**Methodology and value of measuring symptoms in dialysis patients: case study of chronic kidney disease associated pruritus**

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# Abbreviation

|  |  |
| --- | --- |
| CKD | Chronic kidney disease |
| CKD-aP | Chronic Kidney Disease associated pruritus |
| EAG | External Assessment Group |
| ESKD | End-stage kidney disease |
| HRQoL | Health-related quality of life |
| KDQOL | Kidney Disease Quality of Life |
| NICE | National Institute for Health and Care Excellence |
| POS-S Renal | Palliative Outcome Scale-Symptoms Renal |
| PROMs | Patient reported outcome measures |
| SWCRT | Stepped Wedge Cluster Randomised Trial |
| QALY | Quality-adjusted life year |
| VRS | Verbal rating scale |
| WI-NRS | Worst Itching Intensity Numerical Rating Scale |

# Career Pathway

My journey in the field of renal medicine began in 2015 when I joined the Sheffield Kidney Institute as a renal speciality training doctor. It was during this time that I developed a keen interest in managing symptoms in people on haemodialysis (HD).

I commenced my journey with my first manuscript focusing on the symptom burden in people on HD, which I successfully published. This experience led me to a profound interest in the measurement of symptoms, prompting me to pursue a research fellowship opportunity, which ultimately led me to be seconded to SCHARR, actively engaging in research projects that have contributed to the papers included in this thesis. Recognising the challenges of pursuing a traditional PhD pathway alongside clinical duties, I decided to pursue a PhD by publication pathway. This approach allowed me to combine research activities with my training as a renal registrar.

Now, as I near the completion of my training as renal speciality trainee, I will apply for consultant position while continuing to contribute through my research to the clinical and academic knowledge base of symptom management in people on HD. My goal is to blend clinical practice with my experience in research, aiming to make meaningful advancements in the field and ultimately improve patient care and outcomes.

# Lists of papers informing this thesis

In this thesis, I am incorporating four published papers and one manuscript, which has undergone peer review as additional materials. The full texts of all included manuscripts can be found in the appendix section.

**Paper 1:** **Symptom burden according to dialysis day of the week in three times a week haemodialysis patients** (1)

Pann Ei Hnynn Si, Rachel Gair, Tania Barnes, Louese Dunn, Sonia Lee, Steven Ariss, Stephen J. Walters, Martin Wilkie , James Fotheringham : Symptom burden according to dialysis day of the week in three times a week haemodialysis patients. PLOS ONE 17(9): e0274599. <https://doi.org/10.1371/journal.pone.0274599>

**Paper 2:** **The trajectory of a range of commonly captured symptoms with standard care in people with kidney failure receiving haemodialysis: consideration for clinical trial design** (2)

Pann Ei Hnynn Si, Mónica Hernández-Alava, Louese Dunn, Martin Wilkie & James Fotheringham : The trajectory of a range of commonly captured symptoms with standard care in people with kidney failure receiving haemodialysis: consideration for clinical trial design. BMC Nephrol 24, 341 (2023). <https://doi.org/10.1186/s12882-023-03394-w>

**Paper 3:** **Relationship Between Standardised Measures of Chronic Kidney Disease-associated Pruritus Intensity and Health-related Quality of Life Measured with the EQ-5D Questionnaire** (3)

Hernandez Alava, Monica, Alessandro Sasso, Pann Ei Hnynn Si, Matthew Gittus, Richard Powell, Louese Dunn, Praveen Thokala, and James Fotheringham. 2023. “Relationship Between Standardised Measures of Chronic Kidney Disease-Associated Pruritus Intensity and Health-Related Quality of Life Measured With the EQ-5D Questionnaire: A Mapping Study”. Acta Dermato-Venereologica 103 (September): https://doi.org/10.2340/actadv.v103.11604.

**Paper 4:** **Cost Effectiveness of Difelikefalin Compared to Standard Care for Treating Chronic Kidney Disease Associated Pruritus (CKD-aP) in People with Kidney Failure Receiving Haemodialysis** (4)

Praveen Thokala, Pann Ei Hnynn Si, Monica Hernandez Alava, Alessandro Sasso, Thilo Schaufler, Marco Soro & James Fotheringham. Cost Effectiveness of Difelikefalin Compared to Standard Care for Treating Chronic Kidney Disease Associated Pruritus (CKD-aP) in People with Kidney Failure Receiving Haemodialysis. PharmacoEconomics 41, 457–466 (2023). <https://doi.org/10.1007/s40273-022-01237-4>

**Additional material: Health care resource use relating to chronic kidney disease associated pruritus informed by UK real world and clinical trial datasets. This manuscript has gone through peer review process and not been published.**

Pann Ei Hnynn Si, Mónica Hernández-Alava, Marco Soro, Thilo Schaufler, Matthew Gittus, Richard Powell, Louese Dunn, Martin Wilkie, James Fotheringham.

# Abstract

People on haemodialysis (HD) experience significant symptom burden and effects on health-related quality of life (HRQoL). Chronic Kidney Disease associated pruritus (CKD-aP) is one of the common symptoms reported by HD patients. In the UK, patient reported outcome measures (PROMs) are not routinely measured in HD populations. Neglecting to assess and manage symptoms in this cohort, notably CKD-aP, has been shown to prolonged suffering, increased healthcare utilisation, and higher healthcare costs, significantly impacting patients' overall HRQoL and healthcare outcomes.

Hence, this thesis examines these aspects through primary data analysis, a mapping study involving established PROMs for CKD-aP, as well as secondary data analysis from an observational longitudinal study, the SHAREHD trial.

The first manuscript highlights the significance of standardising the timing of symptom assessment measures to accurately capture their dynamics and impact on PROMs. The second manuscript explores the symptoms trajectory in prevalent HD patients, emphasising the importance of considering symptom improvements with standard care in clinical trial design. The third study suggests that pruritus instruments should include additional domains beyond severity to align more closely with generic HRQoL measures such as EQ-5D. The fourth manuscript assesses the cost-effectiveness of Difelikefalin, offering its value in addressing the disease burden of CKD-aP among people on HD and the 5th manuscript explores the economic dimensions of CKD-aP, revealing significant healthcare costs and unmet need.

The overall recommendation resulting from this work emphasises the importance for healthcare practitioners and researchers to use standardised measurement methods and comprehensive assessments when dealing with symptoms in people on HD, particularly CKD-aP. Understanding how symptoms evolve over time and how they interact with economic factors and HRQoL is crucial for optimising patient care and resource allocation. Understanding cost effectiveness and unmet needs in terms of symptoms management enables more effective healthcare interventions to enhance HRQoL and allocate resources efficiently among diverse populations.

# Chapter 1: Introduction

Chronic Kidney Disease (CKD) is a global public health concern, affecting millions of individuals worldwide, with an increasing prevalence that is projected to continue growing in the coming years (5). As CKD progresses, people with kidney disease often require renal replacement therapy, and haemodialysis (HD) becomes a life-sustaining intervention for those with end-stage kidney disease (ESKD). Although HD has significantly extended the lives of people with CKD, it is associated with challenges, including a range of debilitating symptoms that can profoundly impact their quality of life (6).

Among the symptoms reported by people on HD, chronic kidney disease associate pruritus (CKD-aP) is a particularly distressing and debilitating condition, characterised by relentless itching of the skin. CKD-aP affects a substantial proportion of people on HD, with prevalence estimates ranging from 30% to 70% (7). This distressing symptom not only leads to physical discomfort but also carries profound psychological and social implications, often diminishing the overall well-being of affected individuals (8).

The significance of addressing CKD-aP extends beyond mere symptom relief; it underscores the broader issue of recognising the importance of measuring symptoms in people on HD comprehensively. Symptoms refer to not just physical discomfort, but also encompass emotional and psychosocial factors. These aspects can influence patients' adherence to treatment, their overall satisfaction with care, the economic burden, and, consequently, clinical outcomes. Emotional distress or psychosocial stressors, such as anxiety or depression, can lead to decreased motivation or engagement in treatment, potentially impacting treatment adherence and, subsequently, clinical outcomes (9,10).

In the UK, Patient Reported Outcome Measures (PROMs) are not routinely collected for people on HD. This lack of routine measurement is highlighted in several studies and reports (11). While symptoms are common in people on HD, there is significant variation in their assessment and documentation among healthcare professionals (12) . PROMs provide valuable insights into patients' subjective experiences, including their symptoms, functioning, and quality of life, which may not be captured through traditional clinical assessments alone. By systematically collecting PROMs data, healthcare providers can better understand the symptom burden and overall well-being of people on HD, allowing for more personalised and patient-centred care. Additionally, PROMs can serve as important indicators of treatment effectiveness, helping healthcare professionals assess the impact of interventions and tailor treatment plans accordingly. Therefore, the lack of routine measurement of PROMs for people on HD in the UK suggests a potential gap in the assessment and management of symptoms, which could impede efforts to optimise patient outcomes and quality of life in this population.

This thesis entitled "Methodology and Value of Measuring Symptoms in Dialysis Patients: Case Study of Chronic Kidney Disease-Associated Pruritus," is a comprehensive examination of symptom measurement in people on HD, with a particular emphasis on CKD-aP. Through a series of related research papers, it addresses important aspects of symptom assessment, the trajectories of symptoms over time, and the utilisation of healthcare resources in the context of CKD-aP and HD. The primary objective is to refine the methodology for measuring symptoms in HD and CKD populations by developing a comprehensive framework that covers various dimensions of symptom evaluation, such as optimal assessment timing, understanding symptom change and trajectories of symptoms in response to standard HD treatment, and identifying patterns of improvement or exacerbation. As a case study, it investigates how CKD-aP measures correlate to generic HRQoL measures and emphasises the value of measuring these symptoms by highlighting their economic impact and estimating the potential reduction in economic burden through CKD-aP treatment measures.

The thesis comprises four published papers along with an analysis of healthcare resource utilisation that has undergone peer review. Details of the two datasets used in these papers are described in chapter 3. These papers are interlinked, building upon each other to address gaps in the literature regarding systematic symptom measurement to reduce bias and capture the impact of HRQoL, as well as the value of symptom measurement in reducing the economic burden of CKD-aP.

The chapters within the thesis include the detailed review on symptoms in people on HD and a detailed narrative behind the included publications, outlining the methods employed and the author's contributions to each study.

# Chapter 2: Literature review on symptoms in people on HD

This chapter is structured to provide the understanding of symptom measurement and its implications for individuals undergoing HD, particularly focusing on CKD-aP. The preceding section highlights the significance of symptom measurement in people on HD to capture the dynamic nature of symptoms. Building upon this, the subsequent section delves into the specific measures used to assess symptoms in HD population, CKD-aP severity and HRQoL. It explores disease-specific instruments alongside generic measures, outlining their application, key domains, recall periods, and validation studies to assess their effectiveness in capturing the broader impact of CKD-aP on patients' lives. Furthermore, this chapter discusses the health economic implications and disease burden associated with CKD-aP, elucidating the considerable financial burden and resource utilisation challenges attributed by individuals with varying degrees of CKD-aP severity. It highlights the importance of evaluating the cost-effectiveness of interventions for CKD-aP to inform decision-making processes and optimise resource allocation within healthcare system. It also delves into the profound impact on patients' quality of life, emphasising how the disease burden extends beyond economic factors to affect daily functioning, emotional well-being, and overall health outcomes.

## 2.1 Symptoms in people on HD

### 2.1.1 Importance of symptom measuring

Understanding the spectrum of symptoms experienced by people on HD is crucial for providing comprehensive care. The symptoms in this population vary widely and can significantly impact their quality of life and treatment outcomes (13). Effective symptom management strategies, such as multidisciplinary approaches and tailored therapies, have demonstrated promise in alleviating symptoms and enhancing HRQoL in HD patients (14). Thus, symptom measurement serves as a cornerstone for developing and implementing interventions that address the dynamic nature of symptoms and promote better patient care and outcomes (15).

### 2.1.2 Role of PROMs

PROMs play a crucial role in assessing the experiences of patients, capturing various aspects of health status, symptoms, functional abilities, and quality of life directly reported by patients themselves. Using validated instruments and adhering to principles of standardisation in measurement is crucial for several reasons. Firstly, validated tools applied in standardised settings (either on HD days or non- HD days) ensure consistency and comparability across different studies and populations, allowing for meaningful comparisons and generalisability of findings. Moreover, it promotes reliability and validity, enhancing the accuracy and credibility of collected data, thus increasing the reliability and robustness of study results (16). It is noteworthy that, in many cases, the content validity ( the extent to which a test or measure covers all relevant aspects of the concept being assessed) of PROMs is assumed based on face validity (the degree to which a test appears, on the surface, to measure what it claims to measure) rather than being rigorously examined by users (17). While face validity provides an intuitive assessment of a measure’s relevance, deeper exploration of content validity through systematic patient and expert involvement is often lacking. This highlights the need for greater scrutiny in understanding how these scales were developed and adopted and the implications of their use in clinical and research settings. Failure to critically assess the validation process may result in reliance on tools that do not comprehensively capture the intended constructs or that perform inconsistently across different patient populations. Researchers and clinicians must therefore ensure that PROMs are appropriately validated and suited for their specific contexts before integrating them into patient care and decision-making processes. I provided a detailed discussion of each instrument used in this thesis, along with their validation references, in Tables 1 and 2.

### 2.1.3 Significance of symptoms in people on HD

PROMs in HD populations are particularly important due to the significant impact they have on treatment decisions and symptom burden management. People on HD often experience a wide range of symptoms and complications associated with their underlying disease as well as treatment related complications and decreased HRQoL. By routinely collecting PROMs, healthcare providers can systematically monitor the severity and progression of these symptoms, enabling early detection of changes and prompt intervention. This allows for timely adjustments to treatment regimens, such as medication dosages or dialysis prescriptions, tailored to address individual patient needs. By integrating these measures into routine care, healthcare providers are in a position to incorporate patient perspectives in decision-making, fostering a more collaborative approach to treatment. Without routine assessment, healthcare providers may overlook changes in symptom severity, potentially leading to inadequate symptom management and poorer patient experiences. Additionally, failing to address symptom burden in a timely manner may result in decreased treatment adherence, increased healthcare utilisation, and reduced quality of life for patients (17). For instance, studies have shown that patients with CKD-aP often experience substantial impaired HRQoL and without regular measurement and intervention, CKD-aP can lead to persistent itching, sleep disturbances, and psychological distress, significantly impacting patients' overall well-being (17). These challenges can affect treatment adherence, creating a cycle where poor adherence exacerbates symptoms associated with being undertreated on HD, further diminishing quality of life.

### 2.1.4 Assessment Tools for evaluating Symptoms and HRQoL

Various assessment tools are available to evaluate symptoms and HRQoL in CKD and people on HD, including the Palliative Outcome Scale-Symptoms Renal (POS-S Renal), EQ-5D questionnaire, Kidney Disease Quality of Life (KDQOL) Instrument, and Short-Form Health Survey (SF-36 or SF-12) (18–21) . Disease-specific tools like POS-S Renal and KDQOL offer focused insights relevant to CKD and HD, whereas generic tools like EQ-5D and SF-36 allow for broader comparisons across diverse populations. In this section I will provide a detailed overview of the assessment tools (POS-S Renal and EQ-5D) used in this thesis to evaluate symptoms and HRQoL in people undergoing HD (Table 1). Additionally, in session 2.2.1, I will focus specifically on the disease-specific instruments used to assess CKD-aP (Table 2).

**Table 1: Summary of assessment tools used in this thesis for measuring symptoms in HD patients and HRQoL**

|  |  |  |  |
| --- | --- | --- | --- |
| Instruments | Details/domains | Scoring and recall period | Validation studies |
| POS-S Renal (22,23) | This instrument specifically targets symptoms experienced by individuals with renal conditions. It focuses on of 17 symptoms: weakness, poor mobility, pain, difficulty sleeping, breathlessness, drowsiness, feeling anxious, itching, dry mouth, restless legs, feeling depressed, poor appetite, changes in skin, constipation, nausea, diarrhoea and vomiting. | Each symptom is scored on a 5-level ordinal verbal rating scale (none, mild, moderate, severe and overwhelming). Recall period is 7 days. | The POS-S has undergone thorough psychometric evaluation, demonstrating strong validity and reliable internal consistency as well as test–retest reliability in diverse settings (24–26). It has been translated, culturally adapted, and validated in fourteen languages, making it widely utilised on an international scale (22,27,28) |

|  |  |  |  |
| --- | --- | --- | --- |
| EQ-5D(29) | A generic measure of HRQoL that includes a descriptive system comprising five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Respondents rate each dimension by selecting a severity level.  EQ-5D-3L: Offers three levels of severity for each dimension: no problems, some problems, and extreme problems.  EQ-5D-5L: Expands the scale to five levels, ranging from no problems to unbearable or being unable to perform the domain. | From these responses, a utility scale ranging from zero to one can be calculated, where zero represents death and one represents perfect health. The EQ-5D-5L typically uses a recall period of "today," capturing the respondent's health state at the time of completion focusing on the individual’s current health state. While the EQ-5D-3L has been tested in recall mode, the EuroQol Group intentionally prioritised immediate health status measurement (30). This approach ensures the instrument accurately reflects the respondent's present condition, as emphasised by its focus on "your health today." (31,32) | The EQ-5D has demonstrated strong validity and reliability in various populations, including those with chronic diseases and renal disease (33,34) Studies such as Janssen et al. (34,35) confirmed its enhanced sensitivity and reliability, with test-retest reliability showing intraclass correlation coefficients (ICCs) ranging from 0.75 to 0.90.  In the mapping study, due to concerns about the EQ-5D-5L value set, EQ-5D-5L responses were converted into EQ-5D-3L UK utility values using the van Hout crosswalk, in line with NICE guidance at the time (36). |

### 2.1.5 Standardisation in measuring symptoms using validated instruments

Despite the utility of these assessment tools in trials, there is currently no standardisation regarding the timing or location of their collection in relation to the dialysis schedule. Studies have shown that symptoms in people on HD can fluctuate in severity over time, highlighting the importance of repeated assessments to capture these dynamic changes effectively (17). For instance, symptoms like pain, fatigue, and pruritus have been reported to fluctuate more, highlighting the need for frequent monitoring and tailored interventions to address symptom management effectively (4). On the other hand, certain symptoms such as depression or anxiety may exhibit more stability over time. Understanding these fluctuations and stability patterns is essential for optimising symptom management strategies and improving HRQoL. This lack of standardisation in terms of location and timing in relation to HD schedule in measuring symptoms could introduce bias and result in conflicting results, prompting further investigation for symptom assessment.

Various PROMs used in dialysis and CKD patients may differ in their recall periods, which can impact the accuracy of reported symptoms and can influence the reported severity of symptoms, especially considering the fluctuating nature of symptoms in this population. The rapid evolution of symptoms, such as pain, fatigue, or pruritus, can vary significantly within shorter time frames, potentially leading to differences between PROMs depending on their recall periods. Hence, comprehending the dynamic trajectory of symptom evolution and establishing a standardised framework for measuring symptoms in HD patients may represent a potential opportunity for accurate assessment, tailored interventions, and ultimately, improved patient outcomes. Failure to do so can introduce various threats, particularly the accuracy and reliability of symptom assessment as well as, a risk of inconsistency and variability in reported symptoms, leading to discrepancies in data interpretation. When PROMs are not used appropriately or consistently, there is a risk of failing to capture the full spectrum of symptoms experienced by HD patients, leading to an incomplete assessment of patient burden. In addition, inconsistencies in how they are used can create variations which can reduce the precision of statistical comparisons and weaken the reliability of findings. This can limit healthcare providers’ ability to effectively assess and address patient needs. In the following section, we explore CKD-aP, a debilitating symptom in HD patients, discussing its prevalence and profound impact on HRQoL to justify focusing on CKD-aP as a case study.

## 2.2 Chronic Kidney Disease-Associated Pruritus (CKD-aP)

This review focuses on understanding the measures used to assess CKD-aP, its impact on HRQoL, and the economic implications associated with its management. CKD-aP affects approximately 80% of people with ESKD, with 37% reporting moderate to severe degree of pruritus (37). It is associated with poor HRQoL, impaired sleep, depression, and increased mortality (7). The pathogenesis of pruritus in people with ESKD receiving HD is multifactorial, with theories underlying the cause of pruritus including metabolic disequilibrium, endocrine disorders, iron deficiency anaemia and inadequate dialysis (7). Studies have also shown that relative to those with less severe CKD-aP, patients with moderate to severe CKD-aP incur substantial healthcare resource use through a range of other mechanisms including their medications, hospital admission for symptom management and associated skin infection and psychological distress requiring more frequent specialist review and consultations (38). Unfortunately, CKD-aP is a chronic condition where individuals continue to have this symptom for months, even years in some (39). This prolonged persistence of CKD-aP can be attributed to various factors, notably its under-recognition and under-reporting in clinical settings. Additionally, the multifactorial nature of CKD-aP, involving complex physiological mechanisms and diverse symptom presentations, contributes to its chronicity. Furthermore, inadequate management strategies, limited access to effective treatments and the lack of routine measurement and standardised assessment protocols delaying timely intervention exacerbate the chronicity of symptoms.

### 2.2.1 CKD-aP disease specific instruments

Various disease specific instruments are utilised to measure CKD-aP severity and its impact on patients' lives. Among these, the severity-based verbal rating scale (VRS) and Worst Itching Intensity Numerical Rating Scale (WI-NRS) are commonly used to measure the intensity of pruritus symptoms. These instruments primarily focus on quantifying the severity of itching experienced by patients. Additionally, disease-specific quality of life measures, such as the 5-D itch and SKINDEX-10, provide a multidimensional assessment of how CKD-aP affects various aspects of patients' lives beyond just symptom severity. Table 2 explored these measures in greater detail in the following sections.

**Table 2: CKD-aP instruments**

|  |  |  |  |
| --- | --- | --- | --- |
| Instruments | Details/domains | Scoring and recall period | Validation studies |
| Worst Itching Intensity Numerical Rating Scale (WI-NRS)(40) | WI-NRS asks the respondent to indicate the highest intensity of their pruritus over the last 24 hours. | Scoring from 0 (no itching) to 10 (worst itching imaginable) and recall period is last 24 hours. | Strong reliability, with consistent results across test-retest evaluations, and a high correlation with other itch measures, confirming its validity. A reduction of 3 or more points on the scale was identified as a meaningful improvement in itch intensity, as confirmed by patient feedback (41–43) |
| Verbal rating scale (VRS) (44) | VRS asks the respondents to report over the last week how much their itching bothers them. | Ordinal scale (None, slightly, moderately, severely and overwhelmingly). Recall period is last week. | Studies have demonstrated that the VRS is a reliable and validated tool for assessing itch intensity across various conditions, including chronic pruritus and CKD-associated pruritus. It has shown strong validity, correlating well with other itch measurement tools, and has been widely used in clinical and research settings (41,43,45) |
| 5-D itch (46) | The 5-D itch scale is a 5-domain disease-specific instrument evaluating the duration, degree (severity in 5-level VRS), direction (improving, unaltered or worsening), disability (impact on sleep, leisure/social, housework/errands and school/work activities) and distribution (body part affected). | Each dimension is scored individually, and the total score ranges from **5 to 25**, with higher scores indicating greater itch burden. Recall period is 2 weeks. | Elam et.al (47) demonstrated 5D-Itch has strong correlations with the Visual Analogue Scale (VAS) at multiple time points (baseline, 3-day repeat and 6-week follow up). The scale also exhibited high test-retest reliability, as shown in a subset of untreated patients whose mean 5-D scores remained unchanged between day 1 and day 3 (ICC = 0.96). Validation across three ethnic groups confirmed its sound psychometric properties and its close relationship to other measures such as the WI-NRS(47,48). |
| SKINDEX-10 (49) | The Skindex-10 is a concise, patient-reported questionnaire designed to assess the impact of skin conditions, including pruritus, on patients' quality of life. It comprises 10 items that evaluate how frequently patients have been bothered by specific skin-related issues over the past week | Each item is rated on a 7-point Likert scale, ranging from 0 ("never bothered") to 6 ("always bothered"). The total score ranges from 0 to 60, with higher scores indicating a greater negative impact on quality of life. The recall period for the Skindex-10 is the **past week** | Validation studies have demonstrated that the Skindex-10 is a reliable and valid instrument for assessing the effects of skin diseases, including pruritus, on patients' quality of life (50–52) |

### 2.2.2 Relationship between CKD-aP and HRQoL measures

Studies using disease-specific instruments to assess CKD-aP have revealed a strong correlation between worsening pruritus and decreased generic health related quality of life measures, such as the EQ-5D (7). Although disease-specific quality of life measures, such as the 5-D itch and SKINDEX-10 capture domains including severity and how pruritus affects body parts, mental health and social functioning, they are not the preferred measures when evaluating the cost-effectiveness of therapies. Reimbursement agencies and other decision-makers prefer generic instruments such as EQ-5D for cost-utility analyses due to their ability to ensure consistent decision-making across different diseases, facilitating comparisons of healthcare interventions and resource allocation across diverse patient populations (32). Many health economic models that have led to successful policy decisions on dermatological treatments have adopted a severity-focused structure and been informed by generic measures of HRQoL (53). The extent to which disease-specific measures capturing the broader impact of CKD-aP on the patient relate to generic measures used for cost-effectiveness analyses is unknown. Understanding these relationships could inform the design, conduct and analyses of interventional and observational studies of HRQoL in people with CKD-aP, particularly when trying to determine the cost-effectiveness of treatments.

## 2.3 Recall period in PROMs

The recall period in PROMs is a critical factor in accurately assessing symptoms in HD patients, particularly given the nature of symptoms fluctuation. The selection of a recall period for a patient-reported outcome measure depends on several factors, including the nature of the disease or symptoms being measured, patient burden, recall ability, and the intended outcome measurement (54). Recall periods dictate the timeframe over which patients are asked to reflect on their symptoms, with commonly used durations including "today," "the past 24 hours," "the past week," or longer. People on HD often experience highly variable symptomatology, with symptoms being influenced by the HD treatment process, dietary changes and other comorbid conditions. Studies have shown that shorter recall periods, such as "the past 24 hours," may provide more accurate representations of symptom severity by minimising recall bias, however, they may fail to capture fluctuations over time, potentially leading to incomplete assessments of chronic conditions like CKD-aP (55). On the other hand, longer recall periods may lead to overgeneralisations or selective memory, as patients might disproportionately focus on the most severe or recent episodes of itching, ignoring periods of relative stability or mild symptoms (54–56). Patients may unconsciously emphasise or suppress certain symptom experiences due to memory limitations, cognitive load, or emotional responses. For instance, pruritus might feel more burdensome after a poor night's sleep or during a particularly stressful day, leading to exaggerated reporting when using longer recall periods. A systematic review by Arizmendi C, et al. highlighted the importance of aligning recall periods with the temporal nature of the symptoms being measured, particularly in chronic illnesses like ESKD (54). Recall bias can also complicate efforts to correlate patient-reported symptoms with objective clinical markers, such as inflammatory markers or dialysis adequacy as patients may overestimate or underestimate their symptoms due to recent experiences rather than their overall condition (57). This weakens the reliability of PROMs in both clinical practice and research, making it more challenging to draw meaningful conclusions or track symptom progression effectively. To mitigate recall bias in PROMs, several strategies can be employed (57,58). First, anchoring events can be used to help patients place their symptoms within a specific timeframe, such as recalling experiences relative to a major personal or public event (56). Second, using validated questions with clear timeframes in standardised settings (e.g., "In the past 7 days, how often did you experience pain?") help reduce variability in interpretation (57). Third, repeated measurements over shorter intervals rather than a single long-term recall assessment can improve the accuracy of symptom trajectories(58). Lastly, cross-referencing PROM responses with objective clinical data or caregiver reports can provide additional validation and improve reliability (54,56,58). By carefully selecting an appropriate recall period and implementing these strategies, researchers and clinicians can enhance the accuracy and clinical utility of PROMs while minimising recall bias.

## 2.4 Health Economic Implications associated with CKD-aP

Although the cost and service delivery implications of the direct management of CKD and ESKD are well characterised (59), little is known about healthcare resource utilisation in line with varying degrees of CKD-aP severity. The economic burden linked to CKD-aP is considerable, extending beyond direct healthcare expenses and indirect costs to encompass effects on resource utilisation and diminished health benefits. This includes reduced quality of life, the emotional toll of living with unmanaged symptoms, and limitations on daily activities. This assertion is supported by various studies that have highlighted the significant financial implications of managing CKD-aP, demonstrating pruritus among people on HD was associated with increased healthcare resource utilisation and higher costs (37) . Analysis of healthcare resource utilisation in patients with varying degrees of CKD-aP severity has highlighted increased medication use, particularly antipruritic medications, and its associated costs (38). Furthermore, patients with severe CKD-aP often require more frequent dialysis sessions as pruritus can be associated with higher levels of inflammation and uraemia, which may require more intensive dialysis, resulting in increased healthcare expenditures (38). Acknowledging the potential mechanisms through which a person with increasing severity of CKD-aP on HD may consume more healthcare resources is crucial. Understanding the costs associated with medications, dialysis duration, and frequency is important alongside existing knowledge on the negative impact on HRQoL, which more generally informs the health economics of CKD-aP and the value proposition of its treatment (60). A better understanding of resource use and its impact on HRQoL by treating CKD-aP may stimulate further research and lead to improvement in clinical practice.

Studies assessing the impact of CKD-aP treatment, such as Difelikefalin, have shown promising results in reducing CKD-aP severity and improving HRQoL (25). However, cost effectiveness of this new therapy compared to standard existing therapies for CKD-aP has not been explored. Evaluating the cost-effectiveness of interventions for CKD-aP is crucial, especially within the evolving area of healthcare where access to new technologies and the prioritisation of research efforts by both industry and academia. Economic evaluation plays a crucial role in assessing the value and impact of healthcare interventions, providing key insights for a range of stakeholders, including policymakers, healthcare providers, industries and commissioners, to guide decision-making processes. These evaluations aim to ensure the efficient allocation of resources within healthcare systems while considering the patients, whose outcomes ultimately define the success of an intervention. Decisions about whether patient outcomes have been improved are shaped by a combination of clinical evidence, patient-reported outcomes, and the priorities set by healthcare systems.

Health economic evaluation plays a pivotal role in balancing the costs of treatment against the human benefits, making it a valuable tool for understanding the broader impact of healthcare interventions. While costs, both direct and indirect, are often a focus of these analyses, it is equally crucial to emphasise the benefits that treatments can provide, particularly in chronic conditions like CKD-aP. These benefits extend beyond simple symptom relief, encompassing improvements in HRQoL, emotional well-being, social engagement, and overall daily functioning. By addressing the burden of pruritus, effective interventions have the potential to reduce healthcare resource utilisation and improve patient-reported outcomes, which are critical in determining the success of treatment strategies.

However, the benefits of effective pruritus management are not always straightforward or easily understood. The mechanisms linking good treatment to better clinical outcomes can be complex and multifactorial. For example, reducing pruritus may indirectly improve sleep quality, decrease anxiety or depression, and enhance a patient’s ability to participate in social or work-related activities. These improvements, while profoundly impactful on the patient’s personal life, may not immediately translate into measurable clinical outcomes, making them harder to quantify in traditional evaluations. Moreover, the subjective nature of patient-reported outcomes poses challenges in capturing the full scope of these benefits, highlighting the importance of using validated tools in standardised settings in health economic evaluations to effectively measure the symptoms. Such an approach ensures that both tangible clinical improvements and intangible quality-of-life gains are adequately captured and weighed.

In the subsequent chapter, I explore the contextual background of each included paper, elucidating my contributions to each study and presenting a condensed overview of their respective contents.

# Chapter 3: Contextual background and overview/summary of each paper each paper and, my contributions

In this chapter, I will provide details about the datasets used for the papers included in this thesis, summarise each paper, and outline my contributions to each study.

## 3.1 Datasets used to inform this thesis

The papers included in this thesis utilised two datasets: the SHAREHD and Mapping study.

### 3.1.1 SHAREHD (61,62)

This thesis stem from secondary analyses conducted on data derived from the SHAREHD, an observational longitudinal cohort study, a Stepped Wedge Cluster Randomised Trial (SWCRT). This trial aimed to evaluate a quality improvement collaborative designed to facilitate greater independence among individuals with kidney failure undergoing in-centre HD. Expanding patient involvement in treatment tasks offers numerous advantages. It enhances patient engagement, adherence, and satisfaction, while also optimising resource utilisation and reducing healthcare costs. The full study protocol, methodology, and results are detailed in related publications (61,62)

#### Study Design

A stepped-wedge cluster randomised trial was conducted across 12 UK renal centres, enrolling prevalent in-centre HD patients. The centres were randomised into early and late participation in a 12-month breakthrough series collaborative, which incorporated data collection, learning events, Plan-Do-Study-Act (PDSA) cycles, and teleconferences every six weeks. The intervention was supported by a dedicated faculty, co-production with stakeholders, educational materials, and a nursing course. The primary outcome was the proportion of patients performing five or more dialysis-related tasks or transitioning to home haemodialysis. Secondary outcomes included rates of independent haemodialysis, quality of life, symptom burden, patient activation, and hospitalisations. The evaluation lasted 18 months, with a subsequent six-month sustainability period, conducted across 12 renal centres in England. After a baseline control period of six months, six centres underwent the intervention immediately (step one), while the remaining six centres joined after an additional six months (step two). Data collection utilised The Think Kidneys Your Health Survey (YHS) questionnaires, including the POS-S Renal instrument and 5 domains of EQ5D-5L. Participants were asked to complete instruments at baseline, six, 12, and 18 months. Sociodemographic variables including age, gender, ethnicity and education were also collected. The Modified ESKD Charlson comorbidity index (CCI) score (63) was calculated using established algorithms and weights from hospitalisation data obtained through linkage to hospital episode statistics by the NHS Digital Data Access Request Service.

#### Setting

Trained, delegated research nurses gained written informed consent to participate from prevalent HD patients established on centre-based haemodialysis. The study adhered to the declaration of Helsinki, ethical approval was obtained from West London & GTAC Research Ethics Committee (IRAS project ID 212395) and the trial was registered (ISRCTN Number 93999549). This presented analysis was specified in the research protocol (61). The recruitment exclusion criteria were patients too unwell to engage in the study, as judged by the clinical team, or patients unable to understand written and verbal communication in English.

#### Outcome of the SHAREHD study

The intervention did not result in a substantial increase in dialysis-related tasks performed by the overall in-centre patient population. However, improvements were observed in the subgroup of patients performing fewer tasks at baseline and in the uptake of home haemodialysis.

#### My Role within SHAREHD trial

I did not have direct involvement with the SHAREHD study, as it was completed and its outcomes were published before my involvement. However, I have used data from a secondary analysis of the SHAREHD study to inform my thesis and papers 1, 2, 4 and 5. The use of this dataset aligns with the data availability statement provided in the original study, which ensures that data access and usage comply with established protocols. Specifically, the data required to reach the conclusions of the SHAREHD study involved the linkage of identifiable patient information collected during the trial to Hospital Episode Statistics (HES) data, as facilitated by NHS Digital's Data Access Request Service (NHS DARS). This process includes submitting an application to NHS DARS, detailing lawful processing of the dataset and the period for which HES data is required. NHS DARS verifies permissions through this application process, and data sharing agreements between the relevant parties enable data transfer from the University of Sheffield to NHS DARS, and ultimately to researchers conducting the analyses.

Given these safeguards and the protocols outlined in the data availability statement, my use of the SHAREHD dataset is protected and lawful, provided it complies with these conditions

### 3.1.2 Mapping Study (64)

#### Study Design and settings

This study is a cross-sectional study collecting established PROMs which assess pruritus using the WI-NRS, 5D-itch, and HRQoL assessed through the EQ-5D across five UK renal centres between November 2020 and July 2021. The primary objective of this study was to measure the relationship between each of these pruritus measures and EQ-5D to identify which pruritus measure is the most sensitive to changes in HRQoL and then to generate a mapping between one or more of these pruritus measures and the EQ-5D. Ethical approval for the study was granted by the North West – Greater Manchester Ethics Committee (Integrated Research Application System Reference: 285714), and written informed consent was obtained from all participants. Eligible participants were adults over the age of 18 years who had been on in-centre haemodialysis for kidney failure for more than three months. Individuals unable to provide informed consent or comprehend written English were excluded. Importantly, current or past experience of pruritus was not an inclusion criterion, as the study sought to quantify the benefits of both having and not having CKD-aP. Participants were given questionnaires to complete during the initial encounter or at home, with assistance provided to those completing the forms during dialysis, particularly patients unable to fill out the forms due to dialysis-related physical limitations.

#### Data collection and Instruments

The study collected four pruritus-related measures (WI-NRS, 5D-Itch, VRS, and Skindex-10) alongside EQ-5D-5L data. While VRS and Skindex-10 were not included in the mapping analysis, they played a crucial role in data verification and cleaning. The EQ-5D-5L responses were converted into country-specific utility values, ranging from negative values (health states worse than death) to 1 (perfect health), enabling health economic evaluations and comparisons of health-related quality of life (HRQoL) among individuals with chronic conditions. In addition to pruritus severity, data on patient demographics, comorbidities, dialysis prescriptions, and CKD-aP-related medication use were documented; however, information on other skin conditions was not collected.

The sample size was determined based on the requirements of the mapping models, ensuring sufficient representation across the full spectrum of CKD-aP severity. Data from the SHAREHD randomised controlled trial were used to estimate the number of participants needed, leveraging EQ-5D-5L scores and a pruritus severity scale ranging from none to overwhelming, allowing for the design of mixture distribution models. The sampling strategy aimed to ensure a representative cohort of haemodialysis patients with varying levels of CKD-aP severity. Of the 523 individuals approached, 487 consented to participate (93% engagement rate), reducing the risk of non-response bias. However, the exclusion of individuals with language barriers or cognitive impairment may limit the inclusivity of the dataset.

Patients reporting a 5-D itch score of 5 were identified as those who had no pruritus over the past two weeks and considered their itching completely resolved compared to the previous month. The most common score on the 5-D itch index was 8, often reported by participants without recent pruritus experience. However, a subgroup of 65 participants selected "Not present" in the degree dimension while indicating "unchanged" (score of 4) in the direction dimension, rather than the more accurate "completely resolved" option. This inconsistency led to an artificially inflated score of 8 on the 5-D itch scale. Since individuals without prior or current pruritus may not accurately represent the population relevant to the mapping study, they were excluded from further analyses, resulting in a final sample size of 377 observations. Further details on the study protocol, methodology, and results can be found in the related publication(64).

#### My Role within Mapping study

My contribution to the mapping study included initial involvement in writing the protocol for the study. However, due to the timing of my out-of-program approval, I was unable to participate in the data collection phase when the project commenced. Despite this, I played a significant role in subsequent stages, including data entry, data curation, analysis, and dissemination of findings. The details of my involvement in each paper published from this study are outlined in the following section, under the description of each respective paper.

## 3.2 Contextual background and my contributions to each paper

### 3.2.1 My Contributions to paper 1 and 2 (paper 1: symptom burden in relation to dialysis day of the week and paper 2: Symptom trajectory)

My interest in understanding and addressing the symptom burden experienced by people on HD derived from witnessing the impact that symptoms such as pruritus, fatigue, and pain could have on patients' quality of life and overall well-being. Using POS-S Renal data from SHAREHD, I conducted an analysis to investigate potential variations in symptoms based on the dialysis day of the week to inform the findings of paper 1 in this thesis. Following this, I developed a keen interest in symptomatology within the HD population and utilised the same dataset developing an analytical plan aimed at examining how symptoms evolve over time, leading to the development of paper 2. In the SHAREHD study, Your Health Survey (YHS) questionnaires were collected at four time points, providing ample data to evaluate longitudinal changes in symptoms in response to standard dialysis treatment. This analysis contributed to identifying certain symptoms that exhibited clinically meaningful shifts, both at the population and individual levels, I have used data from a secondary analysis of the SHAREHD study to inform my thesis As the first author of these two papers, my contributions to these 2 papers include:

1. **Analysis Planning**:
   1. Developed the research questions and analysis plan for the secondary data analysis of the SHAREHD dataset.
   2. Collaborated with the supervisor to identify key variables and define the analytical approach aligned with the research objectives.
2. **Data Preparation and Curation**:
   1. Conducted data cleaning to ensure accuracy and consistency of the dataset.
3. **Analysis**:
   1. Paper 1: Performed the statistical analysis mixed effects Linear Regression, using SPSS software, following discussions and guidance from my supervisor.
   2. Paper 2: Performed multi-level mixed effects probit regression, using Stata software. The choice of statistical analysis was guided by supervisors.
   3. Performed both statistical analyses independently.
4. **Data Interpretation and Dissemination**:
   1. Interpreted the results of the analysis in the context of the research objectives and existing literature.
   2. Contributed to the dissemination of findings through abstracts, conference presentations, and the final manuscript.
5. **Writing and Responding to Peer Review**:
   1. Led the writing of the manuscript, including drafting the methods, results, and discussion sections.
   2. Actively responded to peer review comments by addressing reviewer feedback, revising the manuscript as necessary, and ensuring clarity and scientific rigor in the final version.

### 3.2.2 My Contributions to paper 3 (The mapping study)

The experiences outlined in the previously mentioned papers led me to recognise the profound impact of debilitating symptoms in people on HD, prompting me to explore deeper into one of the most frequently reported symptoms, CKD-aP. Subsequently, I had the opportunity to be seconded to SCHARR as a research clinical fellow, where I collaborated on a project with SCHARR and Vifor company. Adding to the clinical relevance of CKD-aP, many health economic models that have guided policy decisions on dermatological treatments have typically focused on severity and employed generic measures of HRQoL. However, the extent to which disease-specific measures, capturing the broader impact of dermatological conditions on patients, correlate with these generic measures used in cost-effectiveness analyses remains uncertain. To address these gaps and provide insights for reimbursement decisions, our study presents a UK multi-center primary data collection involving these instruments within a cohort of prevalent individuals with kidney failure on HD.

The 3rd paper resulting from this work were published, with me as a co-author. My contributions include:

1. **Protocol Writing**:
   1. Contributed to the development of the study protocol, outlining research objectives, key variables, and the analytical framework required for the mapping study.
2. **Data Entry and Curation**:
   1. Organised and prepared the dataset for analysis in alignment with the requirements of the mapping model.
3. **Statistical Planning**:
   1. Collaborated with the team to design appropriate analytical approaches to address the research questions.
   2. Contributed to defining variables and methods needed for the mapping study.
4. **Data Analysis**:
   1. **Mapping Model**: The mapping model was performed by MH. However, I provided the demographic data and baseline characteristics required to develop and execute the model.
   2. **Model Fit**: I actively participated in decision-making regarding the model fit alongside other co-authors.
   3. **EQ-5D-3L Crosswalk**: The EQ-5D-3L crosswalk was conducted by MH.
   4. I performed the latent analysis to determine the distribution of the 16 body parts assessed in the 5-D itch scale. Choice of latent classes were guided by supervisors.
5. **Manuscript Writing**:
   1. Contributed to drafting the manuscript, particularly focusing on methods, results, and discussion sections.
   2. Assisted in refining and editing the paper to ensure effective communication of the findings.

### 3.2.3 My contributions to paper 4 and 5

Recognising the significant prevalence of CKD-aP and its considerable impact on HRQoL, I conducted a review to explore existing management strategies to inform data collection domains. Although a number of existing topical and systemic therapies exist, issues such as poor adherence, undesirable side effects and varied efficacy result in a residual unmet need for patients with CKD-aP (38). Despite recent approval of specific treatments for CKD-aP, there remains a concerning lack of adequate management, leading to significant economic burden and unmet needs in CKD-aP management (38,65) . Subsequently, I formulated an analytical plan utilising mapping data and SHAREHD to highlight economic burden and the unmet needs in CKD-aP management by investigating healthcare resource utilisation across varying degrees of CKD-aP severity, arguing for targeted therapies. The manuscript titled "Healthcare Resource Use Relating to CKD-aP: Insights from UK Real-World and Clinical Trial Datasets," which utilises both SHAREHD data and mapping data, has undergone peer review but has not yet been published. The findings of this manuscript directly inform the fourth paper examining the cost-effectiveness of new CKD-aP drug, difelikefalin, compared with standard care for CKD-aP. In the fourth paper, data on the natural progression of CKD-aP, utilities estimated from a mapping study, resource use from both datasets and data from pivotal trials were integrated to assess the cost-effectiveness of difelikefalin. My contributions to this paper 4 include:

**My Contribution to Paper 4 and 5**

1. **Analysis of Resource Utilisation and Costs**:
   1. Conducted the analysis to estimate resource utilisation and associated costs across varying degrees of CKD-aP severity (paper 5)
   2. Performed the resource use analysis independently, utilising both the SHAREHD and mapping datasets to develop and refine the model.
   3. Provided the resource use data for the standard care arm, which was integral to the health economic model.
2. **Health Economic Model**:
   1. While the health economic model was performed by PT, the resource use data required for the standard care arm was derived from my analysis of the SHAREHD and mapping datasets.
   2. I performed analysis of the data from SHAREHD to extrapolate the prevalence of CKD-aP severity in a cohort receiving standard CKD-aP therapy.
3. **Conceptualization**:
   1. Contributed to the development of the conceptual framework for the paper, aligning the research objectives with the analysis outcomes.

In the following section, I will provide a brief summary of each paper. More details of all published papers and the peer reviewed manuscript (paper number 5) are attached in appendix.

## 3.3 Summary of each paper

Table 1: Summary table of each paper

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Paper | Data source | Research questions | Main statistical methods | Main results/Key Findings | Recommendation |
| Paper 1: **Symptom burden according to dialysis day of the week in three times a week HD patients** | SHAREHD | How does the timing of symptom assessment in relation to dialysis sessions impact PROMs completion across different dialysis days, considering patient characteristics, in people undergoing HD for ESKD? | \*Linear mixed-effects regression analysis, alongside descriptive statistics and sensitivity analyses, to explore the relationship between symptom severity and HD schedules | Measuring symptom severity and HRQoL in HD populations doesn't require accounting for dialysis timing or schedule, but the location of completion, whether on a dialysis day or non-dialysis day, could introduce bias that may impact intervention evaluation. | Researchers should ensure standardising in completion of these validated instruments on either dialysis or non-dialysis days to minimise such bias. |
| Paper 2: **The trajectory of a range of commonly captured symptoms with standard care in people with kidney failure receiving haemodialysis: consideration for clinical trial design** | SHAREHD | How do symptoms evolve over time among individuals undergoing in-center HD and how can this knowledge inform the design of clinical trials to alleviate symptom burden and enhance HRQoL in this population? | \*Multi-level mixed effects ordered probit model to estimate changes in symptom prevalence over time. \*Transition probabilities were estimated to assess longitudinal changes. | Changes in symptom severity were frequent within six months under standard care, with clinically meaningful shifts observed at both population and individual levels. | Researchers should consider improvements in symptom severity when determining sample size and statistical power for trials, ensuring trials are designed to robustly detect genuine treatment effects while accounting for potential spontaneous changes associated with standard HD. |
| Paper 3: **Relationship Between Standardised Measures of Chronic Kidney Disease-associated Pruritus Intensity and Health-related Quality of Life Measured with the EQ-5D Questionnaire** | Mapping | 1.To what extent do disease-specific measures the 5-D itch questionnaire and WI NRS, capture the broader impact of CKD-aP on HRQoL compared to generic measures like the EQ-5D questionnaire.  2. To identify clusters of patients with similarly affected body parts and how does the severity of pruritus and EQ-5D vary within each cluster of patients? | \*Latent class models were utilised to identify clusters of patients with similarly affected body parts, while \*\*mixture models were employed to map the pruritus measures to the EQ-5D. | Latent class analysis identified three groups of patients with progressively worsening severity with an increasing number of affected body parts, but the distribution of body parts affected seems to be relatively constant  The WI-NRS and 5-D itch instruments showed correlation, with the latter demonstrating a stronger relationship with EQ-5D. | 5D-Itch better approximate EQ-5D, recommending their inclusion for more comprehensive quality of life assessment in people with CKD-aP. |
| Paper 4: **Cost Effectiveness of Difelikefalin Compared to Standard Care for Treating CKD-aP in People with Kidney Failure Receiving HD** | SHAREHD, mapping, KALM trial and Literature | What is the cost-effectiveness of difelikefalin compared to standard care for treating CKD-aP among people on HD, considering its clinical benefits and impact on patients' quality of life? | \*\***Conceptual modeling** to structure a model capturing \***CKD-aP health states, costs, and utilities**, utilising KALM trial data and SHAREHD SWCRT data to model trajectories for difelikefalin and standard care over a 64-week period, estimating incremental cost per quality-adjusted life year (QALY) gained. | In the base-case analysis, difelikefalin had an incremental cost-effectiveness ratio of £19,558 per QALY compared to standard care over 64 weeks, with scenario analyses showing ratios ranging from £10,154/QALY to £16,957/QALY | Difelikefalin's cost-effectiveness in multiple scenarios highlights its potential as a crucial pharmacotherapy for addressing the considerable burden of CKD-aP. |
| **Peer reviewed manuscript- Health care resource use relating to CKD-aP informed by UK real world and clinical trial datasets** | SHAREHD and mapping | What are the healthcare resource utilisation and associated costs among people on HD with varying degrees of CKD-aP? | \*Descriptive analyses were conducted to examine medication utilisation, HD frequency, duration, and associated costs, stratified by varying degrees of CKD-aP severity. | Severe CKD-aP showed high antipruritic medication usage and costs, indicating high symptom severity despite use of current standard therapies and increased HD cost due to more frequent HD. | The economic impact of CKD-aP on healthcare systems and high symptom severity despite standard therapies justify the demand for new interventions to treat CKD-aP |

**\* Statistical methods performed by me**

**\*\* Statistical methods were performed by co-authors; however, I contributed by preparing and providing the necessary data required to carry out these analyses (detailed contribution described in section above)**

### 3.3.1 Paper 1: Symptom Burden According to Dialysis Day of the Week in Three Times a Week Haemodialysis Patients (1)

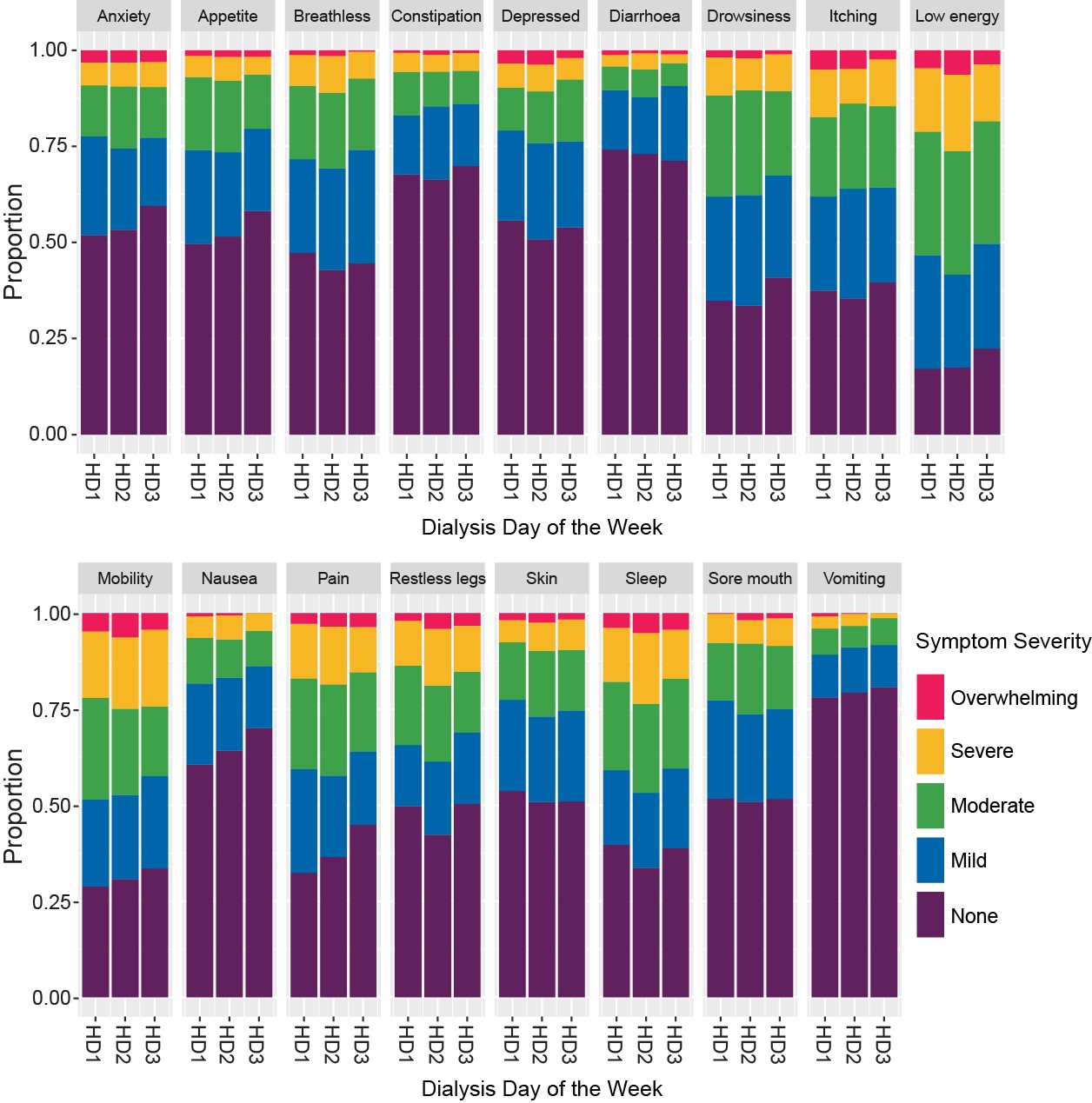
This paper investigates the symptom burden of people undergoing thrice-weekly HD and analyses the impact of dialysis day on symptoms using validated assessment tools.

Method: Data were sourced from the SHAREHD SWCRT. Patients provided information at baseline and subsequent intervals (six, 12, and 18 months) using instruments like the POS-S Renal and EQ-5D-5L. HD1 was assigned to those who dialysed and completed the instruments on Mon/Tue/Sun, HD2 to Wed/Thu/Tue and HD3 to Fri/Sat/Thu respectively. Participants who completed instruments on non-dialysis days were assigned to non-HD day. Descriptive statistics and linear mixed-effects regression were employed to explore symptoms' relationship with HD schedules, treating the day of symptom completion as a continuous variable.

**Result:** The study included 552 in-centre HD patients, among whom 517 completed questionnaires at four time points. Figure 1 in this thesis shows the severity of each of the 17 symptoms, stratified by HD Day. Age, years on dialysis, and comorbidities independently predicted symptom severity, with older patients (>65 years) reporting fewer symptoms. However, no patient characteristic resulted in a change in symptom severity greater than one level of verbal rating scale. Figure2 in this thesis reports the changes in symptom severity associated with increasing time from the long interdialytic interval, HD days compared to non-HD days, and individual HD days (HD1 vs HD2 and HD1 vs HD3). The EQ-5D-5L score showed no significant change over time but was notably lower on non-HD days compared to HD days.

**Discussion**: Changes in symptom severity were noted across different dialysis days, with restless legs and skin changes worsening over time from the two-day break. Non-dialysis days showed higher symptom burden and lower HRQoL compared to dialysis days. Although observed changes in symptom severity were statistically significant, using distribution-based method ½ SD, they were below minimum important differences, suggesting limited clinical significance (66). However, providing these assessments are consistently performed on a specific day, either HD or non-HD day, and comparisons across providers are adjusted for demography, the timing of the assessment in relation to dialysis day of the week does not need to be standardised.

**Figure 1: Symptom severity stratified by HD day (dialysis day of the week). The observations from 4 time points (baseline, 6,12 and 18 months) were used to inform this figure.**



**HD1 -those who dialysed and completed the instruments on Mon/Tue/Sun, HD2 -Wed/Thu/Tue and HD3 - Fri/Sat/Thu.**

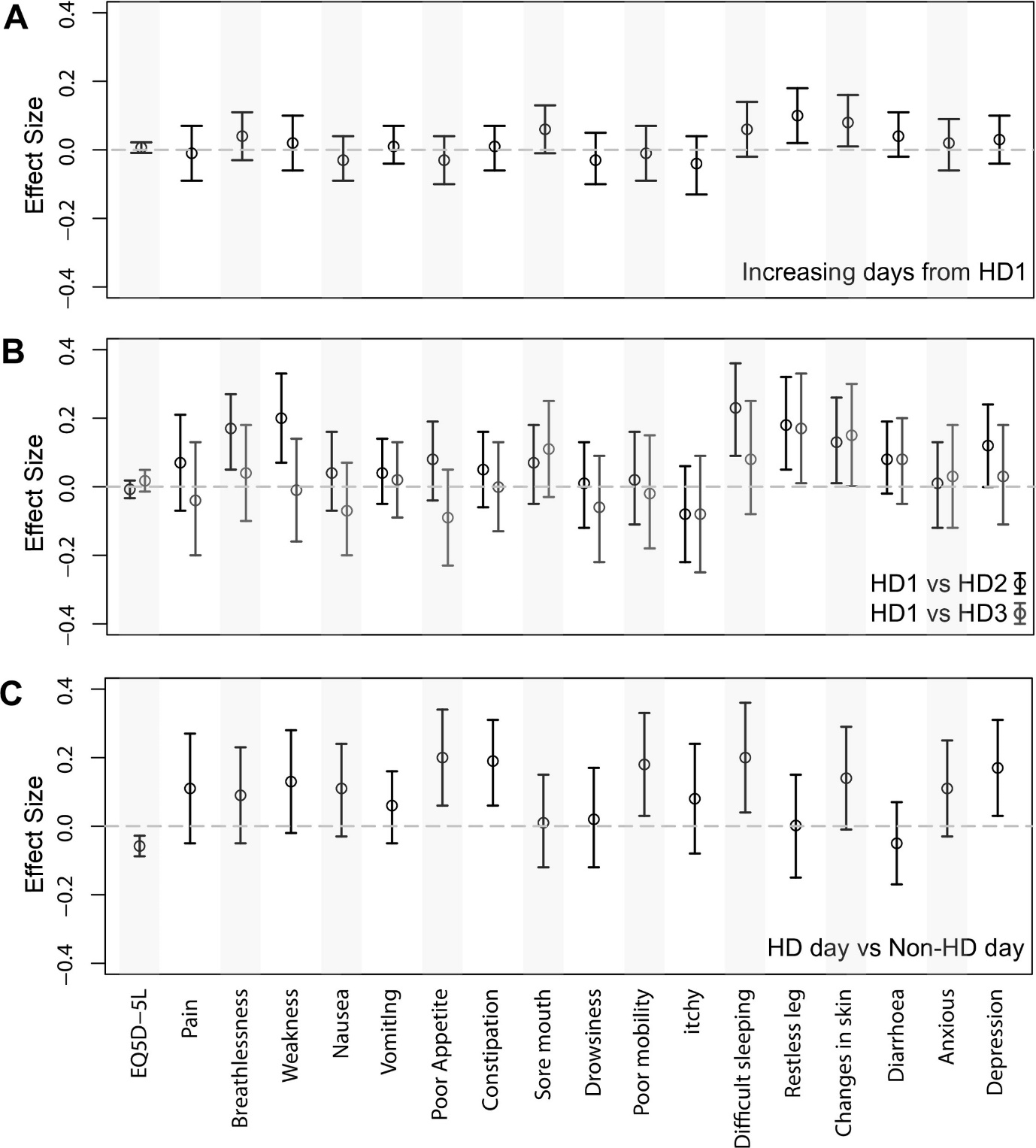
**Non-HD day - those who completed instruments on non-dialysis days.**

**Figure 2: Multivariable mixed effects linear regression comparing each HD day after long break, each HD days from HD1, HD day vs non-HD day**

Panel A: Estimating symptom changes over time after 2-day break (increasing days from HD1)

Panel B: Estimating symptom changes, comparing the HD days individuals to each other (HD1 vs HD2, HD1 vs HD3)

Panel C: Estimating symptom changes, comparing the HD days and non-HD days



### 3.3.2 Paper 2: Symptom Improvement with Standard Care in People Receiving Haemodialysis Across a Range of Symptoms in the POS-S Renal: Consideration for Clinical Practice and Trial Design (2)

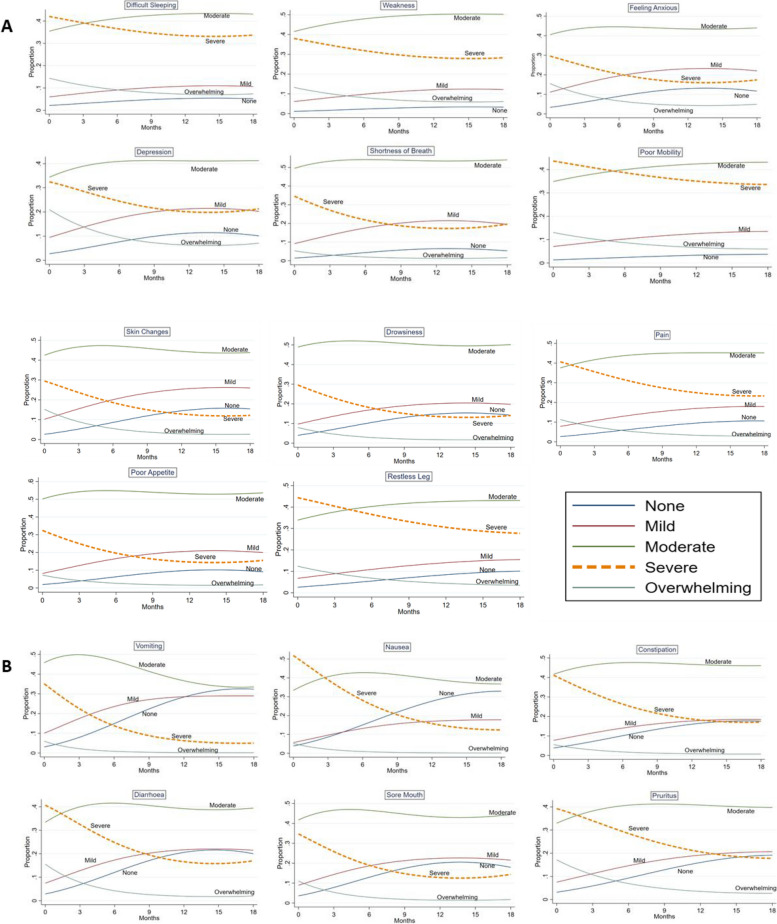
This paperassessed changes in symptom prevalence among individuals undergoing in-centre HD at both population and individual levels.

**Method:** Prevalent HD patients in the SHAREHD trial reported 17 POS-S Renal symptoms (none, mild, moderate, severe and overwhelming scale) at baseline, 6, 12 and 18 months. Respondents reporting moderate or worse for each of these symptoms at baseline were identified. To assess the prevalence change at population level, the multi-level mixed effects probit regression was estimated in people reporting moderate or worse symptoms at baseline. To assess changes at individual level, the proportion of people changing their symptom score (transition probabilities) every 6 months was estimated.

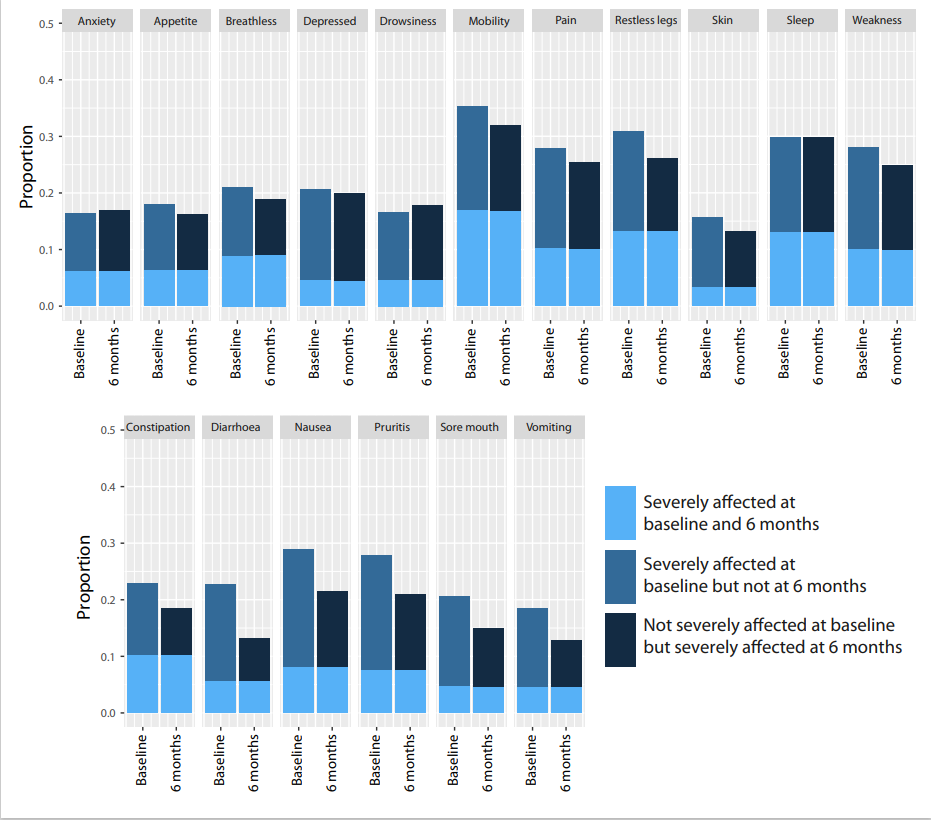
**Results**: Across all 17 symptoms with moderate or worse symptom severity at baseline, the majority of the change in symptom prevalence at population level occurred in the ‘severe’ category (Figure 3). In order to detect within individual changes, the proportion of people changing their symptom score every six months period in this group was estimated (Figure 4 and Table 4). We observed improvement (20% or less) in the prevalence of the 'severe' category for eleven out of seventeen symptoms over 18 months. However, even with this small change, there was significant shifting of individuals moving into and out of the severe category every six months. Meanwhile, larger changes in prevalence of >20% were observed in remaining six symptoms (Table 4). All symptoms had >50% of people in severe group changing severity within 6 months.

**Discussion**: While some symptoms showed a slight reduction in the prevalence of severity overall, there was notable fluctuation within the severe category, with over 50% of individuals experiencing changes in their symptom severity. Given that over half of the patients with severe symptoms show changes within 6 months, we advocate for consistent and frequent symptom evaluations in people on HD to identify those requiring interventions. It's important to acknowledge the significance of factoring in variations or improvements in symptoms when calculating the sample size and statistical power of a trial. By acknowledging the possibility of improvement with routine care, researchers can design trials that sufficiently detect genuine treatment effects, distinguishing them from changes that may occur spontaneously due to standard management.

**Figure 3: Change in symptoms prevalence over 18 months in people with moderately affected or worse at baseline. This figure was stratified by (A) symptoms with ≦20% change and (B) > 20% change in the prevalence in those reporting severe degree.**

****

**Figure 4:** **Proportions of people with moderate or worse severity at baseline moving in and out of severe group over 6 months**



**Table 4: Proportions /probabilities of people with moderate or worse severity at baseline moving in and out of severe group over 6 months**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Group** | **Symptoms** | **Prevalence of Severe category at time point 0** | **Proportions of people (those at time point 0) who remained in the severe category at time point 1** | **Proportions of people Moving out of severe category to other categories (moving out from timepoint 0 to 1)** | **Moving into severe category from other categories (moving into timepoint 1 from 0)** | **Difference between moving in and out** |
| **≦20% change** | **Difficult sleeping** | 29.8% (111/373) | 44.1% (49/111) | 55.9% (62/111) | 55.9% (62/111) | 0% |
| **Weakness** | 28% (134/478) | 35.8% (48/134) | 64.2% (86/134) | 59.7% (71/119) | 4.5% |
| **Anxiety** | 16.0% (34/207) | 38.2% (13/34) | 61.8% (21/34) | 62.0% (22/35) | 0.2% |
| **Depression** | 20.6% (36/175) | 22.2% (8/36) | 77.8% (28/36) | 77.1% | 0.7% |
| **Shortness of breath** | 21.1% (56/266) | 42.9% (24/56) | 57.1% (32/56) | 52.0% (26/50) | 5.1% |
| **Poor mobility** | 35.3% (150/425) | 48.0% (72/150) | 52.0% (78/150) | 47.1% (64/136) | 4.9% |
| **Changes in skin** | 15.7% (37/235) | 21.62% (8/37) | 78.4% (29/37) | 74.2% (23/31) | 4.2% |
| **Drowsiness** | 16.6% (54/326) | 27.8 (15/54) | 72.2% (39/54) | 74.1% (43/58) | -1.9% |
| **Pain** | 27.8% (93/334) | 36.6% (34/93) | 63.4% (59/93) | 60.0% (51/85) | 3.4% |
| **Poor appetite** | 18.0% (42/233) | 35.7% (15/42) | 64.3% (27/42) | 60.5% (23/38) | 3.8% |
| **Restless legs** | 30.9% (97/314) | 43.3% (42/97) | 56.7% (55/97) | 48.8% (40/82) | 7.8% |
| **>20% change** | **Vomiting** | 18% (16/86) | 25% (4/16) | 75% (12/16) | 63.6% (7/11) | 11.4% |
| **Nausea** | 28.9% (43/149) | 27.9% (12/43) | 72.1% (31/43) | 62.5% (20/32) | 9.6% |
| **Constipation** | 23% (31/135) | 45.2% (14/31) | 54.8% (17/31) | 44.0% (11/25) | 10.8% |
| **Diarrhoea** | 22.6% (24/106) | 25% (6/24) | 75.0% (12/24) | 57.1% (8/14) | 17.9% |
| **Sore mouth** | 20.6% (44/214) | 22.7% (10/44) | 77.3% (34/44) | 68.8% (22/32) | 8.5% |
| **Pruritis** | 27.9% (92/330) | 27.2% (25/92) | 72.8% (67/92) | 63.8% (44/69) | 9.0% |

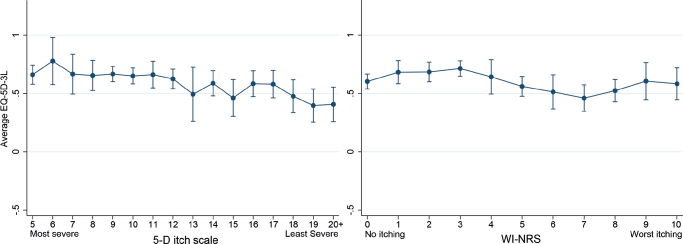
### 3.3.3 Paper 3: Mapping of Measures of CKD-aP Severity to the Generic EQ5D Instrument (3)

This study aimed to understand how disease specific CKD-aP measures, the WI-NRS and 5-D itch scales, correspond to the EQ-5D so that the mapping model can be estimated to translate the disease specific measures to generic one. In addition, this study examined how affected body areas included in 5-D Itch body part distribution relate to overall HRQoL.

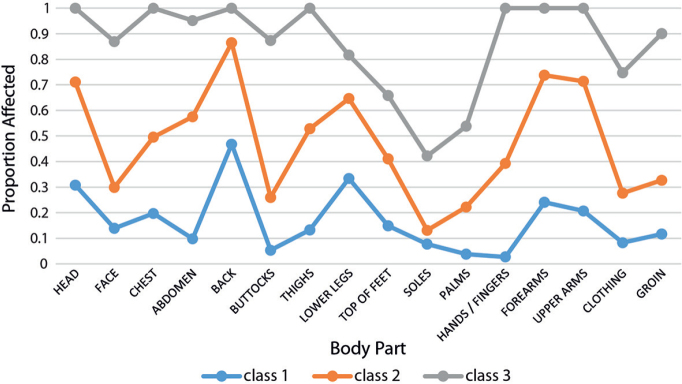
**Method:** This is a cross sectional primary data collection study collecting 4 pruritus-related measures (WI-NRS, 5-D Itch, verbal rating scale and the SKINDEX-10) and EQ-5D-5L assessments. The EQ-5D-5L data were converted into EQ-5D-3L UK utility using a specific crosswalk due to concerns regarding the value set. The analysis involved an Adjusted Limited Dependent Variable Mixture Model (ALDVMM) to relate CKD-aP measures to EQ-5D.. To identify individuals with CKD-aP in particular combinations of body areas, which could lead to varied HRQoL scores, the latent class analysis was used with the 16 body parts assessed by the 5-D itch questionnaires.

**Results:** EQ-5D-3L decreased with increasing pruritus severity, and there was a clear relationship between EQ-5D-3L, WI-NRS, and 5-D itch scores (Figure 5). Mapping models were developed from 5-D itch and WI-NRS scores. The 5-D itch mapping model closely mirrored mean utilities, while the WI-NRS mapping had systematic issues, indicating it wasn't a reliable predictor of EQ-5D-3L. Latent class analysis identified three groups with varying pruritus severity based on affected body parts, revealing increased probabilities of multiple body areas being affected as pruritus severity increased (Figure 6). **Discussion**: The study showed that instruments like 5-D itch, encompassing the impact of pruritus on various aspects of life, proved better predictors of EQ-5D than singular measures of pruritus intensity like WI-NRS. As CKD-aP severity increased, more body parts were affected, yet the body parts distribution remained relatively constant. While WI-NRS is widely recommended in clinical trials, it doesn't predict EQ-5D well, potentially underestimating pruritus impact. Systematic reviews and trials have demonstrated that disease-specific quality of life measures are sensitive to changes in pruritus severity among individuals with CKD-aP, though the extent to which the EQ-5D reflects improvements as CKD-aP severity decreases has not been clearly observed until our study (67). The 5D-itch, with its focus on the progression of pruritus and a closer alignment with EQ-5D compared to the WI-NRS, has proven more effective in assessing overall HRQoL.

**Figure 5: Estimated means of EQ-5D-3L and 95% bootstrapped confidence intervals by 5-D itch index (left) and Worst Itching Intensity Numerical Rating Scale (WI-NRS) (right) (5-D itch scale 20 includes all observations in the range 20–25).**



**Figure 6: Distribution of the 16 body parts assessed in the 5-D itch according to 3 populations identified using latent class analysis.**



### 3.3.4 Paper 4: Cost-Effectiveness of Difelikefalin to Treat CKD-aP (4)

This conceptual modelling aimed to develop a framework CKD-aP health states, costs, and utilities by reviewing literature, clinical data, and economic models, proposing a cell-based cohort structure using KALM trial data.

**Methods**: It focused on difelikefalin's impact over 64 weeks, depicting CKD-aP severity states based on the intensity (degree) question of the 5-D Itch instrument. A 28-day cycle length and 64-week time horizon were used in the model to correspond to the follow-up points and length of follow-up in the KALM trials. The data used in the model for people receiving difelikefalin were based on trajectories of CKD-aP WI-NRS scale observed for difelikefalin arms in the pivotal KALM trials and standard care were modelled using SHAREHD SWCRT's data with costs, healthcare resources, and utilities estimated from various sources. Analyses estimated the incremental cost per QALY gained by difelikefalin and underwent rigorous validation using the healthcare system perspective to ensure robustness.

**Results:** The base-case analysis of difelikefalin over 64 weeks indicated higher costs (£45,314) compared to standard care (£44,717) by £598, with difelikefalin resulting in QALYs (0.659) compared to standard care QAYLs 0.629 and an Incremental Cost-Effectiveness Ratio (ICER) of £19,558 per QALY gained. Probabilistic sensitivity analysis demonstrated consistent clinical effectiveness of difelikefalin compared to standard care. Scenario analyses yielded varying ICERs for difelikefalin compared to standard care, influenced by factors such as treatment discontinuation assumptions and trial data sources.

**Discussion:** The cost-utility analysis suggests that difelikefalin could be a cost-effective treatment for CKD-aP in the UK, with a base-case ICER of £19,558 per Quality-Adjusted Life Year (QALY) gained (within the threshold range of £20,000–£30,000 per QALY used by NICE). Scenario analyses indicate even lower ICERs than the base case. Our model is the first study estimating the cost effectiveness of difelikefalin. Although lacking direct comparisons in published models, the inputs and assumptions are consistent with existing literature on CKD-aP.

### 3.3.5 Additional material: Health Care Resource Use Relating to Chronic Kidney Disease-Associated Pruritus Informed by UK Real World and Clinical Trial Datasets (First author)

This manuscript has gone through peer review process. This study contributed essential data for constructing the cost-effectiveness model mentioned in paper 4. The study investigated healthcare resource utilisation, medication costs, and transportation impact with varying degree of CKD-aP reported by people on HD.

**Method:** The paper utilises two datasets: the mapping dataset and the SHAREHD trial. Descriptive analysis was used to study the resource use.

**Results**: Findings revealed that approximately 42% of HD patients used antipruritic medications, with higher usage in severe CKD-aP cases (56%). Medication costs were higher in severe CKD-aP. Pruritus distribution predominantly affected the groin and upper limbs, yet over 50% of CKD-aP patients were not on anti-pruritic medications. More frequent dialysis was observed among those with moderate to severe CKD-aP. 28 days HD session cost was highest in severe CKD-aP by approximately £20-30 compared to none and mild CKD-aP.

**Discussion:** In this study, more than half the people reporting severe CKD-aP severity despite being on current standard therapy to manage CKD-aP justify the demand for new intervention to treat this condition. Medication use in the none CKD-aP group does not reflect a population who never had CKD-aP. Health Economic analyses employing the proportion of medication usage in the mild group for the none group may be justified for these reasons. The study mapped CKD-aP distribution across body parts: although the groin area being the most affected area, more than 50% of patients were not on antipruritic medications. It is likely that patients may not alert healthcare professionals to this symptom unless they are asked directly. However, limitations include uncertainty about medication exclusivity for CKD-aP and potential recall bias in assessing severity of CKD-aP. Despite the availability of treatments, a substantial proportion of CKD-aP patients continue to experience inadequate symptom relief or remain untreated. This persistent unmet need not only highlights the challenges in effectively managing CKD-aP but also suggests potential gaps in current treatment approaches or barriers to access and utilisation of therapies

# Chapter 4: Synthesis and Discussion

In this chapter, I will summarise the key findings and insights from all the papers discussed in the thesis. I will emphasise the overarching thesis and main argument that my research has sought to address and the conclusions drawn from each paper in support of this thesis. Additionally, I will discuss the generalisability of the findings, evaluating their applicability to broader patient populations and clinical settings.

## 4.1 Symptom Burden and Quality of Life in people on HD

### 4.1.1 Impact of dialysis schedules on symptom burden assessments

People on HD has a substantial symptom burden, yet the relationship between dialysis schedules with PROMs remains unknown, and the necessity for standardising the day of PROM completion is still unclear. The first manuscript explored the significant symptom burden experienced by HD patients and highlighted the importance of standardising symptom measurement in HD patients to mitigate variations in symptom reports, particularly concerning dialysis days, when examining the dynamic nature of symptoms over time. Additionally, it examined the relationship between the long interdialytic interval, dialysis schedules, and PROMs. This exploration is important for several reasons. Firstly, it provided insights into how dialysis schedules do or do not affect patients' reported symptoms. Secondly, it highlighted the necessity of uniform symptom measurement in HD patients to reduce variation in symptom reporting. We hypothesised that this variation rather reflects the natural rapid changes in symptoms between HD sessions. To achieve consistent symptom tracking over time, it's important to measure symptoms at the specific day consistently. Alternatively, capturing these swift symptom variations could be of interest, necessitating daily assessments. By tailoring measurement strategies to accurately capture symptom fluctuations through consistent timing, we can improve the accuracy of health assessments which inform best practices in research methodology, and contribute to the development of evidence-based care guidelines. My research concludes that while evaluating symptom severity and EQ-5D-5L in HD populations need not consider dialysis schedules, but completing these assessments on different dialysis or non-dialysis days might introduce variation in symptoms reported, potentially affecting intervention evaluations.

### 4.1.2 Longitudinal change in symptoms over time

PROMs are frequently used to assess outcomes in clinical trials and the existing literature has examined symptom changes over time in various populations (68). However, there remains a need for a more focused understanding of specific symptom trajectories and their implications for clinical practice and research in the HD population as symptoms in these patients are dynamic, multifactorial, and influenced by both physiological and psychosocial factors. The second manuscript focused on the trajectory of symptoms in response to standard HD in prevalent HD patients over 18 months. A change in the severity of existing symptoms in response to standard HD care was very common and can occur within six months. Considering clinically meaningful changes at the population and patient level in some symptoms, this highlights the importance of accounting for variations or improvements in symptoms when determining the sample size and statistical power of a trial, so that researchers can design trials that are robust enough to detect true treatment effects, distinguishing them from changes that might occur spontaneously in response to standard HD. Additionally, it is important to note that treatment effect size should not be defined solely by one-way improvement. Instead, assessing both improvement and deterioration can provide a more balanced evaluation rather than relying only on a single-directional change in scores. This highlights the importance of carefully considering how to best evaluate change within a population, ensuring that study designs capture the full spectrum of symptom evolution and provide a more comprehensive understanding of treatment impact. Acknowledging the dynamic nature of symptoms over time is also important for tailored therapies for each symptoms necessitating adjustments in management approaches to effectively address patient needs at different stages. Failing to consider this variability may result in inadequate treatment plans for patients whose symptom severity changes over time. This oversight can lead to diminished quality of life, increased patient distress, and unnecessary healthcare utilisation.

## 4.2 Methodological Innovations and Future Research Directions

### 4.2.1 Standardising the use of Patient-Reported Outcome Measures

**Threats of non-standardisation**: Variability in symptom measurement practices can lead to inconsistent symptom reporting, misinterpretation of disease severity, and consequently, suboptimal patient care. Variations or improvements in symptoms can significantly influence the determination of sample size and statistical power in a clinical trial. This happens because statistical power is the probability that a study will detect an effect if there is one to be detected. If symptoms vary widely among participants or improve unexpectedly, it can increase the variability in study outcomes. This increased variability requires a larger sample size to achieve the same level of statistical power, ensuring the trial is adequately equipped to detect meaningful differences or effects of the treatment being tested. The key consideration is to understand the natural evolution of symptoms over time and design a study that accounts for these variations. Therefore, accurately accounting for symptom variations and improvements from the outset is essential for designing effective and efficient clinical trials. Standardisation in symptom measurement is crucial as our research showed that symptom severity and prevalence vary by the day of measurement and exhibit spontaneous improvements over time. Establishing consistent protocols for symptom assessment on specified days ensures accurate, unbiased evaluations and accounts for natural symptom fluctuations in long-term care.

### 4.2.2 Advancing Symptom Measurement Techniques Multi-Dimensional Symptom Assessment

Moving beyond symptom severity, we use CKD-aP as a case study to explore both muti-dimensional symptom measurement and the economic implications, including the cost-effectiveness of treating CKD-aP. Investigating the relationship between CKD-aP severity measures and the EQ-5D is pivotal for understanding of CKD-aP's effects on HRQoL. This investigation is not only fundamental for patients and healthcare providers but also has significant implications for a wider range of stakeholders, influencing decision-making across the healthcare spectrum as most economic models that have led to successful policy decisions on dermatological treatments have been informed by generic measures of HRQoL like EQ-5D. We demonstrated that measures of pruritus severity, such as WI-NRS, may not accurately predict EQ-5D, potentially underestimating its impact of CKD-aP on HRQoL. We highlighted the need for a multidimensional approach, like the 5-D itch scale, to better capture the broader impact of CKD-aP on HRQoL. As CKD-aP severity worsens, the number of body parts affected increases, but the distribution of body parts affected seems to be relatively constant. These data justify recommendations made by others that, when an individual with CKD-aP is identified, the distribution of body parts affected is unlikely to be relevant. These findings have implications for clinical trials: utilising tools like the 5-D itch scale can help researchers more accurately evaluate how different treatments affect various aspects of patients' lives, beyond just symptom relief. By mapping CKD-aP measures to the EQ-5D instrument, we highlighted the close alignment between CKD-aP specific assessments and widely used HRQoL measures. CKD-aP significantly influences the EQ-5D domains: It can lead to fatigue and reduce mobility due to sleep disturbances caused by itching. Daily activities, including self-care, may become challenging as the discomfort interferes with routine tasks. CKD-aP directly impacts the pain/discomfort domain, with the physical irritation of itching and potential skin damage from scratching. Furthermore, it exacerbates anxiety and depression, highlighting the psychological toll of managing a chronic condition. This comprehensive evaluation of CKD-aP and its association with HRQoL underscores the importance of using disease-specific measures in capturing the full extent of symptom burden and its impact on HRQoL. This approach reveals that effectively managing one symptom, such as CKD-aP, could potentially alleviate associated symptoms within the EQ-5D domains, as these symptoms often cluster together.

Therefore, measuring CKD-aP with 5D-itch can lead to the development of more holistic treatment plans that address both the physical and psychological aspects of CKD-aP. In contrast, focusing solely on the intensity of pruritus through isolated measures like WI-NRS could lead to inadequately predict HRQoL and failure to capture the full spectrum of CKD-aP impact. As a result, it can undermine the economic burden and cost-effectiveness implications when determining the adequacy of treatment for CKD-aP. By utilising disease-specific measures capturing the HRQoL, healthcare providers can ensure effective management strategies for CKD-aP that address both patient well-being and healthcare system sustainability.

### 4.2.3 The value of measuring and treating CKD-aP

Measuring and addressing CKD-aP holds significance far beyond treating a single symptom; it opens a gateway to managing other symptoms in CKD. Studies have uncovered symptoms cluster associated with CKD-aP (65). This suggests that targeting one symptom could potentially alleviate others within the same cluster, such as the interlinked symptoms of pruritus, sleep disturbance, depression, fatigue, and pain. By focusing on treating CKD-aP, there's a promising avenue not just for relieving this particular symptom but also for improving broader clinical outcomes and patient satisfaction with dialysis therapy. Such an approach highlights the need for a paradigm shift in how symptoms are treated in nephrology, moving towards interventions that address the root causes of symptom clusters for a more comprehensive impact on patient well-being. However, neglecting the economic impact of CKD-aP treatments can lead to the adoption of costly interventions with limited benefit, escalating healthcare expenses without proportionate improvements in patient care. This oversight may also prevent the identification of economically viable treatment options that could improve access to care for a broader patient population.

## 4.3 Economic Implications of CKD-aP Treatment

### 4.3.1 Healthcare Resource Utilisation and Costs

Acknowledging the potential mechanisms through which a person with increasing severity of CKD-aP may consume more healthcare resources, a better understanding of the costs associated with it is important alongside the existing knowledge on the negative impact on HRQoL which more generally informs the health economics of CKD-aP. This manuscript of health care resource use in CKD-aP adds to the existing literature by examining the financial implications of treating CKD-aP, specifically by assessing healthcare resource utilisation and costs across different levels of CKD-aP severity. By uncovering high healthcare costs and notable unmet needs shown by higher number of people reporting severe CKD-aP despite available standard treatments, the research sheds light on the economic impact of CKD-aP with high disease burden arguing for more effective therapies.

### 4.3.2 Unmet Need

The unmet need in CKD-aP treatment centres on the limited availability of effective, targeted therapies that can comprehensively alleviate the symptoms and its associated impact on HRQoL. CKD-aP significantly impairs patients' quality of life, yet many current treatment options only offer partial relief or come with undesirable side effects. Key areas where unmet needs persist include:

**Safety and Side Effects**: Treatments that are effective in reducing pruritus such as gabapenoids have side effects that limit their usability or acceptance among patients.

**Efficacy**: Many available treatments fail to sufficiently reduce the severity of pruritus, leaving patients with persistent discomfort and in need for more potent medications that can effectively target the underlying mechanisms of CKD-aP. With the recent approval of the novel therapy Difelikefalin for treating CKD-aP, which has demonstrated effectiveness, there is newfound hope for more effective management of this condition.

**Accessibility**: Even when effective treatments are available, access to these therapies can be limited by cost, healthcare policies, or lack of awareness among healthcare providers. Consequently, our research looked into the healthcare resource utilisation with CKD-aP and cost-effectiveness of Difelikefalin in comparison to standard therapies for CKD-aP.

### 4.3.3 Cost-Effectiveness of Difelikefalin

The fourth paper examined the cost-effectiveness of Difelikefalin, demonstrating its potential value in addressing the substantial burden of CKD-aP. This analysis highlighted Difelikefalin's potential as a pharmacotherapy to alleviate the considerable disease burden and unmet needs in managing CKD-aP among HD patients, especially when considering the economic implications with high health care resource use related to managing CKD-aP and associated impaired HRQoL. This is the first study estimating the cost effectiveness of Difelikefalin and our results suggested that the base-case incremental cost-effectiveness ratio of £19,558/quality-adjusted life-year is within the threshold range of £20,000–£30,000 per quality-adjusted life-year used by the National Institute for Health and Care Excellence (NICE).

These findings of economic burden and healthcare resource utilisation associated with standard CKD-aP therapy, along with a cost-effectiveness study derived from my research, were key factors in NICE committee's approval of Difelikefalin.

## 4.4 Generalisability of the findings in this thesis

Although both studies used in this thesis represent a UK cohort with prevalent populations, the exclusion of non-English speakers poses a limitation to the generalisability of the findings. Language barriers can impact multiple aspects of healthcare, including access to services, symptom perception, symptom reporting, and overall treatment experiences (69). Patients who are not proficient in English may experience difficulties in communicating their symptoms accurately, leading to potential underreporting or misinterpretation of symptom burden. Furthermore, linguistic and cultural differences may influence how patients describe and experience symptoms, which can introduce systematic bias in the study’s results. As a result, the exclusion of non-English speakers may underestimate or overlook certain patient experiences, limiting the ability to apply these findings to the broader dialysis population, where linguistically diverse groups make up a significant proportion.

In the UK’s National Health Service, dialysis populations are highly diverse, with patients from various ethnic and cultural backgrounds who may have different healthcare-seeking behaviours, symptom thresholds, and responses to treatment. The study’s findings may therefore not fully capture the heterogeneity of patient experiences, leading to gaps in understanding how symptom burden varies across different language and cultural groups.

Future studies should explore whether language barriers contribute to differences in symptom perception and self-reported outcomes, as well as how these factors influence treatment adherence and healthcare engagement. By addressing these limitations, future research can improve the external validity of findings and ensure that symptom assessment tools and treatment strategies are more inclusive and representative of diverse patient populations. This would contribute to a more equitable, patient-centred approach in managing symptoms in HD patients, ensuring that all individuals, regardless of language proficiency, receive appropriate and effective care.

## 4.5 Conclusion Remarks

These manuscripts underscored the significance of assessing symptom burden in both the HD population and CKD-aP, aiming to enhance patient care and deepen our comprehension of associated outcomes. This thesis collectively addresses the challenges surrounding symptom burden measurement, highlighting the lack of standardisation in measuring symptoms and the fluctuating nature of symptoms in response to standard care, which can vary even between non-dialysis and dialysis days. Additionally, it explores the impact of measuring symptoms on healthcare delivery and resource utilisation, as well as the cost-effectiveness implications. Enhancing our comprehension of symptom trajectories in response to standard care and implementing standardised protocols for the assessment of PROMs have the potential to challenge several existing assumptions regarding symptom measurement in HD and CKD-aP populations. These include assumptions about the reliability of PROMs, the stability of symptoms over time, and the consistency of symptoms across different patients. By systematically evaluating symptom burden using standardised measurement approaches, we can prompt a re-evaluation of the validity of previous trials that relied on PROMs, leading to a more accurate understanding of symptomatology and ultimately improving patient care. Moreover, integrating disease-specific measures of CKD-aP with broader HRQoL assessments can provide a more comprehensive understanding of the impact of symptoms on patients' overall well-being. This shift in measurement practices may prompt changes in clinical management strategies, advocating for the inclusion of novel therapies like Difelikefalin in the management of CKD-aP.

Furthermore, the insights derived from studies on the economic burden and healthcare resource use linked to standard CKD-aP therapies, as well as our cost-effectiveness analysis, significantly contributed to NICE's endorsement of Difelikefalin. By aligning our findings with the frameworks and guidelines set by the NICE and incorporating them into the External Assessment Group (EAG) report, we demonstrated the substantial value and impact of our work. This alignment with NICE’s rigorous standards not only underscores the relevance of our research but also its pivotal role in advancing clinical practice by ensuring that new CKD-aP treatments meet regulatory expectations, address unmet clinical needs, and ultimately enhance patient care outcomes.

Incorporating the patient reported outcomes is essential in shaping the future of symptom assessment and management in the HD and CKD-aP populations. Throughout this thesis, the findings have highlighted the impact of capturing patients' experiences, recognising that symptom burden extends beyond clinical measurements to deeply impact daily life, well-being, and overall quality of life. Patients have repeatedly emphasised the importance of symptom assessment, expressing frustration with inadequate recognition of their concerns and the lack of approaches to addressing symptom fluctuations(70). By integrating patient-reported outcomes into routine care and aligning research priorities with their lived experiences, we can move toward a more patient-centred model of care, one that prioritises not only symptom relief but also enhances overall well-being.

In the context of CKD-aP, other symptoms such as sleep disturbances, fatigue, depression, anxiety, and reduced overall well-being frequently co-exist, forming a symptom cluster (71). While the direct impact of treating pruritus on these other symptoms remains uncertain, reducing the distress and discomfort associated with CKD-aP may help alleviate some of these interconnected symptoms (72). For example, relief from itching may lead to better sleep quality, which in turn can improve mood, reduce fatigue, and enhance daily functioning. Additionally, lowering distress may help patients better manage their chronic disease, potentially leading to a more positive perception of their overall health. Addressing pruritus as part of a broader symptom cluster highlights the importance of a comprehensive symptom management approach, rather than focusing solely on individual symptoms in isolation.

The importance of symptom assessment and patient-centred care cannot be overstated, as it serves as the foundation for improving treatment strategies, optimising healthcare resource utilisation, and ultimately enhancing patient outcomes (73). Patients’ perspectives must guide the development of more responsive healthcare interventions, ensuring that their voices shape both clinical decision-making and policy changes. Future studies must continue to involve patients as active stakeholders in research design, ensuring that assessment tools reflect their priorities and that interventions address the aspects of symptom burden that matter most to them. Ultimately, by centring the patient voice in both research and clinical practice, we can foster more effective, responsive, and compassionate care for individuals living with CKD-aP and on HD, ensuring that their needs and experiences remain at the heart of every advancement in treatment and symptom management.

In conclusion, by embracing tailored symptoms assessment approaches, conducting cost effectiveness studies, evaluating economic implications, and engaging with stakeholders, the implications of my research extend far beyond academia. These findings pave the way for informed decision-making, optimised patient care, and the advancement of CKD-aP management practices, ultimately improving the lives of HD patients worldwide.

# Chapter 5: Implications for research and clinical practice

Based on the findings of this research, several recommendations can be made for research and clinical practice.

5.1 Standardising in measuring PROMs

Health care providers and researchers should prioritise consistent administration of PROMs on dialysis or non-dialysis days, enhancing the accuracy of symptom assessment and facilitate more reliable evaluations of interventions. This approach offers a practical guideline for the scheduling symptoms assessment in people on HD, ensuring that symptom assessments accurately capture patient experiences.

## 5.2 Symptoms Trajectory

Incorporating an understanding of these natural symptom variations into trial designs can enhance the accuracy of detecting genuine treatment effects. This is especially pertinent for distinguishing between symptom severity changes resulting from the intervention under study and those that might occur due to the standard HD care. For researchers, it emphasises the importance of accounting for natural symptom fluctuations in the design of clinical trials to ensure their capability to capture true therapeutic benefits. For healthcare providers, it suggests the value of adopting a dynamic and patient-centred approach to symptom management, tailored to the individual patterns of symptom changes over time. This approach entails remaining vigilant about the evolving nature of symptoms and considering the option of observation before intervention, as symptoms may vary significantly over time.

## 5.3 Mapping CKD-aP measures to EQ-5D

By highlighting that comprehensive CKD-aP assessments with 5D-Itch more accurately predict HRQoL than pruritus severity measures alone, it suggests a need for a shift towards disease-specific instruments in evaluating the impact of CKD-aP on patients' lives, which has significant implications for clinical practice and health policy. Despite Difelikefalin showing promise in improving HRQoL in CKD-aP patients, our findings call for a re-evaluation of current assessment tools and a more nuanced understanding of symptom impact, advocating for the inclusion of multidimensional measures in clinical and research settings.

## 5.4 Health care resource use and Cost Effectiveness Studies

Our CEAs of Difelikefalin, alongside an examination of healthcare resource utilisation, have uncovered a significant unmet need in the management of CKD-aP. Our study found that patients with severe CKD-aP continued to report high levels of symptom severity despite being on antipruritic medications, indicating that current treatments may be insufficient in addressing their needs. These findings strongly advocate for the integration of Difelikefalin into the standard treatment protocol for CKD-aP, suggesting it could substantially mitigate this unmet need. While the direct impact of treating pruritus on other symptoms remains uncertain, reducing distress associated with CKD-aP may contribute to an overall improvement in quality of life for many patients. Furthermore, the insights derived from these studies significantly contributed to NICE's endorsement of Difelikefalin.

# Chapter 6: Dissemination and Impact of included publications

**Paper 1 (Symptom burden in relation to dialysis day of the week):** This study, emphasising the necessity of standardised symptom measurement and its implications for dialysis patients' well-being, has been disseminated through publication in reputable medical journal (PLOS one) and presentations at both national and international conferences (UK Kidney Week, ERA EDTA). This paper has been cited in 2 papers, assessed over 600 times and shared on social media platforms such as Twitter, raising awareness among healthcare professionals about the importance of considering symptom severity concerning dialysis schedules and advocating for standardised PROMs completion.

**Paper 2 (Symptom Trajectory paper):** The study exploring symptom trajectory over time among prevalent haemodialysis patients has been disseminated through peer-reviewed publication (BMC nephrology) and conference presentations (UKKW, ERA EDTA). The impact of my paper has been notable, with nearly 500 assess and positive feedback received during presentations. Furthermore, fellow researchers have sought my expert opinions after reading my paper, indicating a growing recognition of my contributions.

**Paper 3:** This study mapping pruritus measures to the generic EQ-5D instrument has been disseminated through publication in leading medical journal (Acta dermato Venerologica). This research is anticipated to significantly influence future CEAs and studies, especially in cases where EQ-5D data may not have been collected during trials, or when health states in economic models need to be defined in terms of the 5D itch scale. It is expected that this mapping study will be incorporated into the well-regarded HERC Database of Mapping Studies, which is regularly updated and widely utilised by researchers seeking mappings for their analyses. The inclusion of our study in future iterations of the database will affirm its contribution to the field, aiding others in understanding and applying CKD-aP's impacts more effectively in patient-centred care and economic evaluations.

**Paper 4 and 5:** The assessment of Difelikefalin's cost-effectiveness has been disseminated through publication in reputable medical journals (Pharmacoeconomics) and presentations at conferences by co-author. The study evaluating of Healthcare Resource Utilisation in CKD-aP patients has been peer reviewed and presented in UKKW and ERA EDTA. Healthcare decision-makers have used these insights to guide treatment decisions and optimise outcomes in haemodialysis population. The findings and results from these studies have played a crucial role in the NICE approval process, leading to the recommendation and approval of Difelikefalin for use in treating CKD-aP.

# Chapter 7: Conclusion

## 7.1 Unique Contribution of this Work

This thesis presents a unique and comprehensive approach to understanding and addressing the complexity of measuring symptoms in HD patients, with a specific focus on CKD-aP. By synthesising findings from these studies, this research sheds light on various critical aspects of symptom management in HD patients. Firstly, it emphasises the significance of PROMs to ensure consistency and reliability in symptom assessment. This standardising in measuring symptoms helps minimise biases and facilitates accurate evaluation of interventions. Secondly, the research highlights the dynamic nature of symptoms over time, revealing that symptom severity can fluctuate significantly within relatively short intervals, such as six months. Understanding these fluctuations is crucial for designing effective intervention strategies and reshaping trial design to accommodate the changing symptomatology. Additionally, this work delves into the economic implications of symptom severity, particularly focusing on CKD-aP. By assessing healthcare resource utilisation and costs associated with symptom management, the research emphasises the economic burden imposed by unmanaged symptoms. Furthermore, the study evaluates the potential cost-effectiveness of interventions like Difelikefalin in managing CKD-aP. By demonstrating promising findings in terms of improved patient outcomes and reduced healthcare costs, this research provides valuable insights into the economic viability of interventions targeting symptom management in HD patients. Overall, the unique contribution of this work lies in its holistic approach to understanding and addressing the challenges of symptom measurement and management in dialysis patients, ultimately aiming to optimise patient care and enhance our understanding of related outcomes

## 7.2 Strengths and Limitations

**Strength**

* This thesis addresses a previously unexplored question by investigating the longitudinal changes in symptoms at both population and individual levels among individuals on HD. It emphasises the importance of standardising PROMs assessments in this population, advocating for consistent assessment days. This longitudinal approach fills a gap in the existing literature, as there are few studies that have examined symptoms over time in people undergoing HD.
* Both datasets used in this thesis encompass a patient cohort that is both diverse and representative (3,61,62), indicating the study's credibility. Additionally, the utilisation of a validated symptom assessment tool in these studies further strengthens the reliability of the study findings. The mapping study explores prevalent instruments for CKD-aP assessment, ensuring real-world relevance and methodological rigor. The primary data collection in the mapping study and broad inclusion criteria maximise the study's applicability in clinical settings.
* This thesis provides contemporary insights into the economic burden of CKD-aP, offering valuable evidence of unmet needs for healthcare providers and highlighting high healthcare costs associated with varying CKD-aP severity levels. This information promotes the integration of new therapies in managing CKD-aP.
* The economic model benefits from robust data sources, including disease progression data derived from external trial data, utilities estimated from a mapping study, and evidence on resource use and costs obtained from primary data analysis, SHAREHD SWCRT data, and published literature.

**Limitations**

* One of the limitations in this thesis include the assumption of linearity in assessing symptom burden in relation to dialysis days and uncertainty regarding the timing of symptom assessments relative to dialysis sessions (before, during or after HD), posing methodological challenges. This uncertainty is relevant as patients may experience increased symptoms immediately after dialysis, potentially affecting the outcome. Additionally, the study did not explore the associations between change in symptom severity with changes in treatment, hospitalisation events, or acute illnesses.
* The mapping study focus solely on CKD-aP which may limit generalisability to other skin conditions or patient groups, and its applicability beyond the UK may be constrained.
* In terms of health care resource use, limitations include the inability to specify indications of the prescribed medications and potential recall bias in assessing symptom severity.
* Assumptions inherent in modelling analyses and potential differences in costs across settings restrict the generalisability of findings, necessitating caution in interpretation.
* The exclusion of non-English speakers in this study poses a limitation to the generalisability of the findings.

## 7.3 Recommendation for future Work

Moving forward, future research in this area could focus on several key areas:

**Detailed Analysis of Symptom Timing in Relation to Dialysis Sessions**: Our study (paper 1) suggested that these assessments are consistently performed on a specific day, either dialysis or non-dialysis day. We were unable to determine the timing of the completion of the instruments in relation to the dialysis session which can be either before or during or after dialysis session. This may be relevant as patients may feel more unwell immediately after dialysis due to dialysis process itself affecting their symptom burden. Investigating the specific timing of symptom assessments in relation to dialysis sessions (before, during, or after) could provide insights into how the dialysis process itself influences symptom severity and prompts a re-evaluation of whether dialysis adequately addresses patients' needs. Understanding these temporal dynamics may guide more effective symptom management strategies and determine the frequency of necessary assessments for specific research purposes.

**Refinement of Clinical Trial Designs**: Based on the observed variability in symptom severity among HD patients and the lack of evidence on optimal frequencies for measuring PROMs, future research should prioritise the routine and frequent assessment of PROMs in this population taking into account of symptom trajectory with standard care. If future studies should select participants with severe symptoms at baseline, an understanding that spontaneous improvements are possible should be factored into trial designs and standard care evaluations. There's a need to investigate the specific clinical practices contributing to symptom improvements, with the aim of incorporating these findings into targeted interventions and clinical trial protocols.

**Revisiting the 5-D Itch Measure**: Research should aim to address the structural issues within the 5-D itch measure to enhance its applicability to broader pruritus populations, including those without pruritus as the 5-D itch does not seem to perform logically if you have no itching and to consider the influence of recall periods on these measures.

**Medication Use and Comorbidities**: Exploring the reasons behind higher medication use in patients without CKD-aP compared to those with mild or moderate CKD-aP could uncover insights into medication indications for other comorbid conditions. This exploration prompts consideration: should some medications be re-evaluated and discontinued? Additionally, investigating medication use for indications beyond CKD-aP in the context of high comorbidity prevalence can provide a more comprehensive understanding of treatment patterns and their implications for patient care.

**Expanding on existing cost-effectiveness assessments**: Further investigations could explore the economic implications of Difelikefalin therapy and its long-term impact on HRQoL in real-world scenarios. Additionally, considering the existence of other potential CKD-aP treatments like MC2-25, it may be prudent to suggest that stakeholders involved in its commercialisation or evaluation could benefit from insights gained from this research.

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# Acknowledging collaboration and roles of co-authors

I confirm that the work presented here is my own, except for the work where it has been part of joint co-authorship.

Paper 1: Study design: PH, RG, TB, LD, SL, SA, SJW, MEW, JF, Analytical Plan: PH, SJW, JF, Study Management: PH, JF, SL, MEW, Site Setup: LD, SL, Data Collection: JF, RG, LD, SL, Data Analysis: PH, JF, Manuscript Writing: All.

Paper 2: Study design: PH, MHA, MEW, JF, Analytical Plan: PH, MHA, JF, Study Management: PH, LD, MEW, JF, Site Setup: LD, Data Collection: LD, JF, Data Analysis: PH, MHA, JF, Manuscript Writing: All.

Paper 3: Study design: MHA, AS, JBF. Analytical plan: MHA, PH, JBF, PT, study management: LD, JBF. Data collection: LD, MG, JBF. Data Analysis: MHA, PH, JBF, Manuscript writing: All

Paper 4: PT developed the economic model and drafted the outline in collaboration with JF. PEHS performed the analysis to estimate the resource use and costs for the model. JF analysed data from the KALM and SHAREHD studies. MH and AS performed the mapping study to estimate the utilities for the model. All authors contributed to the conceptualisation, writing, editing and finalising of the manuscript.

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# Appendices

## Included publications