concentration of local anaesthesia)		Duncan et al (2003)	
Surgery			
Length of surgery		Delmore et al (2015)	Clegg et al (2009)
Type of surgery (vascular, orthopaedic, neurosurgery, intestinal, cardiovascular, genitourinary, gynaecology)	Delmore et al (2019)	Campbell et al (2010)	Clegg et al (2009)
Mechanical ventilation	Delmore et al (2019)		

All variables are reported in the table using the same descriptions as in the original articles.

Appendix 5.1: BCU Research Ethics Approval

Faculty of Health, Education & Life Sciences Research Office
Seacole Building, 8 Westbourne Road
Birmingham
B15 3TN

HELS_Ethics@bcu.ac.uk

27/Mar/2018

Miss alisen dube

alisen.dube@mail.bcu.ac.uk

Dear alisen ,

Re: dube /1478 /R(C) /2018 /Mar /HELS FAEC - Heel Pressure Ulcer Study

Thank you for your application and documentation regarding the above study. I am pleased to confirm that Birmingham City University has agreed to take on the role of Sponsor.

I can also confirm that the legal liability for death or injury to any person participating in the project is covered under the University's insurance arrangements.

A copy of BCU's insurance details is available at:
https://icity.bcu.ac.uk/Finance/Procurement-and-Insurance/Insurance

If you wish to make any changes to your proposed study (by request or otherwise), then you must submit an Amendment application to us. Examples of changes include (but are not limited to) adding a new study site, a new method of participant recruitment, adding a new method of data collection and/or change of Project Lead.

Please also note that the Committee should be notified of any serious adverse effects arising as a result of this activity.

Keep a copy of this letter along with the corresponding application for your records as evidence of approval.

If you have any queries, please contact HELS_Ethics@bcu.ac.uk

I wish you every success with your study.

Yours Sincerely,

Ms Julie Quick

On behalf of the Health, Education & Life Sciences Faculty Academic Ethics Committee

Appendix 5.2: HRA Approval

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Miss Alisen Dube
Graduate Research Teaching Assistant
Birmingham City University
Faculty of Health, Education and Life Sciences
Westbourne Rd, Edgbaston
B15 3TN

Email: hra.approval@nhs.net
Research-permissions@wales.nhs.uk

11 July 2018

Dear Miss Dube,

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Heel Pressure Ulcers Study: Contributory factors and their impact on quality of life.**
IRAS project ID:	**240842**
REC reference:	**18/WM/0135**
Sponsor	**Birmingham City University**

I am pleased to confirm that HRA and Health and Care Research Wales (HCRW) Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales?
You should now provide a copy of this letter to all participating NHS organisations in England and Wales, as well as any documentation that has been updated as a result of the assessment.

Following the arranging of capacity and capability, participating NHS organisations should **formally confirm** their capacity and capability to undertake the study. How this will be confirmed is detailed in the "*summary of assessment*" section towards the end of this letter.

You should provide, if you have not already done so, detailed instructions to each organisation as to how you will notify them that research activities may commence at site following their confirmation of capacity and capability (e.g. provision by you of a 'green light' email, formal notification following a site initiation visit, activities may commence immediately following confirmation by participating organisation, etc.).

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed here.

Appendix 5.3: Research Site Capacity and Capability

From: Kandola Sonia (RKB) Research Governance Associate <Sonia.Kandola@uhcw.nhs.uk>
Sent: Monday, July 23, 2018 9:19:03 AM
To: Alisen Dube
Cc: Sarahjane Jones
Subject: IRAS 240842 Confirmation of Capacity and Capability at University Hospitals Coventry and Warwickshire NHS Trust

Dear Alisen,

RE: IRAS 240842 Confirmation of Capacity and Capability at University Hospitals Coventry and Warwickshire NHS Trust
Full Study Title: Heel Pressure Ulcer Study: Contributory factors and their impact on quality of life
UHCW R&D Ref: AD380718
IRAS ID: 240842

This email confirms that University Hospital Coventry and Warwickshire NHS Trust has the Capability and Capacity to deliver the above study. It has been agreed that recruitment as this site may commence on 20/07/2018.

You are requested to inform R&D@uhcw.nhs.uk of the date you recruit your first patient.
The following documents are permitted for use within the site file, as per the HRA review:

Document	Version	Date
Study Protocol	4.0	04/07/2018
Participant information sheet (Consultee Information Sheet)	4.0	04/07/2018
Participant information sheet (Patient information sheet)	4.0	04/07/2018
Participant consent form (Participant consent form)	3.0	24/06/2018
Participant consent form (Consultee declaration form)	3.0	24/06/2018
GP/Consultant letter (GP letter)	2.0	11/03/2018
HRA Schedule of Event	1.0	01/05/2018
HRA Statement of Activities	1.0	01/05/2018
Evidence of Sponsor insurance or indemnity (BCU insurance letter)	-	24/07/2017
Letter from funder (letter of support)	-	22/02/2018
Letter from sponsor	-	27/03/2018
Study completion letter	2.0	11/03/2018
Summary CV for Chief Investigator (Alisen Dube)	-	-
Summary CV for supervisor (Mark Radford)	-	-
Summary CV for supervisor (Maxine Lintern)	-	-
Summary CV for supervisor (Sarahjane Jones)	-	-
Follow-up letter	2.0	11/03/2018
Validated questionnaire (EQ-5D-5L)	-	-
Validated questionnaire (EQ-5D-5L self-completion)	-	-
Validated questionnaire (pain assessment tool-proxy version)	-	-

Appendix 5.4: BCU Research Ethics Amendment Approval

Faculty of Health, Education & Life Sciences Research Office
Seacole Building, 8 Westbourne Road
Birmingham
B15 3TN

HELS_Ethics@bcu.ac.uk

13/Feb/2019

Miss alisen dube

alisen.dube@mail.bcu.ac.uk

Dear Alisen ,

Re: dube /1478 /Am /2019 /Feb /HELS FAEC - Heel Pressure Ulcer Study

Thank you for your application for approval of amendments regarding the above study. I am happy to take Chair's Action and approve these amendments.

Provided that you are granted Permission of Access by relevant parties (meeting requirements as laid out by them), you may continue your activity.

I can also confirm that any person participating in the project is covered under the University's insurance arrangements.

Please note that ethics approval only covers your activity as it has been detailed in your ethics application. If you wish to make any changes to the activity, then you must submit an Amendment application for approval of the proposed changes.

Examples of changes include (but are not limited to) adding a new study site, a new method of participant recruitment, adding a new method of data collection and/or change of Project Lead.

Please also note that the Committee should be notified of any serious adverse effects arising as a result of this activity.

If for any reason the Committee feels that the activity is no longer ethically sound, it reserves the right to withdraw its approval. In the unlikely event of issues arising which would lead to this, you will be consulted.

Keep a copy of this letter along with the corresponding application for your records as evidence of approval.

If you have any queries, please contact HELS_Ethics@bcu.ac.uk

I wish you every success with your activity.

Yours Sincerely,

Ms Julie Quick

On behalf of the Health, Education & Life Sciences Faculty Academic Ethics Committee

Appendix 5.5: HRA Amendment Approval

From: PATE, Michael (HEALTH RESEARCH AUTHORITY) <michael.pate@nhs.net>
Sent: 08 March 2019 15:37
To: Alisen Dube; HELS Ethics
Cc: sonia.kandola@uhcw.nhs.uk; AMENDMENTS, Hra (HEALTH RESEARCH AUTHORITY)
Subject: IRAS 240842. HRA and HCRW Approval for the Amendment

Dear Miss Dube

Further to the below, I am pleased to confirm **HRA and HCRW Approval** for the referenced amendment.

You should implement this amendment at NHS organisations in England and/or Wales, in line with the conditions outlined in your categorisation email.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/.

Please contact hra.amendments@nhs.net for any queries relating to the assessment of this amendment.

Kind regards

Michael Pate

Assessor

Appendix 6: PPIE Terms of Reference Form

BIRMINGHAM CITY University

University Hospitals Coventry and Warwickshire NHS

Heel Pressure Ulcer Public Involvement Research Group

Background

Pressure ulcers also known as pressure sores or bedsores can occur in areas like the sacrum, hips, elbows or heels when someone sits or lies too long in one position. Everyone therefore is at risk of developing a presssure ulcer making it everyone's responsibility to prevent deveoping a pressure ulcer. However some people are at a higher risk of developing pressure ulcers and currently heels are the second most body part to be affected by pressure ulcers. We would like to carry out a study to further understand why certain people are more likely to develop heel pressure ulcer and we are looking to member of the public to help us plan and manage this research study.

What is research?

Research is about learning new knowledge and it helps us learn and gain further understanding of different health conditions, ways of improving treatments and our healthcare system.

Who do we want to be involved?

We are looking for people who live within Coventry and Warwikshire area that have an experience of:

- Pressure ulcer (also known as pressure sores or bed sores)
- Heel pressure ulcer
- Looking after someone with a pressure ulcer

What will it involve to take part?

If you decide to take part, it will be on a voluntary basis but you will be expected to attend a number of pre-scheduled meeting over the next 3 years. Dates, time and venue will be shared with you in advance. You will be asked to sign a confidentiality disclaimer form asking you not to disclose any confidential information you may receive as part of your role.

Being part of the research group means you will be actively involved in the decision making process throughout the lifetime of the research study using your real life experience of either looking after someone with a pressure ulcer or having a pressure ulcer.

Your role will involve but not limited to:

- Identifying important questions to be answered by the research study
- commenting and developing patient information leaflets or other research materials
- helping identify ways of reaching the right study population
- help interpret results and ensure they are reported in understandable ways

Reasonable travel expenses will be reinmbursed in return for your participation

Your help will be greatly appreciated and will be shape and improve future care. Together we can help improve our NHS.

If your are interested in taking part please contact:

Miss Alisen Dube, University Hospital Coventry and Warwickshire NHS Trust

Tissue viability team

Clifford bridge road

Coventry , CV2 2NB

Tel: 07415097713

Email: alisen.dube@uhcw.nhs.uk

Twitter: @alisen_dube

Appendix 7: Consultee Study Information Sheet

 **Heel Pressure Ulcer Study: Contributory factors and their impact on quality of life** 

HPrUS

Consultee Information Sheet

Chief Investigator: Miss Alisen Dube

Introduction

We would like to invite your relative/friend/patient to take part in our research study, which is looking at why some people are more likely to develop heel pressure ulcers compared to others. This study will provide us with information which may help us improve the way we look after patients in different health care settings in future.

However, we feel your relative/friend/patient is unable to decide for himself/herself whether to participate in this research due to their medical condition. In such instances we are required by law to identify a suitable person who can act on their behalf as a consultee.

What is a consultee?

A consultee can either be personal or nominated dependant on patient's circumstance.

A personal consultee may be someone who has a personal relationship with the patient but is not involved in their welfare in a professional capacity, research or for financial benefit. Examples of suitable people who might act as a personal consultee are: family member, carer, friend, or a court nominated deputy who has a personal relationship with the patient.

A nominated consultee may be a person involved in the patient's care in a professional capacity, this may be a General Practitioner (GP) or other doctor as nominated by the researcher if a personal consultee is unavailable. A nominated consultee may only be identified when 'reasonable steps' have been made to identify a personal consultee.

What are my duties as a consultee?

As the patient's personal/ nominated consultee your role is to advise the research team whether or not the patient would be happy to take part in the study. We will ask you to consider what you know of their wishes and feelings, and to consider their interests. Please let us know of any advance decisions they may have made about participating in research. These should take precedence. You are not being asked to give consent on behalf of the patient, however if you advise us that the patient would not want to be part of the study then we will abide by this and it will not affect the standard of care they receive in any way.

If you decide your relative/friend/patient would have no objection to taking part we will ask you to read and sign the consultee declaration. We'll then give you a copy to keep. We will ask you to complete a study questionnaire about your relative/friend/patient's general health. You will be fully informed during the study so you can let us know if you have any concerns or you think your relative/friend/patient should be withdrawn.

If you are unsure about taking the role of consultee you may seek independent advice. We will understand if you do not want to take on this responsibility.

Appendix 7b: Consultee Declaration Form

Heel Pressure Ulcer Study: Contributory factors and their impact on quality of life

HPrUS

Chief Investigator: Miss Alisen Dube

Consultee Declaration Form

Study ID			

e with the following statements please initial in the box to the right of each statement.

ase print and sign your name at the bottom.

	Initial boxes below
1. I [name of consultee] have been consulted about [name of potential participant]'s participation in this research project.	
)nfirm that I have read the consultee information sheet dated..... (Version.....) for above study. I have had the opportunity to consider the information, ask questions and have l these answered satisfactorily.	
n aware that the patient does not have to take part in the study, and may withdraw from the dy at any time without having to give a reason, without the patient's standard of care being ected in any way.	
nderstand that relevant sections of his/her medical notes and data collected during the study, y be looked at by individuals from Birmingham City University, regulatory authorities or from NHS Trust, where it is relevant to their taking part in the study and also give permission for se individuals to have access to the patient's records.	
nderstand that confidentiality maybe breached should any safeguarding concerns arise during study.	
gree to their GP being informed of their participation in the study and the result of their rasound Doppler test	
ny opinion he/she would have no objection to taking part in the above study.	

Appendix 8: Patient Information Sheet

Heel Pressure Ulcer Study: Contributory factors and their impact on quality of life

HPrUS

Patient Information Sheet

Chief Investigator: Miss Alisen Dube

We would like to invite you to take part in our research study, which is looking at why some people are more likely to develop heel pressure ulcers compared to others. This study will provide us with information which may help us improve the way we look after patients in different health care settings in future.

Before you decide whether to take part we would like you to understand why the research is being done and what it would involve for you. We will be very happy to go through the information with you and answer any questions you may have. This should take about 10 minutes. You can also discuss the study with other individuals including health care professionals currently looking after you.

Background information

Pressure ulcers are areas of damage to the skin and sometimes the tissues underneath. These types of ulcers develop around bony areas close to the skin as a result of pressure, mostly from sitting or lying in the same position over a long period of time. Pressure ulcers are painful and affect one's quality of life. Heel pressure ulcers are one of the most common types of pressure ulcers and mostly affect people with certain health conditions like diabetes and poor blood circulation. The purpose of this study is to identify what characteristics are shared by individuals who develop heel pressure ulcers and how they differ from those without heel pressure ulcers, how these characteristics affect how quickly the ulcers get better, and how heel pressure ulcers affect long term quality of life. Results from this study will be used to improve the care currently offered in different health care settings.

What is the purpose of this study?

We are interested in finding out why some people are more likely to develop heel pressure ulcers and how heel pressure ulcers affect long term quality of life. It is important to perform this type of study so we can improve the care that is currently offered to patients.

Why have I been invited?

Two groups of patients are being invited to take part in this study: either you have been diagnosed with a heel pressure ulcer or you do not have a heel pressure ulcer but have been admitted to University Hospitals Coventry and Warwickshire NHS Trust (UHCW) for treatment and you are aged 18 years and above. Comparing these two groups of patients will help us to identify factors that might increase the likelihood of developing heel pressure ulcers. All suitable patients admitted to UHCW will be approached to take part in the study and your participation will be equally important regardless of the study group.

Appendix 8a: Consent Form

Heel Pressure Ulcer Study: Contributory factors and their impact on quality of life

HPrUS

Chief Investigator: Miss Alisen Dube

Patient Consent Form

Study ID			

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ase print and sign your name at the bottom.

	Initial boxes below
1. I confirm that I have read the information sheet dated…… (Version……) for the above study. I have had opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason and that my medical care or legal rights will not be affected. Anonymised data collected up to the date I withdraw will be retained.	
3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by the research team at Birmingham City University, regulatory authorities or from the NHS Trust, where it is relevant to my taking part in the study. I give permission for these individuals to have access to my records.	
4. I agree that relevant data and contact details will be held confidentially and securely by the researcher and give my consent on the condition that the researcher complies with their duties and obligations under the Data Protection Act 1998.	
5. I understand that confidentiality maybe breached should any safeguarding concerns arise during the study.	
6. I agree to my GP being informed of my participation in the study and the result of the Ultrasound Doppler test.	
7. I agree to take part in the above study	

Appendix 9: Study GP Letter

Heel Pressure Ulcer Study: Contributory factors and their impact on quality of life

HPrUS

Letter to General Practitioner

Chief Investigator: Miss Alisen Dube

Dear Dr……. Date ……

I am writing to inform your that your patient (add patient name)……, has agreed to take part in a research study aimed at identifying the risk factors associated with developing heel pressure ulcers and the impact of heel pressure ulcers on quality of life . A patient information sheet is enclosed with this letter. The research is sponsored by Birmingham City University (BCU) and University Hospitals Coventry and Warwickshire NHS Trust (UHCW).

As part of the research study (patient's name) ……..had an Ankle Brachial Pressure Index (ABPI) assessment using a Ultrasound Doppler to exclude any peripheral arterial disease (PAD). Below are the results from my examination.

Patient label…….

	Left	Right	Comments
ABPI			
Appearance			
Pain			
Ulceration			

I have obtained consent from the patient to share these results with you and request that you use this information as appropriate to support the patient's care and treatment.

Thank you for your support.

Yours sincerely,

Alisen Dube

Chief investigator (Tissue Viability Research Nurse)

UHCW NHS Trust

alisen.dube@uhcw.nhs.uk

Appendix 10a: Patient Information Sheet (1) (with Doppler Ultrasound Assessment)

 **Heel Pressure Ulcer Study: Contributory factors and their impact on quality of life** 

HPrUS

Patient Information Sheet (1)

Chief Investigator: Miss Alisen Dube

We would like to invite you to take part in our research study, which is looking at why some people are more likely to develop heel pressure ulcers compared to others. This study will provide us with information which may help us improve the way we look after patients in different health care settings in future.

Before you decide whether to take part we would like you to understand why the research is being done and what it would involve for you. We will be very happy to go through the information with you and answer any questions you may have. This should take about 10 minutes. You can also discuss the study with other individuals including health care professionals currently looking after you.

Background information

Pressure ulcers are areas of damage to the skin and sometimes the tissues underneath. These types of ulcers develop around bony areas close to the skin as a result of pressure, mostly from sitting or lying in the same position over a long period of time. Pressure ulcers are painful and affect one's quality of life. Heel pressure ulcers are one of the most common types of pressure ulcers and mostly affect people with certain health conditions like diabetes and poor blood circulation. The purpose of this study is to identify what characteristics are shared by individuals who develop heel pressure ulcers and how they differ from those without heel pressure ulcers, how these characteristics affect how quickly the ulcers get better, and how heel pressure ulcers affect long term quality of life. Results from this study will be used to improve the care currently offered in different health care settings.

What is the purpose of this study?

We are interested in finding out why some people are more likely to develop heel pressure ulcers and how heel pressure ulcers affect long term quality of life. It is important to perform this type of study so we can improve the care that is currently offered to patients.

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Two groups of patients are being invited to take part in this study: either you have been diagnosed with a heel pressure ulcer or you do not have a heel pressure ulcer but have been admitted to University Hospitals Coventry and Warwickshire NHS Trust (UHCW) for treatment and you are aged 18 years and above. Comparing these two groups of patients will help us to identify factors that might increase the likelihood of developing heel pressure ulcers. All suitable patients admitted to UHCW will be approached to take part in the study and your participation will be equally important regardless of the study group.

Appendix 10b: Consultee Study Information Sheet (1) (with Doppler Ultrasound Assessment)

Heel Pressure Ulcer Study: Contributory factors and their impact on quality of life

HPrUS

Consultee Information Sheet (1)

Chief Investigator: Miss Alisen Dube

Introduction

We would like to invite your relative/friend/patient to take part in our research study, which is looking at why some people are more likely to develop heel pressure ulcers compared to others. This study will provide us with information which may help us improve the way we look after patients in different health care settings in future.

However, we feel your relative/friend/patient is unable to decide for himself/herself whether to participate in this research due to their medical condition. In such instances we are required by law to identify a suitable person who can act on their behalf as a consultee.

What is a consultee?

A consultee can either be personal or nominated dependant on patient's circumstance.

A personal consultee may be someone who has a personal relationship with the patient but is not involved in their welfare in a professional capacity, research or for financial benefit. Examples of suitable people who might act as a personal consultee are: family member, carer, friend, or a court nominated deputy who has a personal relationship with the patient.

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What are my duties as a consultee?

As the patient's personal/ nominated consultee your role is to advise the research team whether or not the patient would be happy to take part in the study. We will ask you to consider what you know of their wishes and feelings, and to consider their interests. Please let us know of any advance decisions they may have made about participating in research. These should take precedence. You are not being asked to give consent on behalf of the patient, however if you advise us that the patient would not want to be part of the study then we will abide by this and it will not affect the standard of care they receive in any way.

If you decide your relative/friend/patient would have no objection to taking part we will ask you to read and sign the consultee declaration. We'll then give you a copy to keep. We will ask you to complete a study questionnaire about your relative/friend/patient's general health. You will be fully informed during the study so you can let us know if you have any concerns or you think your relative/friend/patient should be withdrawn.

If you are unsure about taking the role of consultee you may seek independent advice. We will understand if you do not want to take on this responsibility.

Appendix 10c: Consent Form

Heel Pressure Ulcer Study: Contributory factors and their impact on quality of life

HPrUS

Chief Investigator: Miss Alisen Dube

Patient Consent Form (1)

Study ID			

Before we obtain any information from you we need to ask for your consent to show that you are willing to take part in this study and that you understand why you have been invited to participate. If you agree with the following statements please **initial in the box to the right of each statement**.

Finally, please print and sign your name at the bottom.

	Initial boxes below
1. I confirm that I have read the information sheet dated…… (Version……) for the above study. I have had opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason and that my medical care or legal rights will not be affected. Anonymised data collected up to the date I withdraw will be retained.	
3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by the research team at Birmingham City University, regulatory authorities or from the NHS Trust, where it is relevant to my taking part in the study. I give permission for these individuals to have access to my records.	
4. I agree that relevant data and contact details will be held confidentially and securely by the researcher and give my consent on the condition that the researcher complies with their duties and obligations under the General Data Protection Regulation.	
5. I understand that confidentiality maybe breached should any safeguarding concerns arise during the study.	
6. I agree to my GP being informed of my participation in the study and the result of the Ultrasound Doppler test.	
7. I agree to take part in the above study	

Name of Patient (PRINT):	Date:	Signature:
Name of Person taking consent (PRINT):	Date:	Signature:

When completed: 1 copy for participant, 1 for researcher site file, 1 (original) to be kept in medical notes.

Appendix 10d: Consultee Declaration Form

Heel Pressure Ulcer Study: Contributory factors and their impact on quality of life

HPrUS

Chief Investigator: Miss Alisen Dube

Consultee Declaration Form (1)

Study ID			

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5. I understand that confidentiality maybe breached should any safeguarding concerns arise during the study.	
6. I agree to their GP being informed of their participation in the study and the result of their Ultrasound Doppler test	
7. In my opinion he/she would have no objection to taking part in the above study.	

Name of Consultee (PRINT): Date: Signature:

Appendix 11a: Patient Information Sheet (2) (which excluded the Doppler Ultrasound Assessment)

 **Heel Pressure Ulcer Study: Contributory factors and their impact on quality of life** 

HPrUS

Patient Information Sheet (2)

Chief Investigator: Miss Alisen Dube

We would like to invite you to take part in our research study, which is looking at why some people are more likely to develop heel pressure ulcers compared to others. This study will provide us with information which may help us improve the way we look after patients in different health care settings in future.

Before you decide whether to take part we would like you to understand why the research is being done and what it would involve for you. We will be very happy to go through the information with you and answer any questions you may have. This should take about 10 minutes. You can also discuss the study with other individuals including health care professionals currently looking after you.

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Appendix 11b: Consultee Study Information Sheet (2) (which excluded the Doppler Ultrasound Assessment)

Heel Pressure Ulcer Study: Contributory factors and their impact on quality of life

HPrUS

Consultee Information (2) Sheet

Chief Investigator: Miss Alisen Dube

Introduction

We would like to invite your relative/friend/patient to take part in our research study, which is looking at why some people are more likely to develop heel pressure ulcers compared to others. This study will provide us with information which may help us improve the way we look after patients in different health care settings in future.

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If you are unsure about taking the role of consultee you may seek independent advice. We will understand if you do not want to take on this responsibility.

Appendix 11c: Consent Form

Heel Pressure Ulcer Study: Contributory factors and their impact on quality of life

HPrUS

Chief Investigator: Miss Alisen Dube

Patient Consent Form (2)

Study ID			

Before we obtain any information from you we need to ask for your consent to show that you are willing to take part in this study and that you understand why you have been invited to participate. If you agree with the following statements please **initial in the box to the right of each statement**.

Finally, please print and sign your name at the bottom.

	Initial boxes below
1. I confirm that I have read the information sheet dated…… (Version……) for the above study. I have had opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason and that my medical care or legal rights will not be affected. Anonymised data collected up to the date I withdraw will be retained.	
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4. I agree that relevant data and contact details will be held confidentially and securely by the researcher and give my consent on the condition that the researcher complies with their duties and obligations under the General Data Protection Regulation 2018.	
5. I understand that confidentiality maybe breached should any safeguarding concerns arise during the study.	
6. I agree to my GP being informed of my participation in the study.	
7. I agree to take part in the above study	

Name of Patient (PRINT):	Date:	Signature:
Name of Person taking consent (PRINT):	Date:	Signature:

When completed: 1 copy for participant, 1 for researcher site file, 1 (original) to be kept in medical notes.

IRAS ID: 240842 Patient consent Version 0.1 15-01-2019

Appendix 11d: Consultee Declaration Form

Heel Pressure Ulcer Study: Contributory factors and their impact on quality of life

HPrUS

Chief Investigator: Miss Alisen Dube

Consultee Declaration Form (2)

Study ID			

If you agree with the following statements please initial in the box to the right of each statement.

Finally, please print and sign your name at the bottom.

Initial boxes below

Chapter 1 I have been consulted about 's participation in this research project. ☐

2. I confirm that I have read the consultee information sheet dated..... (Version.....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

3. I am aware that the patient does not have to take part in the study, and may withdraw from the study at any time without having to give a reason, without the patient's standard of care being affected in any way. ☐

4. I understand that relevant sections of his/her medical notes and data collected during the study, may be looked at by individuals from Birmingham City University, regulatory authorities or from the NHS Trust, where it is relevant to their taking part in the study and also give permission for these individuals to have access to the patient's records. ☐

5. I understand that confidentiality maybe breached should any safeguarding concerns arise during the study. ☐

6. I agree to their GP being informed of their participation in the study. ☐

7. In my opinion he/she would have no objection to taking part in the above study. ☐

Name of Consultee (PRINT): Date: Signature:

Appendix 12: Study Case Report Forms- Baseline Forms

Heel Pressure Ulcer Study: Contributory factors and their impact on quality of life

HPrUS

Baseline: Study Questionnaire booklet

Participant ID:

Date completed:	

Appendix 13: Study Case Report Forms- 3 months Follow-up

Heel Pressure Ulcer Study: Contributory factors and their impact on quality of life

HPrUS

3 months follow-up: Study Questionnaire booklet

Participant ID:

Date completed:	

Appendix 14: Study Case Report Forms- 6 months Follow-up

Heel Pressure Ulcer Study: Contributory factors and their impact on quality of life

HPrUS

6 months follow-up: Questionnaire booklet

Participant ID:

Date to be completed:	

Appendix 15: Summary Demographics of Screened Patients

	Screened Cases (n=482)	Screened Control (n=131)	Total Screened	p-values
Age -Mean (sd) Median (range)	79.0 (14.3) 82.2(8.9-103.1)	80.2(10.7) 83 (40-98)	79.3 (13.6) 84 (8.9-103.1)	[a]0.3 [b]0.1
Gender - F (%)	295 (61.2)	85 (64.9)	380 (62.0)	[a]0.2 [b]0.1

a =cases-recruited vs not recruited; b=controls-recruited vs not recruited.

Appendix 16: Summary of Study Matching Variables

Variable	Cases (n=53)	Controls (n=50)	Total (n=103)	Parameter estimate (mean difference or odds ratios) (95% CI)	P-value
Age Mean (sd) Median (range)	77.5 (12.3) 78.0 (42.0 - 98.0)	78.3 (12.4) 79.0 (40.0 - 98.0)	77.9 (12.3) 79 (40-98)	0.8 (-5.7; 4.0)	0.7
[a]Gender-F (%)	32.0 (60.4)	31.0 (62.0)	63.0 (61.2)	1.1 (0.4; 2.6)	0.9
Ability to Consent-N (%)	23.0 (43.4)	20.0 (40.0)	43 (41.7)	1.2 (0.5; 2.7)	0.7
AMTS-mean, (sd) Median (range)	5.3 (4.2) 7.0 (0.0 - 10.0)	5.5(4.2) 7.0 (0.0 - 10.0)	5.4 (4.1) 7.0 (0.0 - 10.0)	-0.2 (-1.8; 1.5)	0.8
EoL Status-N (%)	47.0 (88.7)	45.0 (90)	92.0 (89.3)	1.1 (0.3; 5.1)	0.8
Ethnicity (%) White British/ Irish Asian - British Indian	 52.0 (98.1) 1.0 (1.9)	 50.0 (100) 0.0	 102.0 (99.0) 1.0 (1.0)	-	 1.0

a=male reference group

Appendix 17: Summary of Surgical Procedures Completed and use of Anti-Embolic Stockings during admission.

Surgical procedure Y (%)	**Cases (n=53)**	**Controls (n=50)**	**Total (n=103)**	**Estimate Difference OR (95% CI)**	**p-value**
Surgical procedure this admission	7.0 (13.2)	6.0 (12.0)	13.0 (12.6)	1.1 (0.3; 4.5)	1.0
Type of surgery					
Lower limb amputation	3.0 (42.9)	0.0	3.0 (23.1)	-	0.3
Lower limb arthroplasty	3.0 (42.9)	2.0 (33.3)	5.0 (38.5)		
Cardiovascular	1.0 (14.3)	2.0 (33.3)	3.0 (23.1)		
Surgical	0.0	2.0 (33.3)	2.0 (15.4)		
Anti-embolic stockings	1.0 (1.9)	3.0 (6.0)	4.0 (3.9)		1.0

Appendix 18: Relationship between Composite Variables and Presence of HPUs

Comorbidity composite factors	**Cases (n=53)**	**Control (n=50)**	**Total (n=103)**	**Odd ratio (95%CI) p-value**	**Correlation coefficient (p-value <0.05)**
CKD and diabetes					
Exposed	39	20	59	4.1 (1.7; 10.5) 0.0006	0.4
Unexposed	14	30	44		
AF and Asthma					
Exposed	20	17	37	1.2 (0.5; 2.9) 0.7	-0.2
Unexposed	33	33	66		
Perfusion related comorbidities (angina, AF, asthma and HF)					
Exposed	29	24	48	2.0 (0.8; 4.7) 0.09	N/A
Unexposed	24	31	55		

Appendix 19: Consent type and DUS completed (ABPI vs TBPI)

Consent Type	Cases (n=53)	Controls (n=50)	Total (n=103)
Patient with ability to consent	(n=30)	(n=30)	(n=60)
ABPI	11.0 (36.7)	12.0 (40.0)	23.0 (38.3)
TBPI	12.0 (40.0)	16.0 (53.3)	28.0 (46.7)
Declined	7.0 (23.3)	2.0 (6.7)	9.0 (15.0)
Consultee agreed to DUS	(n=23)	(n=20)	(n=43)
ABPI	6.0 (26.1)	4.0 (20.0)	10.0 (23.3)
TBPI	4.0 (17.4)	3.0 (15.5)	7.0 (16.3)
Consultee declined DUS	13.0 (56.5)	13.0 (65.0)	26.0 (60.4)

Appendix 20: Summary of ABPI/TBPI Doppler Ultrasound Assessment by Study Group

Pulse location	**Cases (n=53)**	**Controls (n=50)**	**Total (n=103)**	**Estimate difference (95%CI)**	**p-value**
Brachial systolic pressure (mmHg) Median (Range):					
[a]*Right*	127.0 (78.0-158)	130.0 (72.0-178.0)	129.0 (72.0- 178.0)	-2.9 (-13.9; 7.9	0.6
[a]*Left*	128.0 (80.0-152)	128.0 (66.0-170)	128.0 (66.0, 170.0)	-3.6 (-13.9, 6.7)	0.5
Largest Brachial Pressure	130.0 (80.0-158.0)	130.0 (72.0-178)	130.0 (72.0-178.0)	-2.1 (-12.4; 8.2)	0.7
Dorsalis Pedis systolic pressure (mmHg) Median (Range):					
Right	123.0 (95.0-162.0)	132.0 (96.0-168)	130 (95-168]	-8.2 (-25.8; 9.3)	0.3
[b]*Left*	120.0 (90.0-172.0)	131.0 (82.0-168)	129.0 (82.0 172.0)	-7.5 (-26.0; 11.0)	0.4
Posterior tibial systolic pressure (mmHg) Median (Range):					
Right	134.0 (98.0-168.0)	126.0 (90.0-164.0)	126.0 (90.0-168.0)	3.0 (-15.9-21.8)	0.7

Pulse location	**Cases (n=53)**	**Controls (n=50)**	**Total (n=103)**	**Estimate difference (95%CI)**	**p-value**
Left	113.0 (94.0-168)	127.0 (74.0-164)	125.0 (74.0,168.0)	-7.3 (-26.0; 11.7)	0.4
Peroneal systolic pressure (mmHg) Median (Range)					
Right	94.0 (92.0-96.0)	122.0 (90.0-160.0)	117.0 (90.0,160.0)	-25.8 (-52.5-0.08)	**0.06***
Left	98	122.0 (92.0-158.0)	120.0 (92.0-158.0)	-	-
[c]ABPI Median (Range):					
[h]*Right:*	1.0 (0.8-1.3) n=14	1.0 (0.9-1.2) n=15	1.0 (0.8-1.3) n=29	-0.01 (-0.1; 0.08)	0.8
*PAD severity (Right leg)					
Normal	10.0 (71.4)	14.0 (93.3)	24.0 (82.8)	5.6 (0.4; 295.0)	0.2
Moderate	4.0 (28.6)	1.0 (6.7)	5.0 (17.2)		
[h]*Left:*	1.0 (0.7-1.2)	1.0 (0.8-1.3)	1.0 (0.7- 1.3)	-0.04 (-0.1; 0.06)	0.5
*PAD severity (Left leg)					

Pulse location	**Cases (n=53)**	**Controls (n=50)**	**Total (n=103)**	**Estimate difference (95%CI)**	**p-value**
Normal	9.0 (64.3)	15.0 (93.8)	24.0 (80.0)	8.3 (0.7; 419.7)	**0.07***
Moderate	5.0 (35.7)	1.0 (66.3)	6.0 (20.0)		
ABPI summary for each pedal artery					
Right DP	1.0 (0.8-1.2)	1.0 (0.9-1.2)	1.0 (0.8,1.2)	-0.01 (-0.1; 0.08)	0.8
PAD Severity (Right DP)					
Normal	8.0 (72.7)	16.0 (100.0)	24.0 (88.9)	-	**0.06***
Moderate	3.0 (27.3)	0.0 (0.0)	3.0 (11.1)		
Left - DP	0.9 (0.8-1.1)	1.0 (0.8-1.2)	1.0 (0.8, 1.2)	-0.03 (-0.1; 0.05)	0.4
PAD Severity (Left DP)					
Normal	8.0 (66.7)	13.0 (87.5)	22.0 (78.6)	3.5 (0.4; 44.8)	0.3
Moderate	4.0 (33.3)	2.0 (12.5)	6.0 (21.4)		
PT Right	1.1 (0.8-1.2)	1.0 (0.8-1.2)	1.0 (0.8- 1.2)	0.03 (-0.08; 0.1)	0.6
PAD Severity (Right PT)					

Pulse location	**Cases (n=53)**	**Controls (n=50)**	**Total (n=103)**	**Estimate difference (95%CI)**	**p-value**
Normal	7.0 (70.0)	14.0 (82.3)	21.0 (77.8)	2.0 (0.2; 18.7)	0.6
Moderate	3.0 (30.0)	3.0 (17.7)	6.0 (22.2)		
PT Left	0.9 (0.8-1.2)	1.0 (0.7-1.3)	1.0 (0.7-1.3)	-0.03 (-0.1; 0.08)	0.6
PAD Severity (Left PT)					
Normal	5.0 (41.7)	13.0 (81.3)	18.0 (64.3)	**6.1 (0.9; 48.2)**	**0.05***
Moderate	7.0 (58.3)	3.0 (18.8)	10.0 (35.7)		
Peroneal Right	0.7 (0.69-0.73)	0.9 (0.9-1.2)	0.9 (0.7- 1.2)	-**0.2 (-0.3; -0.1)**	**0.001***
PAD Severity (Right Peroneal)					
Normal	0.0	8.0 (72.7)	8.0 (57.1)	**-**	**0.01***
Moderate	3.0 (100.0)	2.0 (27.3)	6.0 (42.9)		
Peroneal Left	0.8	0.9 (0.9-1.2)	0.9 (0.8-1.2)	n/a	n/a
PAD Severity (left Peroneal)					

Pulse location	**Cases (n=53)**	**Controls (n=50)**	**Total (n=103)**	**Estimate difference (95%CI)**	**p-value**
Normal	0.0 (0.0)	7.0 (70.0)	7.0 (63.6)	-	0.5
Moderate	1.0 (100.0)	3.0 (30.0)	4.0 (36.4)		
Toe Pressure (mmHg) Median (Range):					
Right	86.0 (35.7-118.7)	88.5 (44.0-134.7)	87.2 (35.7-134.7)	-6.1 (-23.7; 11.6)	0.5
Left	75.5 (21.7-124.0)	88.0 (44.7-127.7)	85.8 (21.7-127.7)	-13.6 (-35.4; 8.3)	0.3
Toe Brachial Pressure Index (TBPI)					
Average toe pressure- Right	0.7 (0.3-1.0)	0.7 (0.5-0.9)	0.7 (0.3-1.0)	-0.04 (-1.2; 0.08)	0.5
PAD Severity (Right TBPI)					
Normal	10.0 (58.8)	13.0 (76.5)	23.0 (67.7)	2.3 (0.4; 13.5)	0.6
Moderate	6.0 (34.3)	4.0 (23.5)	10.0 (29.4)		
Severe	1.0 (5.9)	0.0 (0.0)	1.0 (2.9)		
Average toe pressure- Left	0.6 (0.1-1.1)	0.7 (0.3-0.8)	0.7 (0.1-1.1)	-0.06 (-0.2; 0.1)	0.5
PAD Severity (Left TBPI)					

Pulse location	**Cases (n=53)**	**Controls (n=50)**	**Total (n=103)**	**Estimate difference (95%CI)**	**p-value**
Normal	7.0 (63.6)	14.0 (93.3)	21.0 (60.8)	8.0 (0.6; 421.3)	**0.1***
Moderate	3.0 (27.3)	0.0 (0.0)	3.0 (11.5)		
Severe	1.0 (9.1)	1.0 (6.7)	2.0 (7.7)		

a=missing data due to either having fistula, TPN access, or was done in vascular lab and therefore data was not available (n≤6); b=missing due to amputation or was done in vascular lab and therefore data was not available (n≤6);c=calculated using highest pedal and brachial systolic pressure. ABPI calculated based on high pedal pressure/ highest brachial pressure; TBPI calculated based on average mean toe pressure / highest brachial pressure.

Appendix 21: Summary Results from Logistic Regression Analysis using Doppler ultrasound data

Variable	**Univariate** *OR (95% CI) p-value*
Arterial pulse palpable (No)	
Left	
DP N=78	4.8 (1.8; 13.1) **0.002**
PT (n=78)	3.0 (1.2; 7.7) **0.02**
Peroneal (n=78)	3.3 (1.1; 10.3) **0.04**
Composite variable for right pulses	1.8 (1.2; 2.8) 0.01
Right	
DP (n=80)	3.2 (1.2; 8.3) **0.02**
PT (n=75)	2.5 (1.0; 6.6) **0.06**
Peroneal (n=77)	2.5 (1.0; 6.6) **0.03**
Composite variable for right pulses	1.5 (1.0; 2.3) 0.04
Waveform assessment	
Left	
DP (n=79)	
triphasic vs biphasic	4.1 (0.5; 36.7) 0.2

Variable	**Univariate** *OR (95% CI) p-value*
triphasic vs monophasic	14.5 (1.6; 128.4) **0.02**
PT (biphasic vs monophasic) (n=63)	2.0 (0.7; 5.4) 0.2
Right DP (n=79)	
triphasic vs biphasic	4.4 (0.9; 22.8) 0.08
triphasic vs monophasic	5.5 (1.0 - 29.2) **0.05**
Foot Artery PAD severity	
Left foot ABPI (normal vs moderate) (n=30)	8.3 (0.8; 83.2) 0.07
Right DP (n=27)	Unable to calculate OR using univariate analysis as all controls had normal range ABPI. (See Table)
Left PT (n=28) (normal vs moderate)	6.1 (1.1; 33.2) **0.04**
Right Peroneal (n=14)	Unable to calculate OR using univariate analysis as none of the cases assessed had normal range ABPI. (See Table)

Appendix 22: Summary of Pain Assessment using Pain Assessment in Advanced Dementia at Baseline

PAINAD subdomains; Median (Range)	Cases (n=23)	Control (n=20)	Total (n=43)	Estimate Difference (95%)	p-value
Breathing independent of vocalisation	0.0 (0.0; 1.0)	0.0 (0.0;1.0)	0.0 (0.0;1.0)	0.2 (-0.1; 0.4)	0.2
Normal	16.0 (69.6)	17.0 (85.0)	33.0 (76.7)	-	0.3
Occasional laboured breathing. Short period of hyperventilation	7.0 (30.4)	3.0 (15.0)	10.0 (23.3)		
Noisy laboured breathing. Long period of hyperventilation. Cheyne-stokes respirations	0.0	0.0	0.0		
Negative vocalisation	0.0 (0.0-2.0)	0.0 (0.0-2.0)	0.0 (0-2)	0.3 (-.02; 0.7)	0.2
None	12.0 (52.2)	15.0 (75.0)	27.0 (62.8)	-	0.3
Occasional moan or groan. Low-level of speech with a negative or disapproving quality	8.0 (34.8)	3.0 (15.0)	11.0 (25.6)		
Repeated troubled calling out. Loud moaning or groaning. Crying.	3.0 (13.0)	2.0 (10.0)	5.0 (11.6)		
Facial expression	0.4 (0.7) 0.0 (0.0-2.0)	0.3 (0.4) 0.0 (0.0-1.0)	0.3 (0.6) 0.0 (0.0-3.0)	0.2 (-0.2; 0.5)	0.3

Smiling or inexpressive	16.0 (69.6)	15.0 (75.0)	31.0 (72.1)	-	0.4
Sad, frightened, frown	4.0 (17.4)	5.0 (25.0)	9.0 (20.9)		
Facial grimacing	3.0 (13.04)	0.0 (0.0)	3.0 (7.0)		
Body language	0.0 (0.0-2.0)	0.0 (0.0-1.0)	0.0 (0.0-2.0)	0.07 (-0.3; 0.4)	0.7
Relaxed	13.0 (56.5)	11.0 (55.0)	24.0 (55.8)	-	0.5
Tense, distressed pacing, fidgeting	8.0 (34.7)	9.0 (45.0)	17.0 (39.5)		
Rigid. Fists clenched. Knees pulled up. Pulling or pushing away. Striking out	2.0 (8.7)	0.0 (0.0)	2.0 (4.7)		
Consolability	0.7 (0.8) 0.0 (0.0-2.0)	0.5 (0.6) 0.0 (0.0-2.0)	0.6 (0.7) 0.0 (0.0-2.0)	0.2 (-0.3; 0.6)	0.5
No need to console	12.0 (52.2)	11.0 (55.0)	23.0 (53.5)		0.6
Distracted or reassured by voice or touch	7.0 (30.4)	8.0 (40.0)	15.0 (34.9)		
Unable to console, distract or reassure	4.0 (17.4)	1.0 (5.0)	5.0 (11.6)		
Total score	2.3 (2.7) 1.0 (0.0-8.0)	1.7 (2.3) 0.0 (0.0-6.0)	2.0 (2.5) 0.0 (0.0-8.0)	0.6 (-0.9; 2.2)	0.4

Appendix 23: Proportion of Participants with no problems vs those with problems, reported by Group

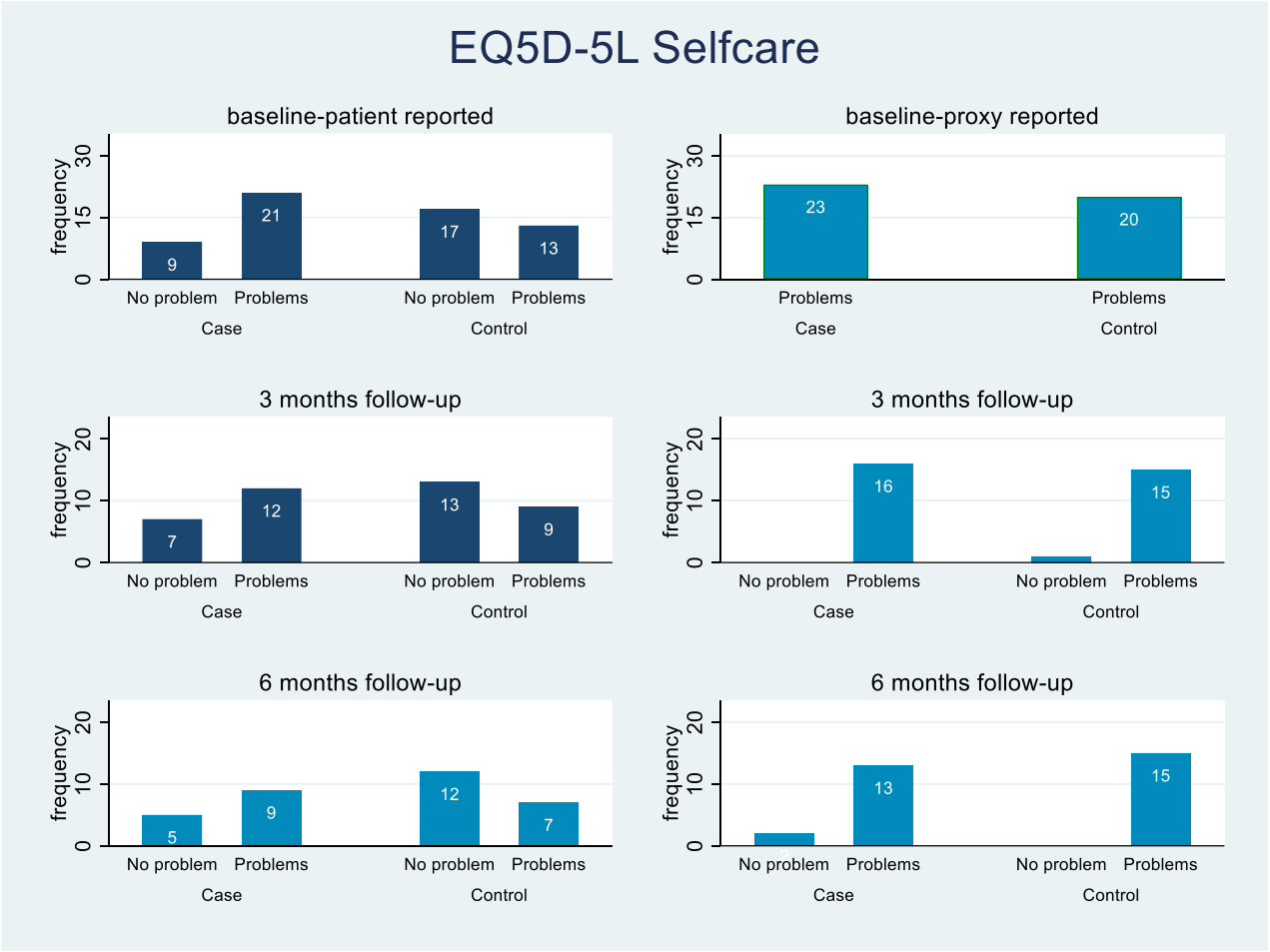

Fig 4: EQ5D-5L: selfcare (no problems vs problems)

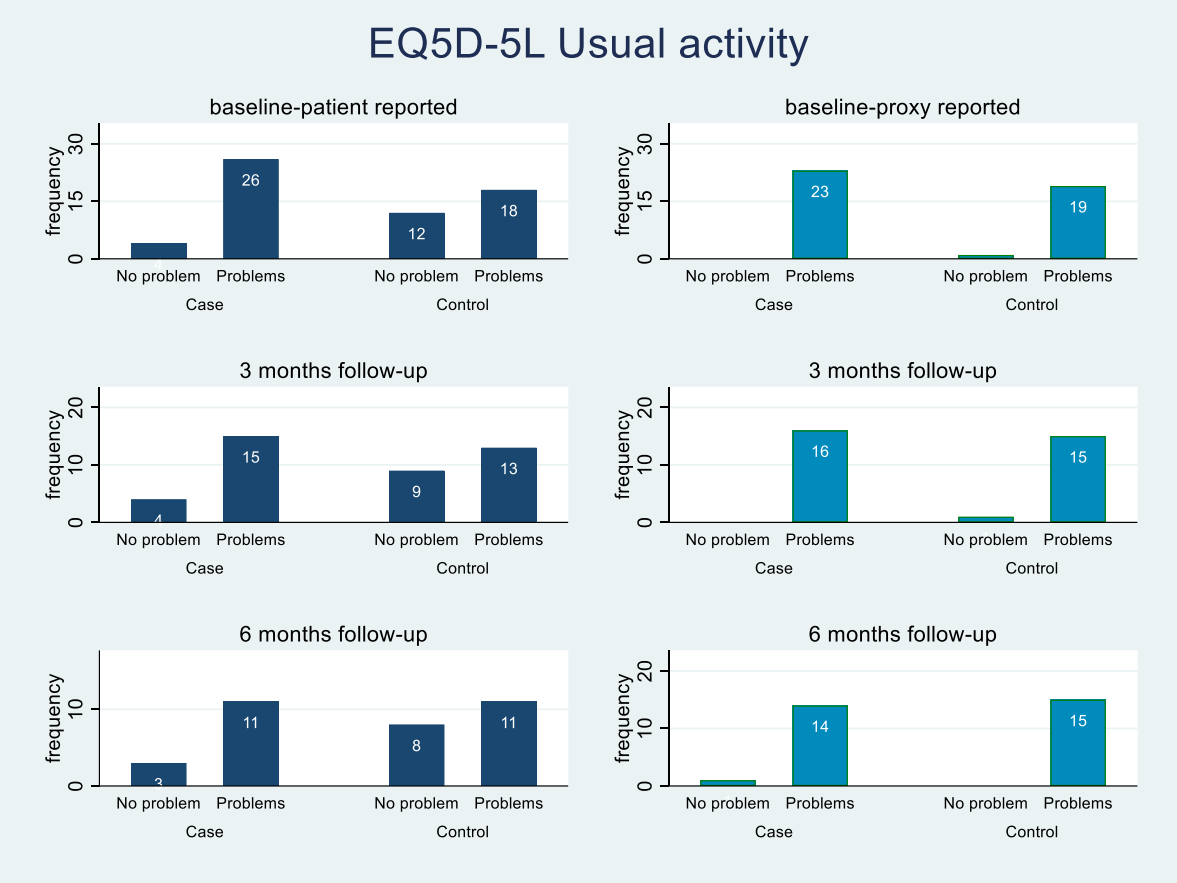

Fig 5: EQ5D-5L: usual activity (no problems vs problems)

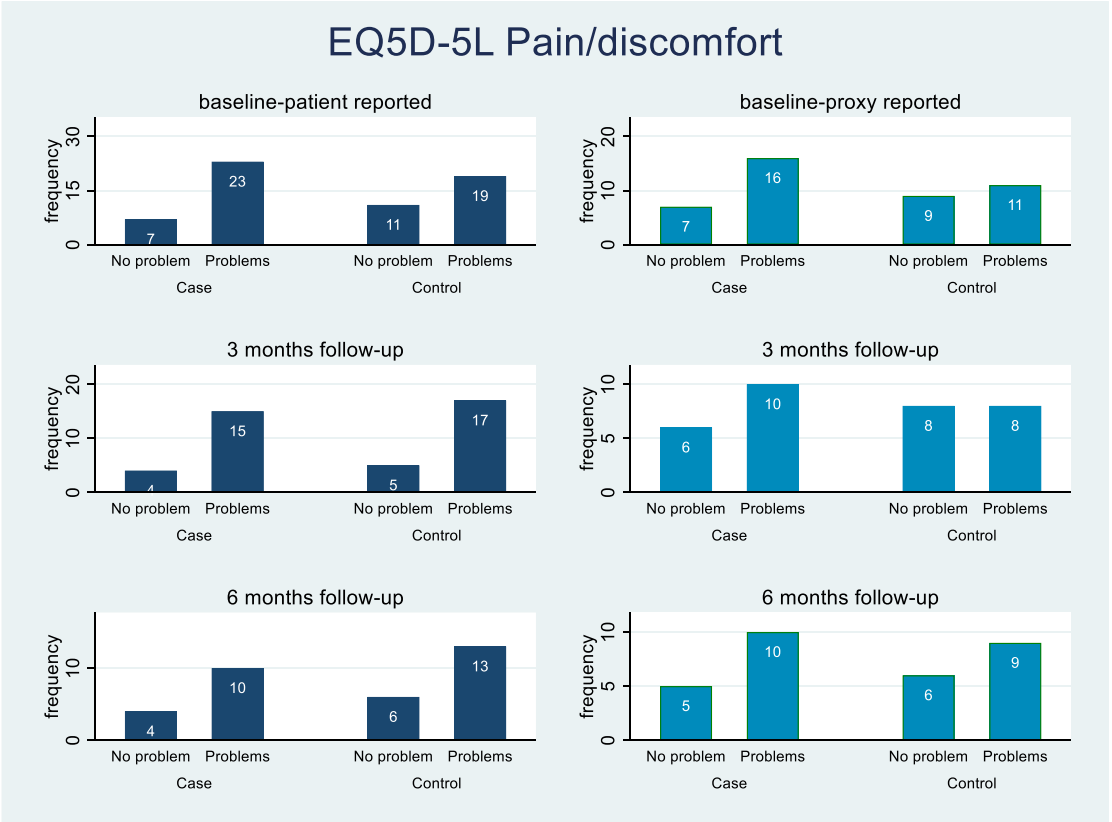

Fig 6: EQ5D-5L: usual activity (no problems vs problems)

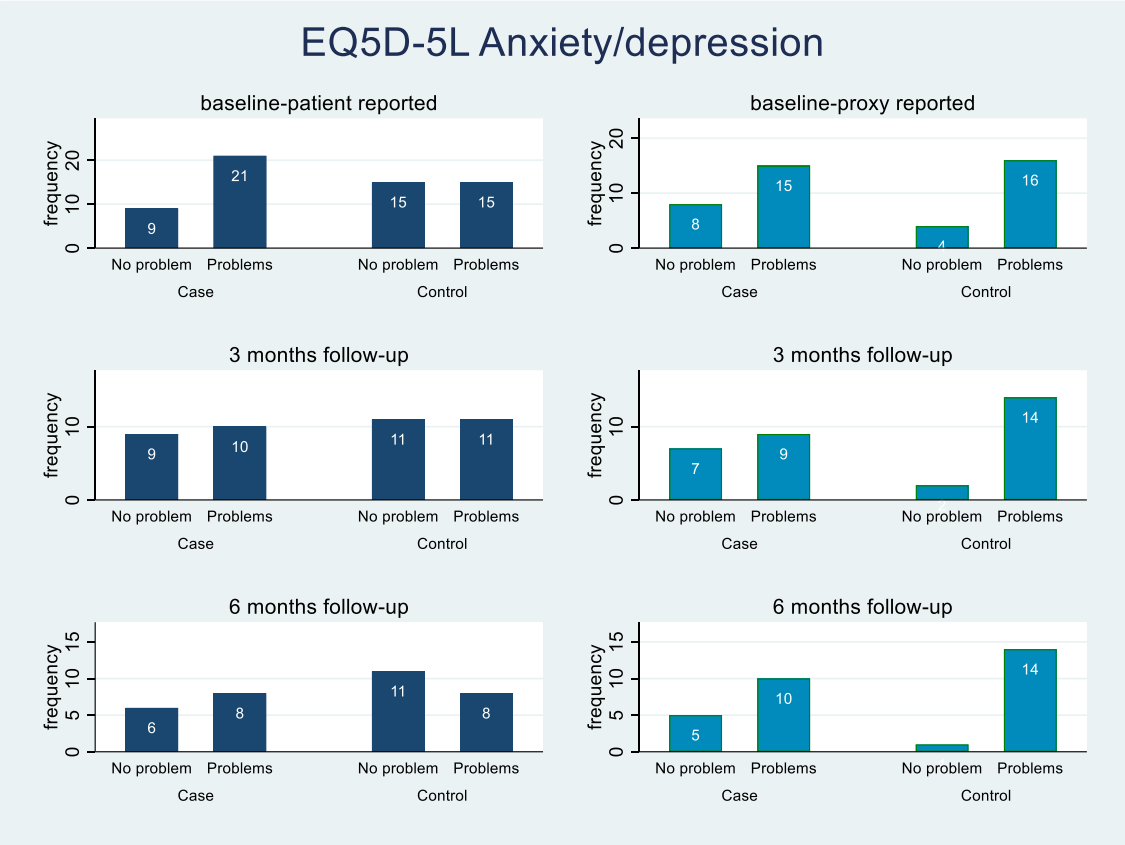

Fig 7: EQ5D-5L: usual activity (no problems vs problems)

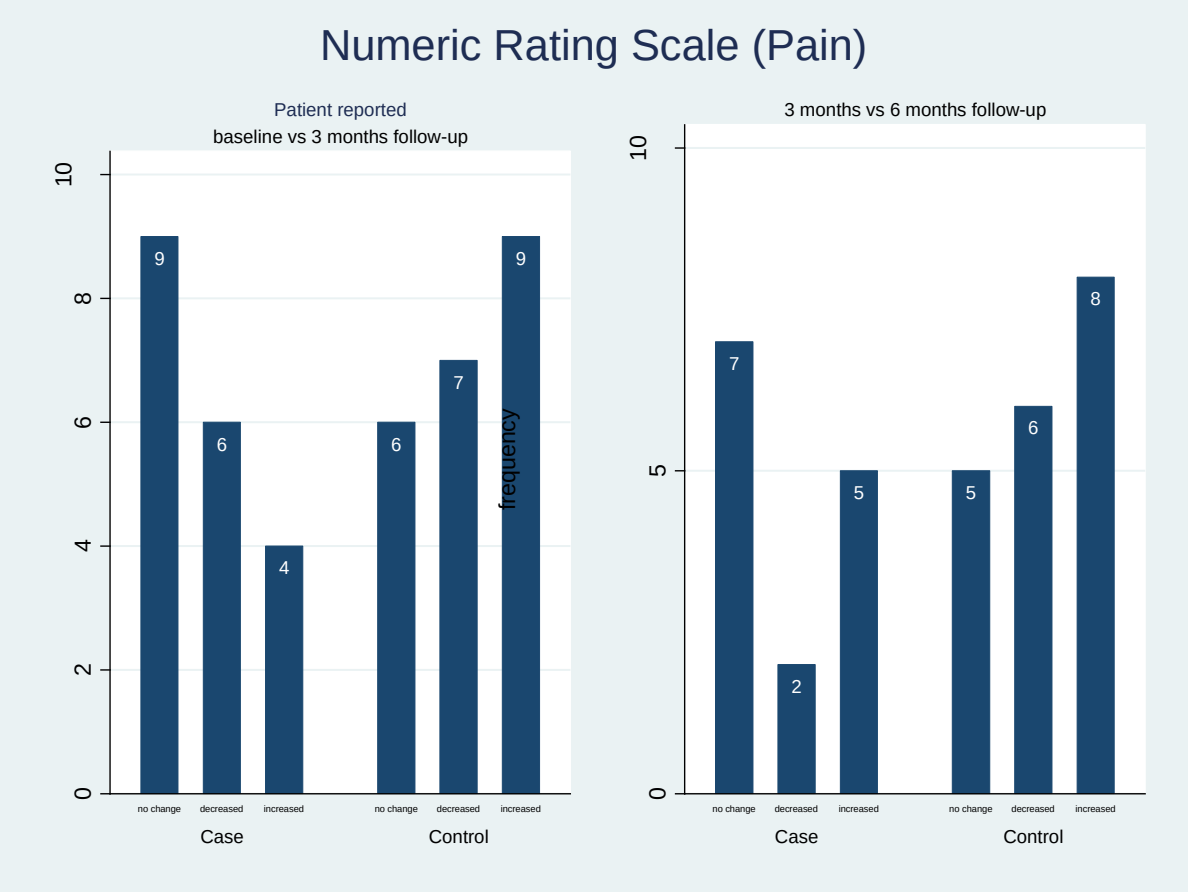

Fig 7: Numeric rating scale: Change of score at each follow-up assessment

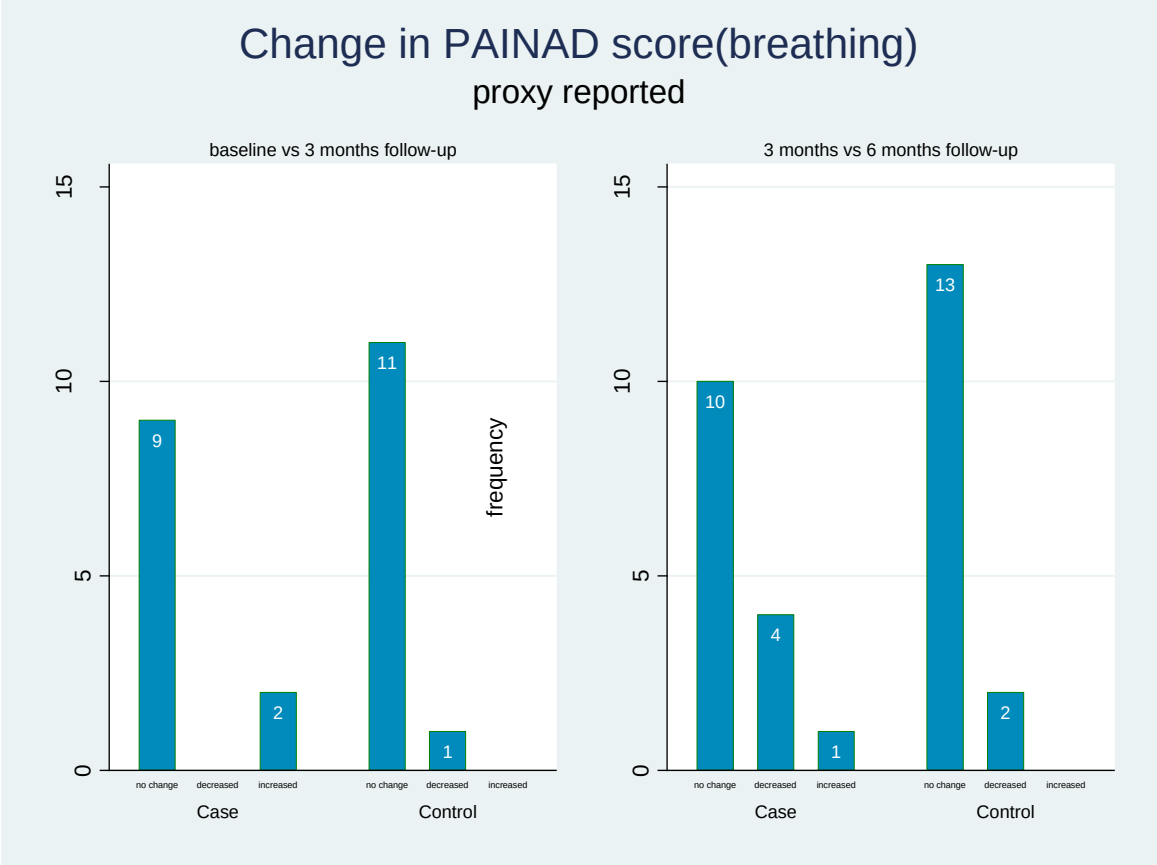

Fig 8: PAINAD (Breathing): Change of score at each follow-up assessment

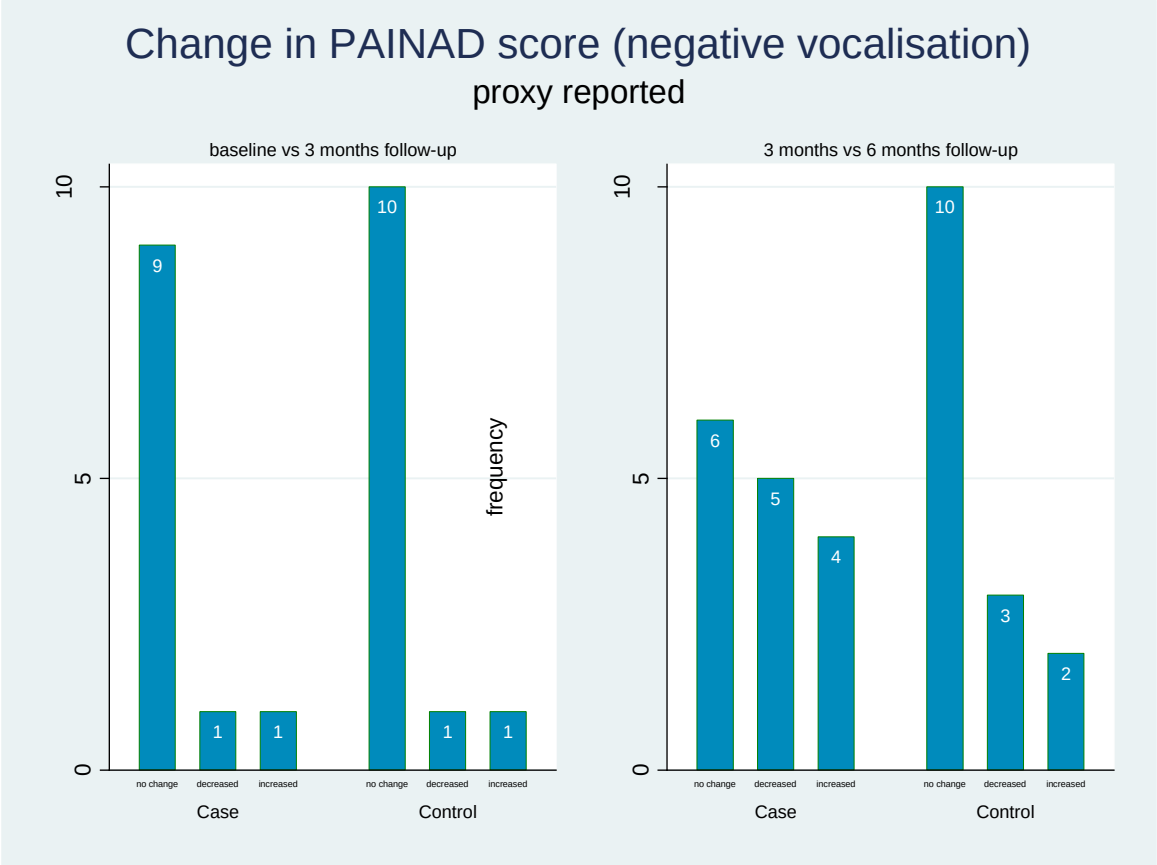

Fig 9: PAINAD (negative vocalisation): Change of score at each follow-up assessment

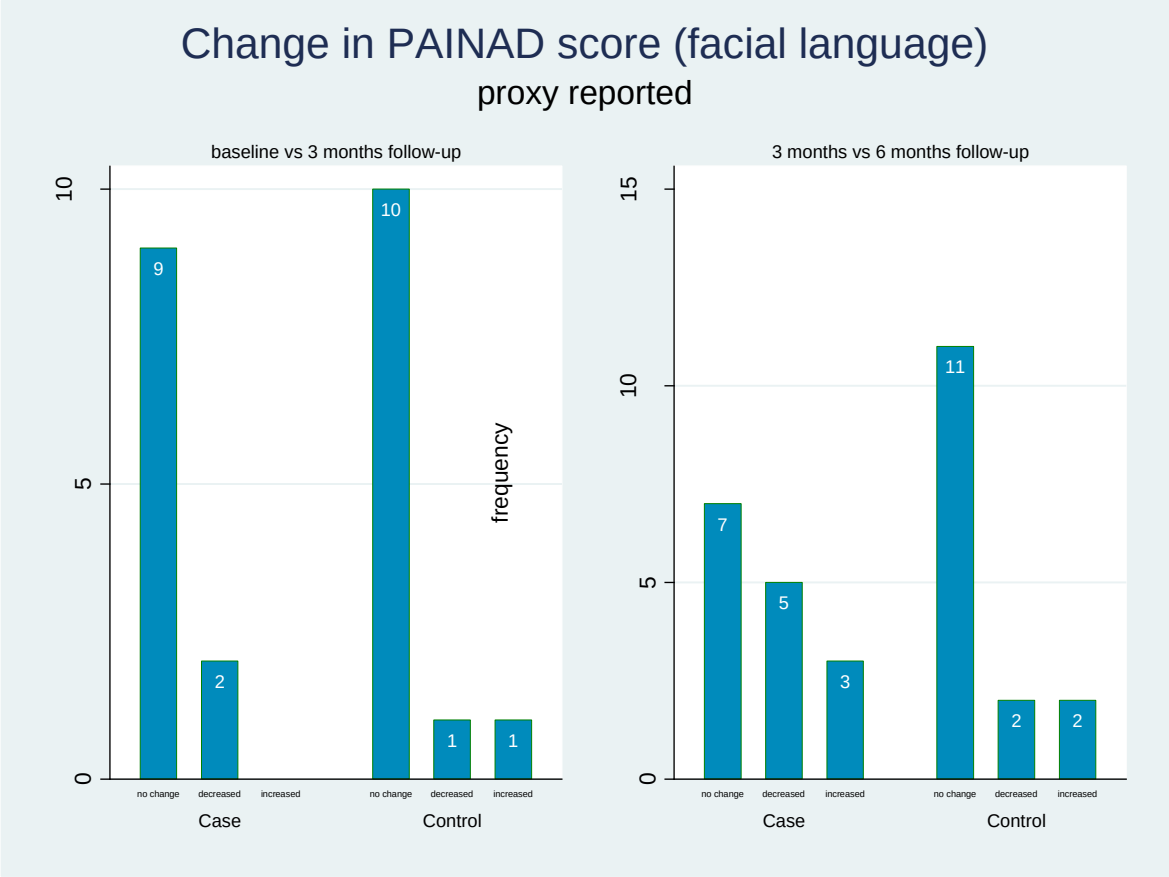

Fig 10: PAINAD (facial language): Change of score at each follow-up assessment

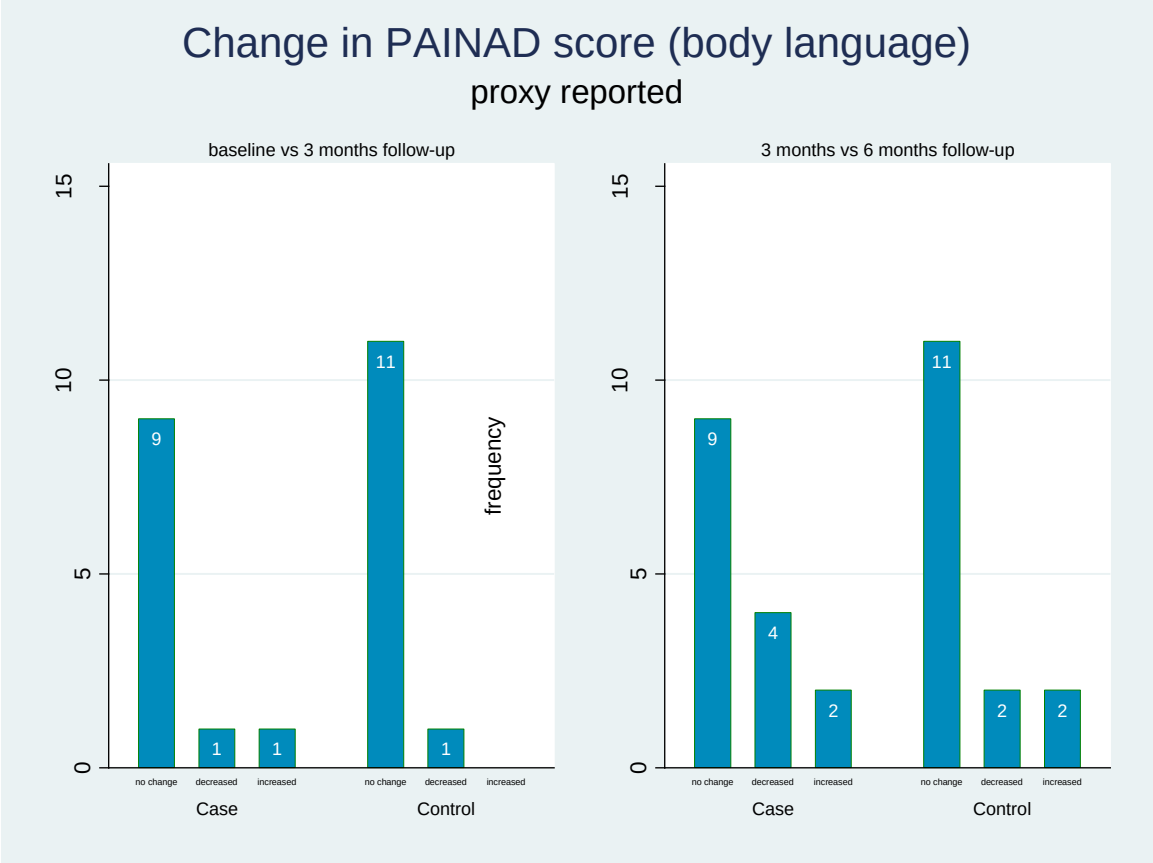

Fig 11: PAINAD (body language): Change of score at each follow-up assessment

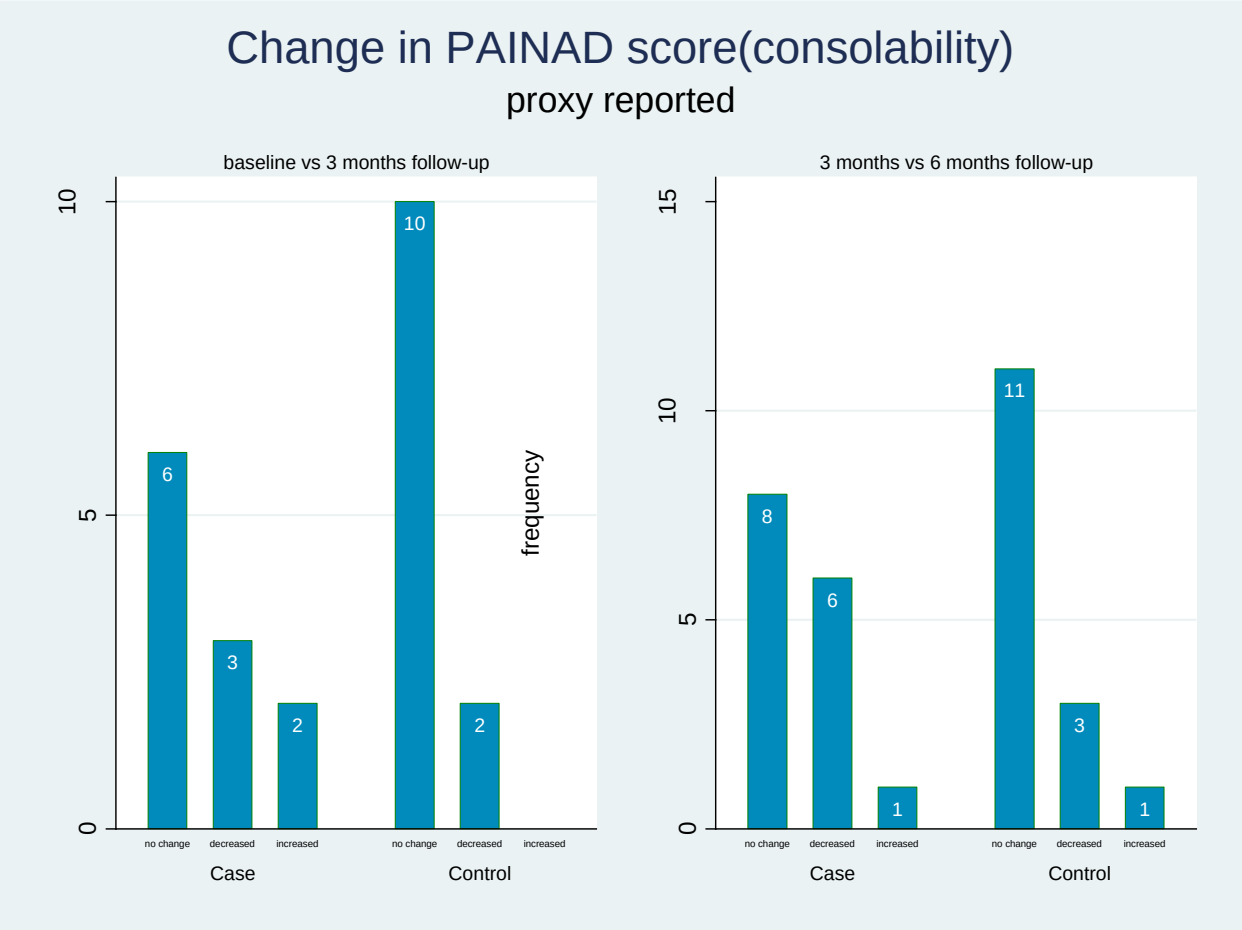

Fig 12: PAINAD (consolability): Change of score at each follow-up assessment

Fig 3: EQ5D-5L: mobility no problems vs problems

Appendix 24: Summary of cause of Death by Study Group

Cause of death	Cases (n=24)	Control (n=16)
CKD	4.0 (66.7)	2.0 (33.3)
Embolism	1.0 (100.0)	0.0
Multi organ failure	1.0 (100.0)	0.0
Pneumonia	3.0(60.0)	2.0 (40.0)
Respiratory failure	1.0 (50.0)	1.0 (50.0)
Dementia	3.0(50.0)	3.0(50.0)
HTN	4.0(57.1)	3.0 (42.9)
Heart Failure	1.0 (33.3)	2.0(66.7)
AF	2.0 (66.7)	1.0 (33.3)
CCF	0.0	1.0 (100.0)
CVA	1.0(100.0)	0.0
Cancer	2.0 (66.7)	1.0 (33.3)
Cardiac amyloidosis	1.0 (100.0)	0.0
PVD	1.0 (100.0)	0.0
DM	3.0(60.0)	2.0 (40.0)
UTI	1.0 (50.0)	1.0 (50.0)
AKI	4.0 (57.1)	3.0 (42.9)
Sepsis	2.0 (100.0)	0.0
Bowel perforation	0.0	1.0 (100.0)
Constipation	0.0	1.0 (100.0)
Osteomyelitis	1.0 (100.0)	
Frailty		2.0 (100.0)
Dysphagia	1.0 (100.0)	0.0
Cirrhosis	1.0 (100.0)	0.0
Unknown	11.0 (57.9)	8.0 (42.1)