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Development, Validation, and Interpretation of the Rheumatoid Arthritis Foot Disease Activity Index (RADAI-F5)

Hoque, Anika

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Development, validation, and interpretation of the Rheumatoid Arthritis Foot Disease Activity Index (RADAI-F5)

Anika Hoque (BSc Hons Podiatry)

A thesis submitted in partial fulfilment of the requirements of Glasgow Caledonian University for the degree of Doctor of Philosophy

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Abstract

Introduction: Rheumatoid arthritis (RA) frequently manifests in the foot and ankle, resulting in a decline in functional ability and overall quality of life. Early detection and intervention of foot inflammation is vital for optimising RA management and enhancing patient outcomes. However, the lack of a valid and reliable measure to assess foot disease in RA, coupled with the omission of these joints from disease indices and infrequent foot examinations in rheumatology settings, poses significant challenges and frequently results in suboptimal management of foot symptoms. To address this, the Rheumatoid Arthritis Foot Disease Activity Index (RADAI-F5) has emerged as a valid and reliable patient-reported outcome measure (PROM) that evaluates RA foot disease activity. A comprehensive examination of the clinical barriers and facilitators related to the tools implementation is essential to ensure its successful integration into rheumatology care settings. Musculoskeletal ultrasound (MSUS) has gained recognition as a valuable imaging technique for RA within rheumatology and podiatry settings. As indicated by rheumatologists, further validation is required to validate the RADAI-F5 against objective measures including clinical examination and MSUS. Moreover, additional evaluation of the measurement properties of the RADAI-F5, which includes determining the minimally important difference (MID) and assessing the tool's predictive validity, is imperative to allow for adequate clinical application and interpretation of the tool. Therefore, the primary objective of this thesis is to further validate and interpret the RADAI-F5, with the goal of effectively integrating it into routine clinical practice.

Methods: This research employed a multi-method approach consisting of five studies; integrating qualitative and quantitative methods. Study 1 employed qualitative methodology to explore the perspectives of RA patients and clinicians on the clinical utility of the RADAI-F5. Themes were identified through interpretative phenomenological analysis. Study 2 employed a cross-sectional design, where the construct validity of the RADAI-F5 was evaluated compared to MSUS and clinical examination. The validity was assessed through correlation coefficients and *a priori*-specified hypotheses. Study 3 was a longitudinal study to determine the MID of the RADAI-F5 in participants initiating biologic medication. These participants completed the RADAI-F5 assessments at baseline and three months and the MID was calculated using an anchor-based method. Study 4 investigated the efficacy of the RADAI-F5 in capturing disease activity in the tibiotalar joints (TTJ) and subtalar joints (STJ), utilising data from Study 2. Multivariable linear regression analyses explored the relationship between the RADAI-F5 scores and these structures. Lastly, Study 5 examined the predictive validity of the RADAI-F5 for adverse self-reported foot disability and impairment outcomes at 12 months, using previously published data. Binary logistic regression analysis was employed to assess the predictive validity of the RADAI-F5.

Results: Study 1 highlighted the potential value of the RADAI-F5 as a clinical tool to promote communication, guide management, help screen foot symptoms, monitor foot disease status, and promote patient education. Nevertheless, one of the main barriers highlighted by key stakeholders included the necessity for further validation of the tool against objective measures. In Study 2, the construct validity of the RADAI-F5 was established by demonstrating moderate-to-strong correlations between the instrument and MSUS-detected foot disease. Study 3 established the MID for the RADAI-F5, yielding a value of 1.02. This knowledge provides initial insights into RADAI-F5 score changes, which holds promise to assist in guiding management decisions in line with patients' perspectives of meaningful change. Results from Study 4 indicate a significant association between active foot arthritis at the TTJ or STJ and higher RADAI-F5 scores. This finding confirms the tools capability to capture disease in these structures, from a data-driven approach. Lastly, Study 5 revealed that two consecutive episodes of moderate-to-high foot disease activity serves as a significant predictor of foot disability in early RA patients. These preliminary findings support the predictive validity of this novel tool.

Conclusion: The RADAI-F5 demonstrates good measurement properties and offers an opportunity to enhance RA foot disease detection and treatment within the therapeutic 'window of opportunity'. The clinical application of this instrument shows potential in enhancing patients' foot outcomes and consequently, quality of life. Collectively, these findings further contribute to the validation and reliability of the tool, while also considering the perspectives of key stakeholders for successful implementation of the RADAI-F5 into rheumatology care settings. Overall, this tool holds potential for early foot disease detection in RA patients, enabling timely interventions to improve radiographic outcomes and functional disability.

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Abbreviations

ACR: American College of Rheumatology

ADL: Activities of Daily Living

AHP: Allied Health Professional

App: Application

BFS: Bristol Foot Score

BL: Baseline

BME: Bone marrow oedema

BMI: Body Mass Index

BMUS: British medical ultrasound society

BSR: British Society for Rheumatology

CASE: Consortium for the accreditation of sonographic education

CDAI: Clinical Disease Activity Index

CI: Confidence Interval

COSMIN: COnsensus-based Standards for the selection of health Measurement INstruments

CRP: C-reactive protein

DAS-28: Disease Activity Score in 28 joints

DAS-44: Disease Activity Score in 44 joints

DMARDs: Disease-Modifying Antirheumatic Drugs

EFAS: European Foot and Ankle Society

EHR: Electronic Health Records

ESR: Erythrocyte sedimentation rate

EULAR: European League Against Rheumatism

FAAM: Foot and Ankle Ability Measure

FAOS: Foot and Ankle Outcome Score

FFI: Foot Function Index

FFI: Foot Function Index- Revised

FFI-Dis: Foot Function Index- Disability subscale

FHSQ: Foot Health Status Questionnaire

FIS: Foot Impact Scale

FIS-AP: Foot impact scale – Activity Participation subscale

FIS-IF: Foot Impact Scale – Impairment and Footwear

FOs: Foot Orthosis

FPI: Foot Posture Index

GCU: Glasgow Caledonian University

GPs: General Practitioners

GRC: Global Rating of Change

GS: Greyscale

HAQ: Health Assessment Questionnaire

HAQ-DI: Health Assessment Questionnaire-Disability Index

HRQoL: Health-Related Quality of Life

ID: Identification

IMT: Intermetatarsal

IPA: Interpretive Phenomenological Analysis

IQR: Interquartile Range

KE: Knowledge exchange

MDA: Minimal Disease Activity

MDT: Multidisciplinary team

MFDPI: Manchester Foot Pain Disability Index

MID: Minimally important difference

MRI: Magnetic resonance imaging

MSK: Musculoskeletal

MSUS: Musculoskeletal ultrasound

MTPJ: Metatarsophalangeal joint

NHS: National Health Service

NICE: National Institute for Health and Care Excellence

NRAS: National Rheumatoid Arthritis Society

NRS: Numeric Rating Scale

OA: Osteoarthritis

OMERACT: Outcome Measures in Rheumatology

OR: Odds ratio

PBMs: Performance-based measures

PD: Power Doppler

PGA: Patient global assessment

PGA-VAS: Patient global assessment- visual analogue scale

PIFU: Patient-Initiated Follow-Up

PRCA: Podiatry Rheumatic Care Association

PROM: Patient-reported outcome measure

PsA: Psoriatic Arthritis

QoL: Quality of Life

RA: Rheumatoid arthritis

RADAI-F5: Rheumatoid Arthritis Foot Disease Activity Index

RAOS: Rheumatoid and Arthritis Outcome Score

RCT: Randomised Controlled Trial

RhF: Rheumatoid factor

ROFPAQ: Rowan Foot Pain Assessment Questionnaire

ROI: Region of interest

SAFE: Salford Arthritis Foot Evaluation

SDAI: Simplified Disease Activity Index

SEFAS: Self-Reported Foot and Ankle Score

SEM: Standard Error of Measurement

SH: Synovial hypertrophy

SIG: Special Interest Group

SJC: Swollen Joint Count

SPSS: Statistical Program for the Social Sciences

SSR: Scottish Society for Rheumatology

STJ: Subtalar Joint

T2T: Treat-to-Target

TJC: Tender Joint Count

TNJ: Talonavicular Joint

TTJ: Tibiotalar Joint

UK: United Kingdom

VAS: Visual Analogue Scale

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Publications and Conference Presentations

Some of the work carried out as part of this thesis has been published as articles in journals and presented at national and international conferences.

Published papers:

- Hoque, A., Steultjens, M., Dickson, D.M. and Hendry, G.J. (2022) 'Patients' and clinicians' perspectives on the clinical utility of the Rheumatoid Arthritis Foot Disease Activity Index', *Rheumatology International,* 42(10), pp. 1807-1817. Doi: 10.1007/s00296-022-05147-8.

- Hoque, A., Steultjens, M., Dickson, D.M. and Hendry, G.J. (2023) 'Assessing the construct validity of musculoskeletal ultrasound and the rheumatoid arthritis foot disease activity index (RADAI-F5) for managing rheumatoid foot disease', *Rheumatology advances in practice,* 7(2), pp. rkad048. Doi: 10.1093/rap/rkad048.

Presentation, abstract publications and short papers:

- Hoque, A., Steultjens, M., Dickson, D.M. and Hendry, G.J. (2022) **"Patients' and clinicians' perspectives on the clinical utility of the Rheumatoid Arthritis Foot Disease Activity Index."** Scottish Society for Rheumatology Autumn conference, Glasgow, 29th October 2021. Poster presentation.

- Hoque, A., Steultjens, M., Dickson, D.M. and Hendry, G.J. (2022) **"Patients' and clinicians' perspectives on the clinical facilitators and barriers of the Rheumatoid Arthritis Foot Disease Activity Index."** Doi: 10.1186/s13047-022-00529-4 Royal College of Podiatry conference, Liverpool, 18-20th November 2021. Oral presentation.

- Hoque, A., Steultjens, M., Dickson, D.M. and Hendry, G.J. (2022) Patients' and clinicians' perspectives on the clinical utility of the Rheumatoid Arthritis Foot Disease Activity Index, *Rheumatology*, Volume 61, Issue Supplement_1, May 2022, keac133.184. Doi: 10.1093/rheumatology/keac133.184. British Society for Rheumatology conference, Glasgow, 25-27th April 2022. Poster presentation.

- Hoque, A., Steultjens, M., Dickson, D.M. and Hendry, G.J. (2022) "Patient and clinician perspectives on implementing the radai-f5 tool to help inform the assessment and management of foot disease in RA: a qualitative study *Annals of the Rheumatic Diseases* 2022; 81:1103. EULAR conference, Copenhagen 1-4 June 2022. Poster presentation.

- Hoque, A., Steultjens, M., Dickson, D.M. and Hendry, G.J. (2022) "Innovation into action: Using the RADAI-F5 to target the window of opportunity for maintaining foot health in

rheumatoid arthritis." Royal College of Podiatry conference, Liverpool 7-9th July 2022. Oral presentation.

- Hoque, A., Steultjens, M., Dickson, D.M. and Hendry, G.J. (2023) Preliminary evaluation of the rheumatoid arthritis foot disease activity index (radai-f5) as a screening tool for foot-related disability. *Annals of the Rheumatic Diseases;* 82**:**567-568. Doi. 10.1136/annrheumdis-2023-eular.3504. European Alliance of Associations for Rheumatology conference, Milan 17th May 2023. Poster presentation

- Hoque, A., Steultjens, M., Dickson, D.M. and Hendry, G.J. (2023) The RADAI-F5: A novel tool. *Podiatry Now online journal;* July/August issue pp. 46 - 47. Short case study.

Declaration

Development, validation, and interpretation of the Rheumatoid Arthritis Foot Disease Activity Index (RADAI-F5)

Anika Hoque (BSc Hons Podiatry)

A thesis submitted in partial fulfilment of the requirements of Glasgow Caledonian University for the degree of Doctor of Philosophy

This thesis is my own work and has not previously been presented for assessment for any other degree.

Covid-19 impact statement:

This section aims to provide an overview of how the COVID-19 global pandemic has influenced various aspects of my doctoral journey.

The COVID-19 pandemic posed challenges in my doctoral journey, leading to adjustments in data collection methods and research timelines. When undertaking my PgCert in Musculoskeletal

Ultrasound, limited availability of individuals with inflammatory arthritis in NHS podiatry clinics delayed my exposure to this patient group. Despite proficiency in general foot scanning, I encountered a lack of confidence in scanning individuals with Rheumatoid Arthritis (RA). Nontheless, with guidance from my ultrasound mentors and support from skilled team members, I navigated this learning curve, mastering specific adjustments and techniques to enhance my skills in scanning individuals with RA.

In adherence to social distancing measures, qualitative interviews for Study 1 (Chapter 3) were conducted remotely to ensure the safety of participants. While this approach facilitated broader national participation, it presented nuanced challenges inherent in engaging with individuals within a virtual framework. The transition to virtual interaction introduced difficulties in building rapport with participants, potentially impacting the depth of data collected. Furthermore, noteworthy limitations encompassed the inability to observe and analyse body language and non-verbal cues, elements conventionally integral to the interpretative framework of qualitative research.

The ethical considerations in recruiting participants from the vulnerable RA group were pivotal, specifically for the FOOTRADIUS study (Chapter 4). Safeguards, including opt-out forms, transportation, limiting contact with other individuals and providing well-ventilated rooms with social distancing had to be in place to ensure participant well-being. Despite adaptations, the study faced additional limitations. The unavailability of on-campus staff for the FOOTRADIUS study affected the blinding of the clinical assessment outcome measure. Moreover, it was not possible to conduct intra-rater reliability assessments for a novel ultrasound (US) scoring method due to a shortage of US trained staff on campus and the imperative need minimise contact with vulnerable participants. Moreover, the FOOTRADIUS study outcomes were significantly affected by the lack of recent Disease Activity Scores (DAS-28), stemming from restricted face-to-face appointments during Covid-19. Some DAS-28 scores used in the study dated back as far as two years, creating a temporal misalignment that potentially introduced discrepancies in evaluating the real-time relationship between US findings and disease activity. These limitations are further highlighted in Chapter 4.

Most notably, in chapter 5 (Minimally Important Difference study), challenges in recruiting individuals with RA receiving biologic drugs were exacerbated by the COVID-19 pandemic. Lockdowns, healthcare facility restrictions, and reluctance to engage in non-essential medical appointments disrupted clinic visits crucial for enrolment of these individuals, resulting in a noticeable sample size deficit, affecting statistical power and generalisability of the study findings. Due to the vulnerability of RA patients and the lack of face-to-face appointments during the

pandemic, I opted not to amend the ethics application, considering it unlikely to result in an increase in the sample size. Consequently, the study was limited to 15 participants to ensure the timely completion of my doctoral thesis, acknowledging this as a significant limitation.

Despite challenges, I demonstrated flexibility in adapting to a dynamic environment. Coursework in my initial year facilitated targeted progress amid the immediate impacts of COVID-19 on my research. This period also afforded me the opportunity to formulate alternative plans in anticipation of prolonged pandemic restrictions, enabling adjustments to the timelines for each study. The flexibility I demonstrated underscores the resilience required to navigate the unique challenges of the pandemic and maintain steady advancement in unprecedented circumstances.

Chapter 1. Introduction

This chapter serves as an introduction to this thesis, providing an overview of the objectives and aims of this research.

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory condition characterised by synovitis and peri-articular involvement. The foot and ankle region is notably susceptible to the effects of this condition, as supported by Reina-Bueno et al., (2021). A significant proportion, ranging from 70% to 90%, of individuals diagnosed with RA report experiencing pain specifically

in this region (Otter et al., 2010; Wilson et al., 2017). Additionally, the impact of RA on these foot joints can lead to significant joint damage, functional impairment, and a negative impact on quality of life (QoL) (Martinec, Pinjatela & Balen, 2019). Therefore, early and preventive management strategies aimed at controlling foot synovitis is crucial for minimising poor radiographic and functional outcomes in RA (Radu & Bangau, 2021).

In recent years, there has been a paradigm shift towards incorporating patients' perspectives alongside clinicians' reports, imaging, and laboratory findings. In 2010, Woodburn and colleagues proposed a fundamental shift in rheumatology podiatry care, advocating for the inclusion of foot disease evaluation in early RA to facilitate timely and comprehensive management (Woodburn et al., 2010). This approach emphasised personalised treatment plans, tight control of foot disease, and disease management based on defined criteria that combine objective image-based techniques and patient-reported outcomes (PROMs) that assess foot disease activity (Woodburn et al., 2010). This rationale aligns with the concept of a 'window of opportunity', emphasising early aggressive therapy initiation to maximise disease control, prevent irreversible joint damage, and improve long-term patient outcomes (Radu & Bangau, 2021). Nevertheless, an RA-specific PROM that can adequately identify foot disease is currently lacking.

Consequently, there was a critical need for the development of an RA-specific PROM that can effectively identify and evaluate foot disease activity. To address this, the Rheumatoid Arthritis Foot Disease Activity Index (RADAI-F5) was developed. The RADAI-F5 is a five-item clinically feasible PROM that has exhibited excellent measurement properties in a previous validation study published prior to this thesis (Hoque et al., 2021) (Appendix A). The RADAI-F5 can potentially be integrated into routine clinical practice, facilitating treat-to-target (T2T) strategies for foot disease management in this patient population. Nevertheless, further investigation is imperative to assess the RADAI-F5's unaddressed psychometric properties such as determining the tools minimally important difference (MID) and predictive validity. Clinician scepticism towards the tool's validity against objective measures also necessitates establishing its construct validity in relation to musculoskeletal ultrasound (MSUS) and clinical examination. Moreover, it is essential to gather insights from both patients and clinicians regarding the barriers and facilitators associated with the implementation of the RADAI-F5, ensuring its successful adoption in rheumatology care settings. Furthermore, questions remain regarding the RADAI-F5s ability to capture disease activity in the tibiotalar joint (TTJ) and subtalar joint (STJ). Addressing these knowledge gaps and establishing further validity and reliability of the RADAI-F5 could contribute to increased awareness and detection of foot disease, potentially leading to improved management strategies for individuals with RA.

1.1 Thesis aims:

This thesis aims to answer the following research questions:

1. What are the perspectives of patients and clinicians regarding the implementation of the RADAI-F5 tool in rheumatology care settings?

2. What is the level of association between the RADAI-F5 and MSUS in detecting foot disease in RA?

3. What is the level of association between the RADAI-F5 and clinical examination in detecting foot disease in RA?

4. What is the MID of the RADAI-F5, using an anchor-based approach?

5. Does the RADAI-F5 effectively capture disease activity in the STJ and TTJ?

6. What is the predictive validity of the RADAI-F5 in terms of its ability to detect future foot-related disability and impairment in an early RA cohort?

A series of five studies were conducted to address the following objectives:

1.1.1 Chapter 3 objectives

- Explore the perceptions of patients and clinicians regarding the clinical utility of the RADAI-F5 in informing the assessment and management of foot disease in RA.

1.1.2 Chapter 4 objectives

- Evaluate the level of association between the RADAI-F5 and MSUS-detected foot disease.

- Evaluate the level of association between the RADAI-F5 and clinical assessments of the foot and ankle.

1.1.3 Chapter 5 objectives

- Evaluate the MID of the RADAI-F5 using an anchor-based approach.

1.1.4 Chapter 6 objectives

- Evaluate if RADAI-F5 scores are independently influenced by TTJ and STJ disease.

1.1.5 Chapter 7 objectives

- Determine the predictive validity of the RADAI-F5 in relation to future RA foot-related disability and impairment.

1.1.6 Thesis structure:

This PhD thesis comprises of eight chapters. Chapter 2 provides a narrative review of RA foot literature and highlights existing knowledge gaps in the field, justifying the studies in this thesis. Chapter 3 involves a qualitative study exploring the perspectives of RA patients, rheumatologists, and allied health professionals (AHPs) on the clinical utility of the RADAI-F5. Chapter 4 presents a cross-sectional study investigating the association between the RADAI-F5, MSUS, and clinical

examination. Chapter 5 focuses on determining the MID for the RADAI-F5 through a longitudinal embedded study. Chapter 6 evaluates the RADAI-F5's efficacy in capturing foot disease at the TTJ and STJ, using data from Chapter 4. Chapter 7 assesses the predictive validity of the RADAI-F5 in evaluating foot-related disability in an early RA cohort. Finally, Chapter 8 provides a comprehensive discussion of the thesis findings, implications for clinical care, and potential future research directions. Table 1 summarises the knowledge gaps, hypothesis, objective, and corresponding chapter for each study. Additionally, throughout this PhD thesis, key stakeholders were actively involved, and each respective chapter highlights the findings from these discussions.

TABLE 1: SUMMARY OF THESIS STUDIES

Knowledge gap	Hypothesis	Objective	Chapter
Limited literature exists on patient and clinician perspectives regarding the integration of a novel RA foot PROM into routine outpatient clinics.	No hypothesis: open-ended exploration to identify emerging themes.	To explore patient and clinician perceptions on the potential use of the RADAI-F5 tool to help inform the assessment and management of foot disease in RA in rheumatology care settings.	**Chapter 3 (Qualitative study)**
It is unclear whether the RADAI-F5 exhibits a strong relationship with objective clinical variables such as MSUS and clinical examinations for tenderness and swelling.	The RADAI-F5 will have a moderate relationship with MSUS features such as synovial hypertrophy, synovitis, tenosynovitis and clinical examinations for tenderness and swelling. A weak relationship will exist between the RADAI-F5 and erosions detected using MSUS	To determine if and to what extent MSUS-detected inflammatory foot disease is associated with self-reported foot disease quantified using the RADAI-F5. To determine if and to what extent clinical examination of foot disease is associated with the RADAI-F5.	**Chapter 4 (FOOTRADIUS study)**
There is currently no knowledge of the MID of the RADAI-F5 from the patients' perspective	No hypothesis	To investigate the MID of the RADAI-F5 at 3 months in RA patients who are commencing a new biologic therapy.	**Chapter 5 (MID chapter)**
There is a gap in understanding whether patients consider the ankle joint complex to be part of their foot, and whether the RADAI-F5 scores are influenced by TTJ and STJ disease. There is a gap in knowledge regarding whether the RADAI-F5 encompasses the TTJ and STJ	No hypothesis	To evaluate if the RADAI-F5 can detect TTJ and STJ disease	**Chapter 6 (Regression analysis study)**
Limited knowledge exists on whether self-reported foot disease activity can effectively predict poor self-reported foot-related disability and impairment.	No hypothesis- exploratory to identify preliminary patterns	To evaluate if the RADAI-F5 can predict foot related disability in an early RA cohort.	**Chapter 7 (Predictive validity study)**

MID: Minimally important difference, MSUS: Musculoskeletal ultrasound, PROM: patient-reported outcome measure, RA: Rheumatoid arthritis, RADAI-F5: Rheumatoid arthritis Foot disease activity Index, STJ: Subtalar joint, TTJ: tibiotalar joint

Chapter 2. Narrative review

This chapter presents a concise narrative review highlighting foot-related issues in RA and limitations in current methods for evaluating foot disease. Additionally, the utility of MSUS imaging in podiatry and the implementation of RA-specific foot PROMs in rheumatology settings is discussed. Finally, this chapter introduces the RADAI-F5 tool. Overall, this chapter highlights the gaps in the literature, underscoring the necessity for the studies conducted within the framework of this doctoral research.

2.1 Chapter overview

RA is widely acknowledged as the most common inflammatory joint disease, with estimated prevalence rates ranging from 0.5% to 1% in the United Kingdom (UK) population (Allen, Carville & McKenna, 2018). Notably, there is a gender disparity in RA incidence, as women are approximately three times more susceptible to experiencing RA onset (Sokka et al., 2009). While RA can manifest at any age, it is predominately observed in individuals aged 40 to 60 years (Olofsson et al., 2017), with some reports indicating an earlier onset at 30 years of age (Pawlowska et al., 2011). RA is characterised by chronic inflammation that predominantly affects small joints, such as those in the hands and feet, but also involves extra-articular manifestations (Olofsson et al., 2017; Bonfiglioli et al., 2018). Moreover, due to its chronic nature, RA can result in long-term disability, physical inactivity, social isolation, unemployment, and a substantial decline in QoL (Ionescu et al., 2022). In Scotland, RA ranks 23rd in disease burden (Jeffery, 2014), consequently imposing significant financial costs on individuals and healthcare systems. The total yearly cost of RA to the British economy, encompassing expenses related to caregivers, nursing homes, private expenditures, sick leave, and work-related disability, ranges between £3.8 and £4.8 billion (Bullock et al., 2019; Sturgeon et al., 2016). These findings highlight the significant burden that RA places on the UK healthcare system and the broader economy.

The presence of inflammation in the feet is widely acknowledged as a distinctive feature of RA. Foot inflammation is commonly observed during the early stages of RA and continues to persist throughout the progression of the disease (Terao et al., 2013). RA-related foot pathology can manifest in various forms, including synovitis, joint destruction, deformities, and functional impairments. These multifaceted manifestations contribute to the development of challenges associated with walking and performing routine daily activities (Rao, Riskowski & Hannan, 2012). Despite consensus on the high prevalence of foot involvement in RA, standardising the assessment and monitoring of foot disease activity presents a significant challenge. The absence of a

standardised approach to assessing foot disease in RA leads to inconsistent diagnosis and treatment decisions for the foot and ankle (Otter et al., 2010). Despite the technological progress that allows for the assessment of intrinsic RA foot kinematics through methodologies such as three-dimensional foot models, motion capture systems, force plates, and electromyography (Barns et al., 2013; Woodburn et al., 2003; Deschamps et al., 2011), it is pertinent to acknowledge that these models predominantly focus on the investigation of foot biomechanics. They do not directly encompass the underlying inflammatory processes linked to RA in the feet.

Over the past decade, there has been a notable shift in recognising the significance of integrating the patients' perspective. This shift highlights the importance of using PROMs in conjunction with imaging and laboratory results to provide a comprehensive assessment of healthcare outcomes (Hsiao & Fraenkel, 2017; Santana et al., 2018;). PROMs refer to standardised questionnaires or assessments completed by patients, aiming to collect information about their health, symptoms, functional abilities, and QoL (Churruca et al., 2021). In the context of RA, a considerable body of research has utilised PROMs to assess disease-related foot burden, specifically focusing on indicators such as RA-related foot disability or self-reported foot pain. These measures serve as valuable indicators of foot involvement in RA and contribute to the adoption of a comprehensive approach in evaluating the impact of the disease (Walmsley et al., 2010).

While these PROMs and pain scores provide valuable insights into the subjective experiences of individuals with RA, reliance on these measures has limitations. Firstly, the perception and reporting of pain can vary among individuals, and factors such as psychological distress and coping mechanisms can influence symptom reporting (Backman, 2006). Secondly, it is important to note that the presence of pain does not always signify ongoing foot disease activity, similar to how pain alone does not necessarily indicate suboptimal inflammatory control. Moreover, existing foot PROMs for RA primarily evaluate disability, impairment, and QoL outcomes, rather than specifically addressing foot disease activity. To address this, developing foot-specific PROMs that explicitly measure and track foot disease activity is crucial, offering valuable insights for informed local and systemic foot management in the RA patient population.

Clinical examination and MSUS offer objective measures for evaluating foot involvement in RA (Bowen et al., 2013). While foot examinations including joint palpation, visual observations and/or performance-based measures (PBMs) are recommended, they are seldom performed in rheumatology clinics (Stolt et al., 2022). Imaging techniques such as MSUS provide valuable insights into the disease process as they enable identification of synovitis, soft tissue inflammation and joint erosions, thus allowing for a more accurate assessment of RA foot involvement. However, MSUS has its own limitations, including the need for specialised training (Agrawal,

Bhagat & Dasgupta, 2009), accessability to the equipment, and the potential for false negatives or positives (Lento & Primack., 2008). Moreover, the scarcity of trained podiatrists proficient in MSUS exacerbates the challenges faced in diagnosing and monitoring foot disease in rheumatology care settings.

The lack of a standardised, valid, reliable, and clinically feasible assessment method for evaluating foot disease involvement in RA highlights the imperative need for the development of a comprehensive tool that can be utilised by all members of the rheumatology multidisciplinary team (MDT). In 2010, Woodburn and colleagues emphasised a new podiatry care framework for early-stage RA, advocating for tight foot disease control and disease monitoring based on predefined criteria integrating objective image-based techniques and PROMs. Despite the aforementioned publication over a decade ago, there remained a notable absence of a suitable PROM specifically designed to address foot disease in RA. Additionally, the exclusion of foot joints from the Disease Activity Score for 28 joints (DAS-28), coupled with the challenges of routine clinical foot examination and limited availability of MSUS in rheumatology care settings, creates a significant gap in assessing and managing foot disease in RA (Bakker et al., 2012).

To address these constraints, the RADAI-F5 has emerged as a promising and clinically viable tool that holds the potential to offer a solution. Briefly, the RADAI-F5 (Appendix B) is a valid and reliable 5-item PROM specifically developed to assess foot disease activity in RA (Hoque et al., 2021). The RADAI-F5, derived from the Modified RADAI (mRADAI-5) (Leeb et al., 2014; Rintelen et al., 2009) was developed through specific modifications to the mRADAI-5, including the addition of an introductory statement: "Thinking only of your feet," as well as subsequent revisions to the original questions. The RADAI-F5 questions are scored on a numerical rating scale (NRS) and are presented as follows: "How active was your arthritis IN YOUR FEET over the last 6 months?" (rated on a scale of 0 to 10, where 0 indicates complete inactivity and 10 represents extreme activity); "How active is your FOOT arthritis today with respect to joint tenderness and swelling?" (rated on a scale of 0 to 10, where 0 signifies complete inactivity and 10 denotes extreme activity); "How severe is your arthritis pain IN YOUR FEET today?" (rated on a scale of 0 to 10, where 0 indicates no pain and 10 signifies unbearable pain); "How would you describe your general FOOT health today?" (rated on a scale of 0 to 10, where 0 indicates very good and 10 represents very bad); "Did you experience foot joint stiffness on awakening yesterday morning? If yes, how long did this stiffness IN YOUR FEET last?" (rated on a scale of 0 to 10, where 0 signifies no stiffness and 10 indicates stiffness throughout the entire day). The RADAI-F5 is evaluated based on an average summary score, ranging from 0 to 10. The prospective implementation of RADAI-F5 may contribute to addressing identified challenges in the current

management of the RA foot, supporting a patient-centered approach for the detection and monitoring of the RA foot disease.This chapter serves to establish the groundwork for the validation of the RADAI-F5.

2.2 Primary disease process:

Comprehending the inflammatory process in RA and its impact on the feet requires an understanding of synovial joint anatomy. In RA, immune-mediated inflammation triggers excessive synovial fluid production, resulting in joint swelling and disruption of normal joint components (Figure 1) (Versus Arthritis, 2022). Persistent synovitis leads to the development of an abnormal tissue layer known as the pannus (Takeuchi et al., 2019), which invades and erodes cartilage and bone, leading to irreversible joint damage and deformity. This erosion and bone damage contribute to decreased bone density, compromised joint structure, and an increased risk of fractures. Furthermore, inflammation can affect the joint capsule, resulting in reduced joint alignment. Ligaments and tendons, essential for joint stability, is often impacted by synovitis or tenosynovitis resulting in joint laxity and instability (Tamer, 2013). This often results in RA-related foot abnormalities including hindfoot valgus, flattened arches, subluxed metatarsal heads, hallux abducto valgus, and clawed toes (Chakraborty, Hati & Chandra, 2022). These abnormalities, coupled with forefoot and hindfoot joint synovitis, can intensify functional impairment in individuals with RA (Chakraborty, Hati & Chandra, 2022). Figure 2 illustrates frequent foot pathologies and lesions associated with RA.
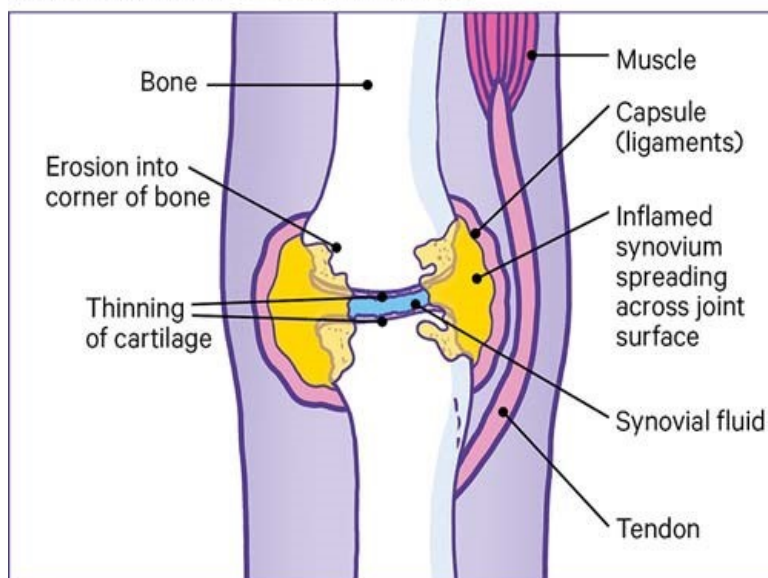
FIGURE 1: PRIMARY DISEASE PROCESS IN RA JOINT [REPRODUCED FROM VERSUS ARTHRITIS (2022)]
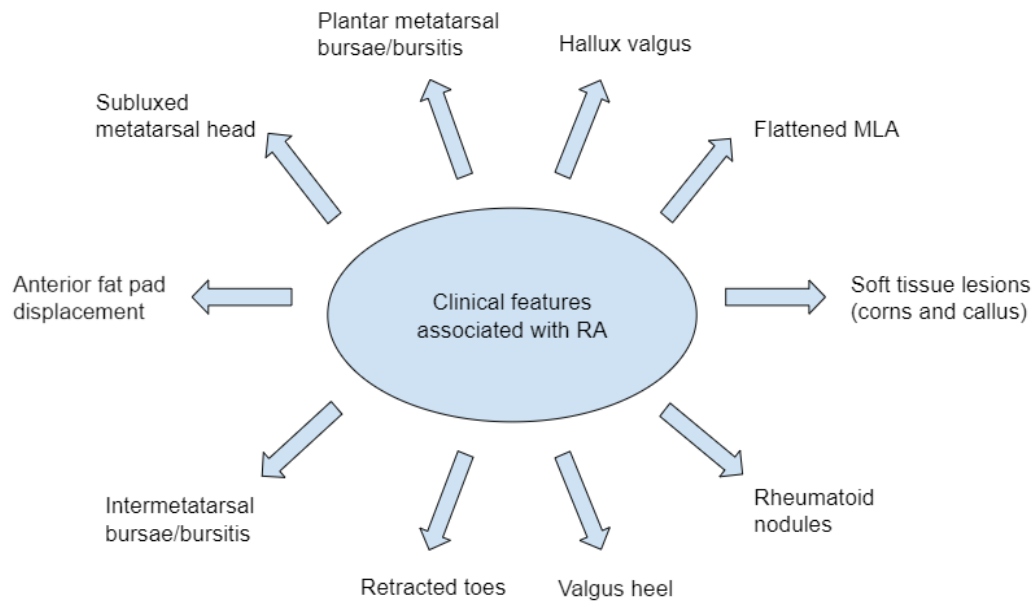
FIGURE 2: COMMON FOOT PATHOLOGIES AND LESIONS ASSOCIATED WITH RA

2.3 Measures of disease activity:

RA exhibits considerable heterogeneity in terms of its clinical manifestation and progression across individuals, highlighting the importance of regular disease assessment. Validated indices such as the Disease Activity Score for 44 joints (DAS44), DAS28, Clinical Disease Activity Index (CDAI), and Simplified Disease Activity Index (SDAI) are often employed in rheumatology for assessing RA disease activity (Aletha & Smolen, 2005; Messelink et al., 2023). Of these, the DAS28 is the most commonly utilised metric to determine global disease activity and guide medical care (Allen, Carville & McKenna, 2018; Mena-Vázquez et al., 2023). The DAS28 consists of 28 tender joint counts (TJC), 28 swollen joint counts (SJC), patient global assessment (PGA), rated on a Visual Analogue Scale (VAS), and incorporating either erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) levels. Figure 3 depicts the DAS-28-ESR index.

FIGURE 3: DISEASE ACTIVITY SCORE IN 28 JOINTS (DAS28-ESR), DEPICTING THE OMISSION OF FOOT AND ANKLE JOINTS FROM THIS INDEX

Despite the widespread use of the DAS-28 in clinical and research settings (Mena-Vázquez et al., 2023), the adoption of the DAS-28 index in day-to-day clinical practice has been scrutinised. This can be attributed to challenges related to data collection and score calculation (Pincus, 2006; Orr et al., 2018). The Covid-19 pandemic has further hindered its regular completion due to reduced frequency of face-to-face appointments. Moreover, assessing patients' overall health status is often considered subjective (Orr et al., 2018). A recent meta-analysis conducted by Ferreira et al., (2021) has questioned the relevance of integrating PGA into remission assessments. This concern stems from the reliance on subjective perceptions of disease burden, which may be influenced by noninflammatory mechanisms. Additionally, the DAS-28 development lacked patient input in PGA-Visual Analogue Scale (PGA-VAS) wording, resulting in no established 'gold standard' (French et al., 2013). Inconsistent phrasing of the PGA-VAS in the literature lacks standardised clarity, introducing variations that impact disease activity assessments and treat-to-target objectives (Prevoo et al., 1995; van der Heijde, 1998; French et al., 2013). The heterogeneous wording of PGAs requires cautious interpretation, as evidenced by variations in DAS28 scores. A growing body of evidence indicates that patients in near-remission with persistently elevated PGA may not experience improvements in pain, fatigue, or physical function, even with well-controlled inflammation (Martins et al., 2015; Brkic et al., 2022). A study by Ferreira suggested that 12% to 38% of RA patients fail remission due to a PGA score >1, leading to potential overtreatment (Ferreira, Gossec and Silva, 2022). Moreover, the discordanance observed between PGA and objective markers of inflammation emphasises the need to address elevated PGAs when formulating treatment recommendations (Brites et al., 2021). Several studies have indicated that only swollen joints and acute phase reactants, rather than PGA, exhibit a strong association with radiographic progression (Aletha & Smolen, 2011; Studenic et al., 2020; Navarro- Compán et al.,

2015). This challenges the inclusion of PGA in remission assessments, as preventing joint damage is a crucial goal in the treatment of RA. The limitations of the PGA in the DAS-28 highlight the need to account for potential variations in PGA versions across studies, introducing variability that impacts the comparability of DAS-28 scores between the studies in this thesis and other studies utilising different PGA formulations.

Additionally, a notable drawback of the DAS28 is the exclusion of foot and ankle joints from the clinical evaluation of TJC and SJC (Figure 3) (Van der Leeden et al., 2010; Bakker et al., 2012). This omission from the more comprehensive DAS-44 is attributed to practical considerations such as time constraints and restricted accessibility of the feet in comparison to the hands (Greenmyer et al., 2020; Otter et al., 2008). However, it is important to note that in a study conducted by Landewe et al., (2006), it was reported that the exclusion of foot joints from the DAS-28 led to discordant observations of remission in 96% of patients when compared to the DAS-44. These findings raised concerns regarding the validity of the remission cut-off point employed in the DAS-28, whilst emphasising the significance of incorporating foot joints into the evaluation of RA to accurately capture systemic disease (Landewe et al., 2006).

Excluding foot joints from the DAS-28 has been extensively documented to underestimate foot inflammation. Despite achieving remission according to the DAS-28 criteria, approximately one-third of patients still exhibit foot synovitis, increasing their risk of structural joint damage (Wechalekar et al., 2016). This omission results in a significant number of RA patients with foot synovitis receiving suboptimal treatment and foot-health needs remain overlooked (Van der Leeden et al., 2010; Bakker et al., 2012; Landewe et al., 2006; Wechalekar et al., 2016; Simonsen et al., 2021). Consequently, the omission of foot assessments from the DAS-28 may lead to delayed systemic disease management for patients. Contrary to this, it is important to recognise that medication decisions should not be determined based off the DAS-28 in isolation. Rheumatologists rely on a myriad of assessments such as patient history, physical examination, laboratory tests, and PROMs in conjunction with the DAS-28 to inform pharmacological management (Combe et al., 2007; Radu & Bangau, 2021). Ultimately, the decision to escalate medication should be based on a holistic assessment of the patient's overall disease burden, including the feet and treatment response, considering individual patient characteristics, and weighing potential risks and benefits before making informed treatment adjustments. However, a PROM that quantifies active foot disease could help facilitate appropriate pharmacological management, appropriate referrals from AHPs to rheumatologists and mitigate the aforementioned challenges.

Other commonly used outcome measures for assessing RA disease activity include the CDAI and SDAI, which combine clinical variables including joint counts, patient-reported disease activity, acute phase reactants, and physician assessment (Aletha & Smolen, 2005). These indices offer a standardised and practical approach to assessing RA disease without requiring complex tests or specific joint assessment techniques. However, it is important to note that these disease activity indicators also do not encompass the foot and ankle joints, thus limiting their ability to capture global disease. Wechalekar et al., (2016) reported that a significant percentage (25–36%) of individuals in remission according to SDAI and CDAI still exhibited foot synovitis. In contrast, a cross-sectional study by Won-Lee and colleagues (2019) revealed that among patients in remission according to SDAI and CDAI, only 6.7% and 4.2% were diagnosed with foot and ankle arthritis using the DAS44, respectively. Whereas in patients in DAS28-ESR and DAS28-CRP remission, 12.1% (21/174) and 11.1% (38/343) exhibited foot and ankle arthritis, respectively. These findings may suggest that within the context of this study, the DAS-28, the SDAI and CDAI may be more suitable for detecting foot disease activity. Nevertheless, foot synovitis can still persist in patients who are considered eligible for a remission classification as defined by the SDAI and CDAI. Therefore, there is a still potential for foot synovitis to be under-treated, highlighting the need for a standardised, valid and reliable approach to assess active foot disease.

Consequently, it has been widely recommended to include the examination of the foot and ankle joints to identify early swelling and tenderness, supporting accurate and timely management (Simonsen et al., 2021; Alazzawi et al., 2017). However, it is important to acknowledge that clinical examination of the RA foot has limitations in terms of subjectivity, reliability, and poor correlation with imaging techniques. Comparative studies between clinical examination and magnetic resonance imaging (MRI), considered the gold standard imaging modality in RA, have demonstrated low sensitivity (55-83%) and specificity (23-46%) for clinical examination in evaluating tibiotalar synovitis (Rojas- Villarraga et al., 2009). Szkudlarek et al. (2004), who examined the metatarsophalangeal joints (MTPJs) using MSUS and clinical examination, also revealed a significantly higher detection rate of joint effusion and synovitis with MSUS compared to clinical examination. Moreover, clinical examinations exhibit significant inter-observer variability, leading to inconsistencies in findings among practitioners (Vergne-Salle et al., 2020).

2.4 Advancements in Imaging Techniques for RA Foot Assessment

Imaging has been essential in the diagnosis and staging of RA disease, while also providing useful in driving treatment choices. Conventional radiography has been the imaging modality of choice for measuring structural damage in the RA population. Nevertheless, MSUS and MRI are gaining popularity in clinical and research contexts due to its sensitivity in detecting inflammation

(synovitis, tenosynovitis, and bursitis) and identifying early signs of bone degeneration. The next section will discuss different imaging modalities within RA.

2.4.1 Radiography

Conventional radiography is a cost-effective, accessible and reliable imaging modality for RA as it effectively identifies structural deterioration, particularly bone erosions (Raghav et al., 2010). Radiographs previously played a critical role in diagnosing and classifying RA according to the ACR 1987 criteria (Arnett et al., 1988), while also evaluating the effectiveness of disease-modifying antirheumatic drugs (DMARDs) and biologic drugs (Ramos-Petersen et al., 2021). Despite National Instiute for Health and Care Excellence (NICE) guidelines recommending X-ray use for evaluating adults with persistent synovitis and suspected RA in the hands and feet (NICE, 2018), its routine application in podiatry is limited, typically reserved for drug trials or orthopedic referrals. Furthermore, in rheumatology care settings, the clinical utility of radiographs in evaluating and monitoring the impact of foot inflammation on sustaining remission and radiographic progression is mainly limited to initial diagnosis.

Radiographs possess inherent limitations that impact its clinical utility within rheumatology care settings. X-rays cannot directly identify active inflammation associated with the disease process, which is crucial for appropriate treatment planning in RA (Suleman et al., 2018). Furthermore, erosions may not become visible on radiographs until up to two years after disease onset, potentially causing a delay in appropriate management and resulting in further radiographic damage (McQueen et al., 2001). Additionally, radiographs are unable to capture the involvement of peri-articular soft tissues and the use of ionising radiation poses a notable concern (Suleman et al., 2018). These limitations have the potential to impede early intervention and hinder effective disease control. While radiographs have traditionally been regarded as the gold standard imaging modality for RA, there is a growing preference for MRI and MSUS, as they provide additional information on inflammatory characteristics associated with RA, facilitating early disease detection and guiding management.

2.4.2 MRI

MRI is increasingly recognised as the preferred imaging modality for RA due to its ability to provide enhanced soft tissue contrast and high-resolution images, without the use of ionising radiation (Sudoł-Szopińska et al., 2017). Its superiority is further supported by its ability to detect synovitis, making MRI the recommended imaging modality by EULAR for early detection and monitoring of disease (Colebach et al., 2013). MRI can detect synovitis, tenosynovitis, and pre-erosion changes associated with RA, providing crucial information that can influence therapeutic disease management (Weaver et al., 2022). Additionally, MRI is particularly valuable in

identifying bone marrow oedema (BME), which serves as a precursor to erosions in early RA (Backhaus & Scheel, 2006).

In the context of foot synovitis, MRI has proven to be a valuable tool with superior sensitivity in detecting RA foot-related pathology compared to clinical examination (Sudoł-Szopińska et al., 2017; Backhaus et al., 2006). Studies have shown that foot joint inflammation in RA is common and can be as prevalent as inflammation in the hand joints. Additionally, it is possible for foot joint inflammation to exist without any noticeable signs of inflammation in the corresponding hand joints (Sudoł-Szopińska et al., 2017; Backhaus et al., 2006; McQueen et al., 2009). Furthermore, studies conducted by Dakkak et al., (2019) have demonstrated that MRI-detected tenosynovitis in the foot predicts progression to RA. Nevertheless, the clinical utility of MRI for evaluating foot disease in RA is hindered by extensive training requirements, challenges related to specific patient groups (e.g., claustrophobia or metal pacemakers), limited accessibility due to high costs, and the lack of trained clinicians in MRI. These limitations severely restrict its effective use in detecting and monitoring foot disease in RA (Lento & Primack, 2008).

2.4.3 MSUS

In comparison to MRI, MSUS possesses favourable attributes such as safety, accessibility, cost-effectiveness, and the ability to dynamically evaluate joint and soft tissue structures (Sudoł-Szopińska et al., 2017; Backhaus et al., 2006; Dakkak et al., 2019). MSUS imaging is gaining popularity in the fields of rheumatology and podiatry due to its advantages as a point-of-care tool. It offers real-time, multiplanar images to both the US practitioner and patient, thereby improving the patient's clinical experience (Sudoł-Szopińska et al., 2017). In RA, MSUS plays a crucial role in diagnosing and monitoring foot joint synovitis, as it offers greater sensitivity and reliability compared to clinical examination (Di Matteo et al., 2020; Razaei et al., 2014). Some of the more common pathologies detected on MSUS in RA include effusions, synovial hypertrophy (SH), synovitis, tenosynovitis, bursae and bursitis, as well as bone erosions (Bullock et al., 2019; Suleman et al., 2018; Razaei et al., 2014; Bowen et al., 2010). To maintain a standardised assessment of MSUS lesions demonstrating pathophysiological manifestations in RA, the definitions outlined in Table 2 are consistently applied throughout this thesis.

TABLE 2: DEFINITIONS OF US-DETECTED RA PATHOLOGIES

Pathology	Definition
Synovial hypertrophy (Wakefield et al., 2005)	Presence of abnormal hypoechoic, non-displaceable or poorly compressible intra-articular tissue. This can sometimes appear as isoechoic (Wakefield et al., 2005)
Synovial effusion (Wakefield et al., 2005)	Abnormal intra-articular anechoic intra-articular area that is easily displaced by the transducer.

Synovitis (D'Agostino et al, 2017)	Synovial hypertrophy which exhibits Power Doppler signals.
Tenosynovitis (Ammitzbøll-Danielsen et al, 2018)	Abnormal anechoic and hypoechoic thickening of tendon sheath, that is poorly compressible and non-displaceable seen in 2 perpendicular planes. Doppler signals may be seen within the paratendinous synovial sheath.
Erosion (Bruyn et al., 2019)	Intra and/or extra articular discontinuity and irregularity of bone surface, seen in two perpendicular planes and may exhibit Power Doppler signals.
Intermetatarsal bursa (Bowen et al., 2010)	Intermetatarsal bursal hypertrophy is visualised as a distinct fluid-filled collection with areas that appear hypoechoic or anechoic. Typically, this collection protrudes more than 1 mm below the level of the metatarsal head.
Submetatarsal/ plantar metatarsal bursa (Bowen et al., 2010)	Presence of fluid collections within the sub-metatarsal fat pad. These collections appear as anechoic or being heterogeneous.
Bursitis: (Hirji, Hunjun & Chouder, 2011)	A bursa with Power Doppler signals

2.4.4 Utilising MSUS in Podiatry

MSUS in podiatry is growing due to its significant value in diagnosing and treating rheumatic and musculoskeletal (MSK) conditions, as well as its potential to improve diagnostic and therapeutic outcomes (Dando et al., 2021). Notably, the ground-breaking work by Bowen et al., (2010) on the utilisation of MSUS by podiatrists has led to a substantial increase in its adoption over the past thirteen years. Furthermore, Woodburn et al., (2010) advocated for a transformative approach to podiatry care, emphasising the essential role of MSUS as a key competency for specialist podiatrists. Since these influential publications, the use of MSUS has been more widely utilised and endorsed among AHPs (Dando et al., 2021). A notable illustration of this phenomenon is the successful implementation of MSUS within NHS Ayrshire and Arran. The integration of MSUS in podiatry clinics within this service area has yielded substantial cost savings enhanced patient outcomes, as demonstrated by a case study conducted by Knox (2021). The study further emphasised that MSUS significantly reduced wait times compared to radiography and decreases unnecessary referrals for foot and ankle MRI exams, highlighting its valuable role in podiatric care (Knox, 2021).

Dando et al., (2021) conducted an extensive international survey, revealing the widespread adoption of MSUS among podiatrists. The study demonstrated that 99% of MSUS-trained podiatrists incorporated this imaging modality into their routine diagnostic practices for a range of purposes, including assessing foot injuries, guiding injections, monitoring disease progression, evaluating treatment outcomes, and facilitating research in podiatry. Newcombe et al., (2022)

investigated the impact of MSUS on patient education in podiatry for individuals with rheumatic and MSK diseases. Their findings suggested that MSUS scans improved patients' understanding of foot pain in 93% of cases, with 98% considering them more beneficial than other educational resources. This suggests that the utilisation of MSUS scans may lead to improved adherence to podiatry treatments and advice. In a related study (Newcombe et al., 2020); the usefulness of diagnostic MSUS in podiatry was assessed by comparing clinical diagnoses without MSUS to diagnoses with MSUS findings and examining its impact on treatment planning. The results demonstrated agreement between MSUS and clinical diagnoses in 55% of cases and MSUS led to modifications in management plans for one-third of patients, highlighting the use of this imaging modality in guiding appropriate management. While these studies had limited sample sizes, they contribute to the growing body of evidence supporting the application of MSUS in podiatry for diagnosing and managing inflammatory foot pathologies.

The reliability of MSUS in assessing the feet, particularly when performed by different podiatry operators or using different equipment, has been subject to limited investigation. However, a study conducted by Serban et al., (2020) evaluated the inter-observer agreement for ultrasound findings in various foot structures, including the ankle joint, talo-navicular joint (TNJ), STJ, the plantar fascia and Achilles and tibialis posterior tendons. The study reported a very good level of inter-observer agreement (kappa: 0.82–0.88) for structures such as the TTJ joint, tendons in the ankle region and TNJ, while the STJ demonstrated a good level of agreement (kappa: 0.71–0.75). Similarly, Mico et al. (2011) reported moderate to good agreement values (kappa = 0.47–0.62) for the ankle region. Additionally, Bowen et al. (2008) reported good inter-observer agreement between a podiatrist and radiologist in the assessment of the forefoot using MSUS in patients with RA. The study revealed substantial agreement for bursitis (kappa 0.64, p < 0.01) and erosions (kappa 0.52, p < 0.01), while fair agreement was observed for synovitis (kappa 0.22, p < 0.05). Moreover, subsequent to an additional MSUS training session, a substantial level of agreement (kappa 0.70) was observed between the two investigators. These findings lend support to the reliability of MSUS as an imaging modality within podiatry and rheumatology settings.

While significant research supports the use of MSUS in podiatry, limitations regarding its clinical utility must be acknowledged. Operator dependence and the potential for artefacts increase the risk of misdiagnosis (Henderson and Dolan, 2016). Moreover, the limited penetration of high-frequency sound waves hinders imaging of deep tissues and bones, particularly in obese or oedematous patients (McQueen et al., 2009). Patient factors such as body habitus and movement during scanning can further affect the feasibility and accuracy of MSUS findings (Sudoł-Szopińska et al., 2015). Additionally, the cost and limited accessibility of MSUS in healthcare facilities pose

challenges to its widespread adoption (Sudoł-Szopińska et al., 2015). Logistical challenges, including a steep learning curve, limited training opportunities, and increased appointment times can hinder the implementation of MSUS in busy podiatry and rheumatology clinics.

MSUS also faces limitations in distinguishing between pathologies such as synovial hypertrophy (SH), synovial effusion, and synovitis. These pathologies are defined by ultrasound characteristics that may not always be easily distinguishable (D'Agostino et al., 2017). For instance, SH can sometimes appear isoechoic, making it challenging to differentiate from other pathologies. Additionally, accurately differentiating between synovial effusion and synovitis can be difficult due to similar ultrasound features. This limitation complicates the interpretation and measurement of these pathologies for diagnosis and monitoring purposes. Given the influence of timely and targeted treatment on patient outcomes, the existing constraints of MSUS emphasise the need to establish a valid, reliable, and feasible approach for assessing foot disease in RA. This approach should be readily implementable by all members of the rheumatology MDT and AHP's, particularly those lacking MSUS training.

2.5: PROMS

As highlighted in the previous two sections, it has been observed that regular examination of the foot and ankle joints is scarce in rheumatology care settings, resulting in missed opportunities for early intervention and effective management of foot-related complications (Wilson et al., 2017). Furthermore, current clinical examination of the foot and ankle is often limited in rheumatology settings (Carter, Walmsley & Rome, 2019). While podiatrists may be involved in performing foot examinations, it is important to acknowledge that their assessments may not always be comprehensive or specialised in the context of rheumatic diseases. Podiatrists generally focus on routine services, such as basic foot care and mechanical therapies (Williams et al., 2011; Hennessey, Woodburn & Steultjens, 2016), rather than addressing, the specific inflammatory complexities associated with the RA foot. Although Rheumatology NHS Centres of excellence, equipped with specialised expertise and resources, have made notable strides in focusing on clinical assessments around inflammation and adopting MSUS, the majority of podiatry clinics either lack access to MSUS or have untrained staff members in this imaging modality. This limitation significantly hampers the ability to effectively manage RA-related foot inflammation within podiatry settings. To address these gaps, PROMs have gained recognition in rheumatology MDTs, as a valuable, cost-effective tool for informing clinical decision-making (Churruca et al., 2021; Pickles et al., 2022). Current guidelines for managing RA reflect this recognition by emphasising the use of validated PROMs to evaluate a patient's physical function, pain, and

psychosocial implications of their disease (Boers et al., 2014; Tugwell et al., 2011; Pickles et al., 2022).

2.5.1 Utilising the COSMIN framework for PROM validation

To ensure the suitability of a PROM for integration into clinical research or practice, a meticulous evaluation of its psychometric properties is imperative to ensure robustness in terms of its validity, reliability, and interpretability. The COSMIN (COnsensus-based Standards for the selection of health Measurement Instruments) initiative stands as a dedicated effort to enhance the quality of studies related to measurement properties. It achieves this by offering a comprehensive framework and practical tools for assessing the measurement properties of PROMs. This initiative has developed an internationally recognised framework that establishes a consensus-based taxonomy, terminology, and definitions of psychometric properties specific to health-related PROMs. Encompassing three domains—reliability, validity, and responsiveness—COSMIN addresses nine crucial measurement properties that play a pivotal role in evaluating the quality and precision of research outcomes (Mokkink et al., 2018; Prinsen et al., 2018). These domains and their corresponding definitions are presented in Table 3, and their consistent application is maintained throughout this thesis. Utilising the COSMIN taxonomy in validating the RADAI-F5 establishes a standardised and evidence-based framework, ensuring both consistency and rigour in the validation process (Prinsen et al., 2018).

TABLE 3: COSMIN DEFINITIONS OF DOMAINS AND PSYCHOMETRIC PROPERTIES FOR HEALTH-RELATED PROMS (ADAPTED FROM MOKKINK ET AL., 2016)

Domain	Measurement property	Definition
Reliability		The degree to which the measurement is free from measurement error
	Internal consistency	The degree of the interrelatedness among the items.
	Reliability	The proportion of the total variance in the measurements, which is because of 'true' differences among patients.
	Measurement error	The systematic and random error of a patient's score that is not attributed to true changes in the construct to be measured.
	Inter-rater Reliability	Determines the agreement between different raters when assessing the same individuals using the instrument
	Intra-rater reliability	Measures the degree of consistency when the same rater assesses the same individuals using the instrument on two or more occasions.
Validity		The degree to which an instrument measures the construct(s) it purports to measure.
	Content validity	The degree to which the content of an instrument is an adequate reflection of the construct to be measured

	Criterion validity	The degree to which the scores of an instrument are an adequate reflection of a 'gold standard'.
	Construct validity	The degree to which the scores of an instrument are consistent with hypotheses based on the assumption that the instrument validly measures the construct to be measured
	Convergent and divergent validity	Determines the extent to which the instrument correlates with other measures assessing similar or different constructs, respectively.
	Cross-cultural validity	Assesses the extent to which an instrument can be used across different cultural or language groups while maintaining its validity.
	Face validity	Involves an assessment of whether an instrument appears to measure the intended construct at a surface level, without deep examination of its properties.
	Structural validity	Investigates the extent to which the instrument's underlying structure reflects the theoretical construct it aims to measure.
	Predictive validity	Evaluates the extent to which the instrument's measurements can predict future outcomes as expected based on the construct it assesses.
Responsiveness		The ability of an HR-PRO instrument to detect change over time in the construct to be measured
	Minimally Important Difference	Determines the smallest change in an instruments score that is considered clinically significant.
	Minimal Detectable Change	Small change in the score that falls beyond the margin of measurement error.
Interpretability		The degree to which one can assign qualitative meaning to an instrument's quantitative scores to aid in clinical interpretation of scores.

2.5.2: Common foot PROMs in RA

In the field of podiatry, the incorporation of validated and reliable PROMs enables a patient-centred approach to treatment, providing a more comprehensive understanding of the impact of foot problems on individuals (Dando et al., 2021). Numerous foot-specific PROMs have been developed and validated in the RA population (Walmsley et al., 2010; Ortega-Avila et al., 2019). Table 4 provides a description of the content of these PROMs, while Table 5 presents an overview of their methodological quality. Despite the availability of several PROMs for evaluating the impact of RA on the foot, it is imperative to underscore the absence of a meta-analysis of these PROMs. This is attributed to the heterogeneity of dimensions and outcomes included in existing studies (Ortiga-Avila et al., 2019). The incorporation of interpretations in Table 5 is due to the variability in cut-off points employed by different studies for measurement properties such as construct validity, Intraclass Correlation Coefficient (ICC), and Cronbach alpha levels. Interpretations contextualise results within each study's methodology, providing a nuanced understanding of the psychometric properties of each instrument.

TABLE 4: CONTENT OF RA VALIDATED FOOT-SPECIFIC PROMS (ADAPTED FROM WALMSLEY ET AL, 2010; ORTEGA- AVILA ET AL., 2019)

PROM	Authors	Items	Type of response scale	Constructs assessed
FFI	Budiman-Mak et al (1991)	23	10 cm VAS	Foot pain Foot-related disability Foot-related Activity limitation
FFI-R	Budiman-Mak et al (2013)	68	6-point rating scale	Pain and stiffness Difficulty Activity limitation Social issues
FHSQ	Bennett et al(1998)	13	5-point adjectival rating scale	Foot pain Foot function Footwear General Foot Health
MFPDI	Garrow et al (2000)	19	3-point adjectival rating scale	Functional limitation Pain intensity Personal appearance
ROFPAQ	Rowan (2000)	39	5-point adjectival rating scale	Sensory pain Affective pain Cognitive dimensions of pain Questionnaire Comprehension
FAAM	Martin et al (2005)	29	5-point Likert scale	ADL Foot and Ankle Ability
BFS	Barnett et al, (2005)	15	3 to 6-point adjectival rating scales	Concern and pain Footwear general foot health Mobility
LFIS	Helliwell et al (2005)	51	Dichotomous scoring	Impairment Activities Participation, Footwear
SAFE	Walmsley et al (2012)	61	Dichotomous scoring	Impairment Disability Footwear Foot and ankle symptoms Factors that can influence foot symptoms. Impact on everyday function Family life Footwear Feelings Social life Visual impact Work
SEFAS	Coster et al (2012)	12	5-item response scale	Pain Function Limitation of function
RADAI-F5	Hoque et al (2020)	5	5-item response scale	Foot disease activity

Key: BLS: Bristol Foot Score, FAAM: Foot and Ankle Ability Measures, FAOS: Foot and Ankle Outcome Score, FFI: Foot function index, FFI-R: Foot Function index revised form, FHSQ: Foot Health Status Questionnaire, LFIS: Leeds Foot Impact Scale, MFPDI: Manchester Foot Pain Disability Index, PHQ: Podiatry Health Questionnaire, RADAI-F5: Rheumatoid Arthritis Foot Disease Activity Index, ROFPAQ: Rowan Foot Pain Assessment Questionnaire, SAFE: Salford Rheumatoid Arthritis Foot Evaluation, SEFAS: Self-reported Foot and Ankle Score.

TABLE 5: METHODOLOGICAL QUALITY OF RA VALIDATED FOOT-SPECIFIC PROMS (ADAPTED FROM ORTEGA-ÁVILA ET AL., 2019)

Instrument	IC	Rel.	CV	CCV	HT	Criterion validity	Resp	Interpretability
FFI (Budiman-Mak et al 1991)	+ ICC total = 0.87 **Interpret** Very good reproducibility	+ α total = 0.96 **Interpret** High level of internal consistency	− **Interpret** Item selection was conducted by expert non-patient agreement	+ **Interpret** Culturally adapted/ translation to Brazilian/Portuguese, Polish, Korean, Italian, Taiwan Chinese, French, Spanish and German	+ **Interpret** Construct validity assessed and in line with *a-priori* hypothesis	+ r=0.52 **Interpret** Moderate positive correlation	+ SRM total= 1.02 ES total = 1.12 **Interpret** acceptable responsiveness to clinical change	− **Interpret** No qualitative meaning to instrument's quantitative scores
FFI-R (Budiman-Mak et al 2013)	+ ICC = 0.93 **Interpret** Very good reproducibility	+ α total = 0.95 **Interpret** High level of internal consistency	− **Interpret** Did not include patient or clinicians in item generation	+ **Interpret** Culturally adapted/ translated to Brazilian, Turkish and Norwegian	+ r= 0.96 **Interpret** Strong positive correlation.	+ **Interpret** Criterion validity assessed	+ MIC = -19 ROC_{AUC} value = 0.82 **Interpret** Responsiveness established using patient approach Good discriminative ability	− **Interpret** No qualitative meaning to instrument's quantitative scores
FHSQ (Bennett et al 1998)	+ ICC= 0.92 **Interpret** Excellent reproducibility	+ α = 0.88 **Interpret** High internal consistency	− **Interpret** Expert panel of podiatric physicians, measurement experts, and potential respondents was used to rate questions	+ **Interpret** Culturally adapted/ translated to Spanish and Brazilian	+ **Interpret** construct validation by categorising foot diseases	+ **Interpret** Established using confirmatory factor analysis	− **Interpret at** Not tested	− **Interpret** No qualitative meaning to instrument's quantitative scores

				content coverage				
MFPDI (Garrow et al 2000)	+ ICC= 0.92 **Interpret** Very good reliability	+ α = 0.99 **Interpret** High reliability	+ **Interpret** Qualitative interviews with 32 patients visiting foot clinic	+ **Interpret** Culturally adapted/ translated to Danish, Spanish and Greek	+ **Interpret** Construct validity supported by moderate to very strong correlations with the SF-36 physical subscales and VAS_{mean}	+ **Interpret** Substantial correlation between SF-36 mental and general health subscales ($r = 0.20$, $P = 0.04$; $r = 0.21$, $P = 0.03$) with functional limitation and activity restriction subscales	− **Interpret** Does not have reported sensitivity, responsiveness, or minimal important difference data	− **Interpret** No qualitative meaning to instrument's quantitative scores
ROFPAQ (Rowan, 2000)	+ ICC sensory = 0.88 ICC affective= 0.93 ICC cognitive = 0.82 **Intepret** High reliability	+ α sensory = 0.88 α affective = 0.93 α cognitive = 0.82 **Intepret** Acceptable values of internal consistency (0.7 and 0.9)	+ **Interpret** Established with focus group interviews with people with chronic foot pain.	− **Interpret** Not translated to other languages	+ ρ sensory = 0.88 ρ affective = 0.69 ρ cognitive = 0.70 **Intepret** Demonstrates moderate to strong correlations with FFI pain subscale	+ **Interpret** Spearman correlations with Headache scale from 0.154 to 0.489	− **Interpret** Not tested	− **Interpret** No qualitative meaning to instrument's quantitative scores

Instrument								
FAAM (Martin et al 2005)	+ ADL subscale ICC = 0.89 Sport subscale ICC = 0.87 **Interpret** Good test-retest reliability	+ α = 0.98 **Interpret** High internal consistency	+ **Interpret** Both clinician experts and patients were involved in the final item reduction	+ **Interpret** Culturally adapted/translated to French, Japanese, Persian, German, Italian, Turkish, Brazilian, Spanish, Chinese, Thai and Dutch	+ **Interpret** ADL and Sport subscales of FAAM correlated strongly with SF-36 physical function ($r = .84$; $r = .78$) and weakly with SF-36 mental function ($r = .18$; $r = .11$).	- **Interpret** No gold standard comparison	+ MDC ADL subscale = ±5.7. MDC Sports subscale= ± −12.3 MCID ADL subscale= 8 MCID sports subscale = 9 points The Guyatt's responsiveness index for the ADL subscale and the Sport subscale was respectively 2.75 and 1.40. **Interpret** Responsiveness established for various subscales over 4 weeks	− **Interpret** No qualitative meaning to instrument's quantitative scores
BFS (Barnett et al, 2005)	− **Interpret** Not tested	+ α= 0.90 **Interpret** High level of internal consistency	+ **Interpret** Developed with patients using qualitative interviews	+ **Interpret** Culturally adapted/translated to Spanish	− **Interpret** Not tested	− **Interpret** Not tested	+ **Interpret** Foot scores sensitive to change	− **Interpret** No qualitative meaning to instrument's quantitative scores
LFIS (Helliwell et al 2005)	+ IF ICC of 0.84 AP ICC of 0.96 **Interpret** Positive demonstration of test-retest	− **Interpret** Not reported	+ **Interpret** Qualitative pilot study with 30 RA subjects	+ **Interpret** Culturally adapted/translated to Dutch, German and Hungarian	− **Interpret** Initial postal survey showed preliminary construct validity against HAQ, FFI, and	− **Interpret** No gold standard to establish criterion validity	+ SES = 0.58 SRM = 0.58 GRR = 0.88. ROC_{AUC} value = 0.645	− **Interpret** No qualitative meaning to instrument's quantitative scores

					MFPDI, but further details were not reported		**Interpret** Moderate responsiveness	
SAFE (Walmsley et al 2012)	+ ICC= 0.96 to 1 **Interpret:** Perfect 1-week test-retest reliability	− **Intrepret** Not reported	+ **Interpret** RA patients involved in content generation Clinicians involved in instrument development	− **Interpret** Not translated to other languages	− **Interpret** Not tested	+ MFPDI = 0.83 LFIS = 0.79 **Interpret** Strong positive correlation, indicating good criterion validity	− **Interpret** Not tested	− **Interpret** No qualitative meaning to instrument's quantitative scores
SEFAS (Coster et al 2012)	+ ICC forefoot= 0.92 ICC Hindfoot= 0.93 **Interpret** High degree of reliability	+ α forefoot= 0.84 α hindfoot= 0.86 **Interpret** High reliability	+ **Interpret** Content validity evaluated by patients	+ **Interpret** Culturally adapted/ translated into Danish and German	+ **Interpret** 80% of predefined hypotheses were confirmed	− **Interpret** No gold standard to establish criterion validity	+ ES forefoot= 1.29 ES hindfoot/ ankle patients it was t= 1.05 SRM forefoot= 1.27 SRM hindfoot= 0.99 **Interpret** High responsiveness	− **Interpret** No qualitative meaning to instrument's quantitative scores

Instrument								
RADAI-F5 (Hoque et al 2020)	+ ICC = 0.87 **Interpret** Very good reproducibility	+ α = 0.90 **Interpret** High level of internal consistency.	− **Interpret** 82% of RA participants rating the instrument as relevant and easy to understand. However, patients and clinicians not involved in item generation	+ **Interpret** Translated and culturally adapted to Spanish	+ **Interpret** Construct validity confirmed with 60% in line with *a-priori* hypotheses.	− **Interpret** Not assessed	+ Cohen's d = 0.91 Standardized response mean: 0.97 distribution-based MID: 1.16 GI value: 0.70 **Interpret** Consistent medium-to-high responsiveness	+ **Interpret** Foot disease activity categories established to assist with interpretation of scores

Key: ADL: Activities of Daily Living Subscale, α= Cronbach's alpha, AP: Activity and Participation Subscale, BLS: Bristol Foot Score, ES: Effect size, FAAM: Foot and Ankle Ability Measures, FAOS: Foot and Ankle Outcome Score, FFI: Foot Function Index, FFI-R: Foot Function Index Revised Form, FHSQ: Foot Health Status Questionnaire, GI: Guyatt's Index, HAQ: Health Assessment Questionnaire, ICC: Intra-class Correlation Coefficient, IF: Impairment and Footwear Subscale, LFIS: Leeds Foot Impact Scale, MDC: Minimal Detectable Change, MCID: Minimally Clinically Important Difference, MIC: Minimally Important Change, MFPDI: Manchester Foot Pain Disability Index, PHQ: Podiatry Health Questionnaire, RADAI-F5: Rheumatoid Arthritis Foot Disease Activity Index, ROCAUC: Area under the Receiver Operating Characteristic Curve, ROFPAQ: Rowan Foot Pain Assessment Questionnaire, SAFE: Salford Rheumatoid Arthritis Foot Evaluation, SEM: Standard Error Mean, SF-36: The Short Form Health Survey 36-item, Smethod: Simulation Extrapolation Method, SRM: Standard Response Mean, VAS*mean*: Visual Analogue Scale Mean Scores IC: Internal consistency, Rel.: Reliability, CV: Criterion validity, CCV: Cross-cultural validity, HT- Hypothesis Testing, Resp: Responsiveness,, ρ: Spearman Rank Correlation Coefficient.

Rating: +: Reported - :Not reported/ Did not meet standards

Commonly used PROMs for assessing foot health in RA include the Foot Function Index (FFI) (Budiman-Mak et al., 1991) and Foot Impact Scale (FIS) (Helliwell et al., 2005). However, these tools have notable limitations. The FFI lacks traditional patient content validity in item development and does not evaluate important variables such as footwear and participation restriction. Despite addressing some of these limitations (Budiman-Mak et al., 2013), the revised version (FFI-R) still falls short in incorporating patient involvement in item production. The FIS demonstrates good validity and reliability but shows reduced sensitivity, specificity, and discriminative qualities compared to the FFI (Muradin & Van der Heide, 2016). Furthermore, the FIS scores suffer from lack of interpretability components and minimally important difference (MID) values, which poses challenges for clinical interpretation of the PROM scores. Furthermore, as demonstrated in Table 5, only a limited number of RA-specific foot PROMs have been subjected to evaluation concerning their predictive and longitudinal validity. Without comprehensive evaluation of this measurement property, it becomes challenging to determine the suitability of these PROMs for clinical decision-making, treatment planning, and monitoring of patients' functional outcomes over time (Volpato et al., 2011; Guralnik et al., 1994; Gagnier et al., 2021). Additionally, these PROMs have varying numbers of items (ranging from 23 to 68), which can lead to respondent burden and limit their clinical feasibility due to the time required for completion (Hoque et al., 2021). Moreover, despite the abundance of PROMs specific to foot-related RA, their primary focus has been predominantly on evaluating foot-related disability and impairment. Given their emphasis on disability rather than foot disease activity, their utility in informing pharmacological management is limited. Consequently, the RADAI-F5 was developed to overcome these limitations and offer a comprehensive approach for assessing active foot disease in this patient population.

2.5.3: The RADAI-F5

As highlighted in Table 5, the RADAI-F5 (Appendix B) exhibits good preliminary measurement properties in line with the COSMIN Study Design checklist (Hoque et al., 2021). In a previous validation study, the RADAI-F5 exhibited theoretically consistent associations, confirming its construct validity with the mRADAI-5, FFI, FIS, and DAS28-ESR. Furthermore, the questionnaire demonstrated high internal consistency, good reproducibility and good content validity (Hoque et al., 2020). Additionally, with an average completion time of 5 minutes, the tool is clinically feasible. Furthermore, Martinez-Jiménez et al., (2022) established the cross-cultural validity of the RADAI-F5 in a Spanish-speaking RA population. Nonetheless, a number of measurement properties such as the tools anchor-based MID, predictive validity and discriminative validity have not yet been established.

However, it is crucial to acknowledge that while PROMs have the potential to enhance management strategies; their potential for implementation may vary across healthcare settings. In primary rheumatology care, the use of PROMs has been limited (Brower et al, 2021), due to a myriad of barriers, including technical, social, cultural, legal, and logistical challenges (Tan et al., 2023). Moreover, substantial heterogeneity is observed in the choice of outcome measures across different NHS trusts (Kirkham et al., 2013). The large number of available RA PROMs complicates the selection process for clinicians. Additionally, studies indicate that clinicians are hesitant to use PROMs routinely due to concerns of increased workload without significant improvements in care efficacy (Nguyen et al., 2021; Brower et al., 2021). Therefore, successful adoption of the RADAI-F5 in rheumatology care settings necessitates a comprehensive understanding of the underlying facilitators and barriers associated with its implementation. Currently, there is a paucity of research capturing the perspectives of patients and clinicians regarding the integration of a foot PROMs specifically within rheumatology care contexts. Chapter 3 of this thesis aims to bridge this knowledge gap to facilitate the effective implementation of RADAI-F5 in rheumatology MDT clinics.

2.6 Management

In the management of the rheumatoid foot, two distinct approaches are commonly employed: systemic disease management and localised disease management. Systemic management of RA emphasises early intervention and a T2T strategy for achieving low disease activity or remission (Huang et al., 2022). Prompt initiation of targeted therapies, such as DMARDs and biologic agents, is recommended to effectively control disease activity and prevent joint damage (Bowman & Guest, 2016). In instances where the intended target is not attained, therapy is often adjusted (Huang et al., 2022). In contrast, localised RA disease management specifically targets an anatomical region, such as foot-related symptoms and impairments. To optimise patient outcomes, addressing both systemic disease control and localised foot symptoms is necessary (Smolen et al., 2020).

2.6.1 Podiatric management

Podiatrists play a crucial role in the assessment and management of foot-related manifestations of RA, providing specialised care to optimise foot function and improve QoL (Allen, Carville & McKenna, 2018). Podiatric interventions for RA typically involve various approaches, including mechanical debridement of skin lesions and providing nail care (PRCA, 2008). Customised foot orthoses (FOs) are frequently prescribed as a first-line conservative intervention for RA-related foot pain and to target joint and soft-tissue issues, herby reducing forefoot plantar pressure and pain (Simonsen et al., 2022). Additionally, physical therapy approaches, such as exercise programmes have shown promise for managing soft tissue pathologies. Footwear interventions, including footwear with cushioning and a wide toe box, have also demonstrated improvements in foot comfort, gait parameters, and physical function (Frecklington et al., 2018).

However, access to sufficient podiatric services for individuals with RA remains inadequate (Hendry et al., 2013; McCulloch et al., 2018; Rome & Otter, 2021; Hoque et al., 2022), and when care is provided, it often lacks a comprehensive scope. This may be attributed to the absence of a standardised framework for detecting active foot disease in RA, resulting in a lack of outcome-driven care, risk stratification, and tailored treatment plans. Moreover, clinicians often encounter challenges in differentiating between inflammatory and mechanical symptoms, potentially leading to inadequate management of systemic disease. Clinicians will often treat foot pain (Otter et al., 2010), but it is important to note that foot pain alone does not definitively indicate active foot disease, as it can stem from non-inflammatory biomechanical factors. Additionally, the presence of pain does not necessarily imply inadequate inflammatory control, as pain can persist due to joint damage or be associated with generalised pain conditions (Simonsen et al., 2021). This highlights the need for improved podiatric protocols to effectively address foot disease in individuals with RA.

The impact of disease duration on persistent foot or ankle pain in RA has shown differing findings. According to Borman and colleagues, patients with a longer disease duration consistently experience higher levels of pain and reduced disease activity compared to those in earlier stages of the disease (Borman et al., 2012). Additionally, a study by Van der Leeden (2007) explored the relationship between foot disease duration and foot function, pain, and disability in RA patients with foot complaints. The results demonstrated a significant correlation between longer disease duration and impaired foot function, as evidenced by alterations in pressure distribution and reduced walking speed. While there was no direct correlation between disease duration and self-reported foot pain or disability, disease duration was significantly associated with foot function and walking speed. This underscores the critical importance of early and ongoing foot assessment

in this patient population, aiming to mitigate the detrimental effects of the disease on gait and foot function.

In a publication by Van der Heijde (2001), evidence was provided linking radiographic structural damage to disease activity, making it a reliable measure for assessing treatment effectiveness. The paper also highlighted the strong association between local inflammation and the progression of joint damage, underscoring the importance of early intervention and tight disease control. Functional disability in RA was strongly correlated with disease activity, particularly in cases with longer disease duration. These findings establish a clear connection between radiographic changes, functional outcomes, and disease progression in RA, while unequivocally demonstrating the burden of foot-related symptoms in RA. Consequently, proactive management strategies that are appropriately disease-staged, and address both disease activity and structural damage are essential to optimise foot function and enhance overall patient well-being.

To address the unmet need for optimal foot care in RA it is crucial to establish a robust and integrated model of care that prioritises outcomes, risk stratification, and evidence-based interventions. This requires the development of a localised anatomical care model specifically tailored to address active foot disease in RA. The utilisation of RADAI-F5 in podiatry and rheumatology clinics holds potential for enhancing patient experience and the quality of care. This tool holds promise to play an important role in the early detection of foot diseases associated with RA, thus offering a pathway towards the development of more effective treatment strategies and potentially enhancing patient outcomes.

2.7 Additional areas for exploration

The incorporation of stakeholder engagement into this research, as supported by organisations like the National Institute for Health Research (NIHR, 2009) and National Institute for Health and Care Excellence (NICE, 2015), is acknowledged as an essential element of the research process. Stakeholder engagement has proven to elevate the quality, relevance, and clinical outcomes of research by influencing various stages, including the selection of research topics, project design, recruitment, data collection, analysis, and dissemination (Chalmers, 1995; Oliver, 1995; Goodare & Smith, 1995; Greenhalgh et al., 2019). Significant discussions with key stakeholders have identified additional areas for exploration within the context of RADAI-F5. These insights, detailed in Appendix C, contribute to the overall research framework, offering a greater understanding of RADAI-F5 that is pertinent to end-users of this tool.

In recent years, there has been a growing recognition on the importance of incorporating patients' perspectives into practitioner-led disease assessments (Hsiao & Fraenkel, 2017). Interpreting PROMs can present challenges due to various factors, including the influence of subjective

elements (Churruca et al., 2021). One particular challenge lies in the rating of pain constructs, which can vary between individuals, making the interpretation of PROM-derived data complex, especially when comparing results across different patients or patient groups (Churruca et al., 2021). To capture meaningful improvements in patients' health status using PROMs, it is crucial to establish the MID, which represents the smallest score change that patients perceive as important and meaningful. Determining the MID for the RADAI-F5 is important for assessing treatment response and guiding clinical management. Although the MID for the RADAI-F5 has been determined using a distribution-based approach in our previous validation study (Hoque et al., 2021), it lacked consideration of patient perspectives. As such, Chapter 5 of this thesis will assess this measurement property using an anchor-based approach.

Hindfoot and ankle involvement is often overlooked in RA despite its significant contribution to impairment and disability (Abdelzaher et al., 2022; Baan et al., 2011). Despite the pronounced impact of ankle and hindfoot pathologies on walking ability in RA, a standardised approach for assessing and managing the STJ and ankle joint is noticeably absent (Alazzawi et al., 2017). Clinical decision-making often relies solely on the clinical examination of the ankle, focusing on the presence of tender and swollen joints. However, the reliability of clinical examination can be compromised by various factors such as deformities, anatomical overlays, obesity, and peripheral oedema (Wakefield et al., 2008). Moreover, Lehtinen et al. (1996) demonstrated that in cases of painful RA ankles with normal X-rays, both ultrasound and low-field MRI exhibited superior performance compared to clinical examination in detecting synovitis and tenosynovitis. However, limited accessibility to these imaging modalities poses a hindrance to comprehensive evaluation of the ankle. Therefore, the development of an earlier and more accurate approach for identifying and treating joint inflammation would offer a significant clinical advantage. Furthermore, it is important to note that while some PROMs like the Foot and Ankle Outcome Score (FAOS) and the Self-Reported Foot and Ankle Score (SEFAS) specifically acknowledge and account for the ankle joint in their items, instructions and titles, there is a lack of explicit mention of the ankle in the RADAI-F5 and certain other foot-related PROMs. This raises uncertainty regarding whether patients consider their ankle disease as part of their foot disease activity score when completing the RADAI-F5 or similar measures. Therefore, it is crucial to determine the capability of the RADAI-F5 in capturing foot disease in this region. This aspect will be explored in Chapter 6.

Early detection and management of foot-related disability in RA patients is crucial for preventing or minimising joint erosions, deformities, and subsequent functional limitations (Tenten-Diepenmaat et al., 2019). Timely intervention can also improve treatment outcomes and increase the likelihood of achieving disease remission or tight disease control, while potentially reducing

the need for expensive interventions, such as surgeries and long-term disability support (Bullock et al., 2019). While the RADAI-F5 exhibits good measurement properties (Hoque et al., 2021), its predictive validity has not yet been established, highlighting a key knowledge gap. Predictive validity is a key component of the COSMIN taxonomy and it represents a key measurement property for implementation in clinical practice where prevention of poor functional outcomes is an important management goal. Chapter 7 aims to address this gap by examining the predictive validity of the RADAI-F5 in assessing foot-related disability in an early RA group.

2.8 Overall summary

This chapter highlights the significance of managing foot disease in RA and the role of foot PROMs in rheumatology care. The treatment objective in RA is early control of inflammation and prevention of joint damage and disability through a T2T approach. However, existing disease assessment methods in RA, including the DAS-28, clinical examination, and imaging, have limitations. RA-specific foot PROMs offer a viable alternative but can be burdensome for respondents and lack direct quantification of foot disease activity. The RADAI-F5 offers a promising solution to overcome these limitations by providing an accessible tool for the rheumatology MDT, particularly for AHPs who may not have specialised expertise in MSUS. However, further research is necessary to explore additional measurement properties of the RADAI-F5. Additionally, it is crucial to determine the interpretability of the RADAI-F5 to facilitate its integration into routine clinical practice in the field of rheumatology. These aspects will be the central focus of this thesis.

Chapter 3. Patient and clinician perspectives on the clinical utility of the RADAI-F5: A qualitative study

This chapter aims to establish the clinical utility of the RADAI-F5 from the perspectives of RA participants and healthcare professionals, employing a qualitative methodology. The study's findings provide evidence regarding the facilitators and barriers to implementing the RADAI-F5 in rheumatology clinics. The findings from this study also serve as a foundation for the subsequent chapter.

The work included in this chapter was published in *Rheumatology internationall* (Hoque et al., 2022) (Appendix D).

3.1 Background:

RA is a chronic autoimmune condition that primarily affects the joints, causing significant pain, inflammation, and limitations in physical function (Guo et al., 2018). Although RA commonly affects multiple joints throughout the body, its impact on the feet is particularly notable. Qualitative research has provided valuable insights into the lived experiences of individuals with RA foot symptoms highlighting the difficulties these patients encounter with mobility and self-care activities, leading to functional limitations and reduced independence (Williams et al., 2013; Wilson et al., 2017; Ramos-Petersen, 2021; Laitinen et al., 2022). Furthermore, the chronic nature of the disease and its impact on foot health can result in psychological distress, reduced self-esteem, and social isolation (Lin et al., 2021). Capturing the complexities and nuances of the impact of foot disease is vital to inform the development of appropriate interventions, services, and policies that optimise healthcare service delivery in this patient population.

A holistic approach that encompasses patients' experiences is essential for developing comprehensive treatment plans and tailoring interventions to address individual needs and priorities (Dager et al., 2017). The omission of foot joints from routine assessments, and disease indices such as the DAS-28, gives rise to apprehensions surrounding clinicians' capacity to adequately detect and address foot disease in this patient population (Rutowski et al., 2022; Salaffi & Ciapetti, 2013). Considering the growing emphasis on patient-centred care, PROMs have the potential to serve as patient-friendly, location-independent, time-efficient, and a cost-effective tool for monitoring foot health in the RA population (Hendrikx et al., 2016). Their implementation can facilitate outcome-driven care and assess aspects of RA foot health that are significant to patients but may be under-appreciated by clinicians (Gibbons et al., 2016). Furthermore, the implementation of patient perspectives in healthcare practice, supported by EULAR (Studenic et al., 2022), has proven to be a valuable method that enhances patient-clinician interactions,

facilitates patient empowerment and supports shared decision-making, playing a crucial role in holistic care (Van der Wees et al., 2014).

Various self-reported instruments, such as the FFI (Budiman-Mak et al., 1991) and FIS (Helliwell et al., 2005), have been developed to assess the impact of RA on foot function, disability, and impairment. A comprehensive overview of RA foot-specific PROMs can be found in Section 2.5.2. Despite NHS recommendations to incorporate PROMs into clinical practice (Kingsley & Patel, 2017), their application in routine clinics is scarce. This is attributed to feasibility concerns arising from the nature of busy rheumatology and podiatry clinics and the substantial respondent burden due to the length of these PROMs (23 and 51, respectively). Furthermore, the abundance of PROMs in rheumatology and podiatry presents challenges in selecting an appropriate tool, as clinicians often lack time to administer multiple PROMs effectively (Maher & Kilmartin, 2010). Additionally, existing foot PROMs predominantly focus on foot disability and impairment rather than foot disease activity, limiting their utility in guiding pharmacological management. In response to this limitation, the RADAI-F5 was developed as a dedicated PROM for assessing foot disease activity in RA, exhibiting robust psychometric properties in line with COSMIN recommendations (Mokkink et al., 2019; Gagnier et al., 2021).

For successful development and integration of PROMs in healthcare settings, involving and engaging key stakeholders is essential (Ruseckaite et al., 2022). Stakeholders can provide valuable insights into real-world experiences and interactions between patients and clinicians. Many health research funding organisations advocate for stakeholder engagement as a vital way to achieve impactful outcomes, recognising its role in connecting research production with practical application (Goodyear-Smith et al., 2015). While clinical staff contribute their expertise in terms of clinical knowledge and assessment, patient involvement is equally essential to ensure their unique perspectives, experiences, and priorities can be considered (Ruseckaite et al., 2022). This collaboration facilitates the development and implementation of PROMs that accurately capture the outcomes that hold utmost significance to patients (Terwee et al., 2018). Though theoretical obstacles, such as logistical and technological limitations, have been recognised in incorporating PROMs into clinical practice (Fung et al., 2008; Boyce et al., 2014; Kasturi et al., 2020; Primdahl et al., 2020), a scarcity of qualitative research exists on the viewpoints of patients and rheumatologists regarding the adoption of foot PROMs.. Obtaining a comprehensive understanding of the benefits and challenges related to the integration of the RADAI-F5 into routine practice is essential for the successful adoption of this novel tool. Therefore, this study aims to explore patient and clinician views on the clinical utility of the RADAI-F5 to inform the assessment and management of foot disease in RA.

3.2 Methods:

3.2.1 Study Design:

Qualitative research plays a crucial role in gaining a comprehensive understanding of people's views, beliefs, and attitudes towards a particular phenomenon (Pathak, Jena & Kalra, 2013). The utilisation of a qualitative approach provides a unique opportunity to capture and analyse rich and detailed narratives, leading to the generation of new findings that possess a level of depth and complexity that might not be attainable through a quantitative approach (Aspers & Corte, 2019). In the context of examining patients' and clinicians' perspectives on the clinical utility of implementing the RADAI-F5 tool into rheumatology care, a qualitative approach is deemed the most suitable methodology for providing rich descriptions and insights.

Given the exploratory nature of the present study, Interpretive Phenomenological Analysis (IPA) was selected as the optimal methodology to address the study aims. IPA is relevant within the field of health psychology, enabling researchers to gain a deeper understanding of individuals' lived experiences and reflections (Alase, 2017). The study utilises IPA to explore how RA patients and healthcare professionals personally interpret and give meaning to their experiences living with or managing RA. This aligns with the objective of understanding participants' subjective perspectives and insights. IPA draws from phenomenology, which focuses on the study of human experience and how they are understood, both first-hand (by participants) and second-hand (by the researcher) (MacLeod, 2019). This phenomenon is known as double hermeneutic, where the principal investigator undertakes a pivotal position in the interpretation and analysis of the participants' experiences. This IPA approach facilitates a nuanced understanding of the complexities involved in interpreting qualitative data, offering valuable insights to inform clinical practice and improve patient care in the context of foot disease management in RA.

3.2.2 Stakeholder involvement

The research methodology and data collection procedures included active engagement with key stakeholders. Stakeholder sessions involved participants with both early and established cases of RA, encompassing healthcare professionals with diverse experience levels in rheumatology and podiatry. Recruitment of individuals for these sessions was facilitated through Versus Arthritis gatekeepers, with additional involvement from healthcare groups such as the MSK Lanarkshire podiatry group and the North West clinical effectiveness group. The informed engagement of participants, including RA patients, rheumatologists, podiatrists, and physiotherapists, was ensured through the provision of detailed information about the research project. Subsequently, individual and group discussions were conducted to facilitate a comprehensive exploration of their perspectives of this study.

Participants were actively engaged to provide feedback, emphasising positive aspects, areas for improvement, and potential concerns related to the RADAI-F5 tool. The North West Clinical Effectiveness Group stressed the "need for a tool to assess foot disease in RA patients, with considerations for implementation and utility in clinical practice" (Appendix C). Two rheumatologists and one podiatrist proposed a long-term feasibility study for the RADAI-F5, intending to gather additional information on the benefits and barriers of implementing the tool and determining implementation strategies in clinical practice (Appendix C). While this recommendation could not be pursued within the constraints of the PhD study, it remains a valuable suggestion for future research.

The qualitative interview topic guide employed in this study was disseminated to all participants, allowing for their feedback to ensure that each question adequately addressed their concerns and perspectives. Patient representatives were additionally engaged to review patient-facing documentation, with a focus on assessing comprehensibility, understandability, and sensitivity towards participants' needs and preferences. This meticulous approach was undertaken to ensure that the research adhered to ethical standards and maintained a patient-centric focus, as advocated by Greenhalgh et al. (2019).

3.2.3 Participants
The study participants were divided into two groups: RA participants, AHPs, and rheumatologists. Inclusion criteria for RA participants consisted of:

a) A clinician-confirmed diagnosis of RA

b) ≥18 years of age

c) The ability to engage in an online interview conducted in English, as translation services were unavailable

Clinicians, including rheumatologists, rheumatology nurses, rheumatology registrars, physiotherapists, podiatrists, and orthotists, were eligible to participate if they:

a) Routinely treated and managed individuals with RA

b) ≥18 years of age

c) Had the ability to engage in an online interview conducted in English

Exclusion criteria encompassed the inability to provide informed consent due to severe hearing and/or cognitive impairments/mental disorders. This applied to both RA participants and clinicians.

3.2.4 Recruitment:

Participants were recruited using convenience and snowball sampling methods, using three distinct approaches. Primarily, individuals with RA and AHPs were contacted via email, facilitated by gatekeepers affiliated with Versus Arthritis Scotland and the National Rheumatoid Arthritis Society (NRAS). For rheumatologists, email communication was facilitated by a gatekeeper from the Scottish Society for Rheumatology (SSR). Gatekeeper emails encompassed a Study Invitation, Participant Information Sheet (Appendix E), and an Informed Consent Form. The gatekeepers subsequently dispatched follow-up emails after two and six weeks. Secondly, the principal investigator (AH) employed social media platforms, particularly Twitter, to disseminate a study advertisement on two occasions, with a four-week interval. The intention was to maximise the reach and engagement of potential participants through the re-tweeting of the advertisement through established contacts. Lastly, the principal investigator personally reached out to AHP contacts and rheumatologists who had previously collaborated on research projects within the Glasgow Caledonian University (GCU) MSK Research Health Group. Participants were limited to UK residents, who were requested to contact the researcher through email after a minimum waiting period of 48 hours to ensure sufficient time for deliberate consideration of their participation. Eligible individuals who expressed interest were subsequently contacted to complete the consent form and schedule an online interview. In IPA, ensuring data adequacy is crucial for comprehensively capturing participants' experiences and understanding the research phenomenon (Alasse, 2017). Therefore, recruitment for this study continued until additional data collection no longer provided significant new insights or perspectives, indicating data adequacy.

3.2.5 Setting:

Participants were instructed to select a comfortable, quiet, and private setting for their interviews to ensure an optimal environment for open and focused communication (McGrath et al., 2019; Alase, 2017). The interviews were carried out using either telephone or Microsoft Teams, based on the preference expressed by participants. This approach was motivated by two reasons: firstly, it aligned with the social distancing measures implemented during the COVID-19 pandemic, and secondly, it facilitated access to national research participants.

3.2.6 Data Collection:

The duration of the semi-structured interviews ranged from 35 to 70 minutes. Verbal consent was obtained from participants for audio and video recording. To streamline the interview process, the research team collaborated to create a semi-structured topic guide. This approach was chosen to provide a framework of pre-determined questions while also allowing for flexible exploration of the research topic (Jashmed, 2014). This topic guide was informed by a comprehensive review of the existing literature pertaining to RA-specific foot PROMs and the implications of RA foot

disease (Kasturi et al., 2020; Mosor et al., 2021; Wilson et al., 2017; Lunt et al., 2020; Graham et al., 2012; Hendry et al., 2013; De Souza et al., 2016). Furthermore, input from key stakeholders, including RA patients and specialist clinicians, was integrated to enrich the topic guide. The final version of the topic guide underwent a thorough review by the stakeholder representatives, including five RA patients, one rheumatologist, two physiotherapists, and three podiatrists to ensure that all questions remained relevant and aligned with the research aim.

The interview questions employed in this study were designed to be open-ended, allowing participants to freely express their perspectives without predetermined assumptions. Probes and prompts were included in the topic guide to facilitate in-depth discussions between the researcher and participants. The topic guide (Appendix F) encompassed various dimensions, such as the lived experiences of individuals with RA-related foot disease, the current management of foot disease in RA, and the factors influencing the clinical implementation of the RADAI-F5 tool. Prior to the interviews, all participants were given the opportunity to complete or review the RADAI-F5 questionnaire, which aided in guiding discussions related to the tool. It is important to note that the RADAI-F5 scores for RA participants were not recorded during this process. Furthermore, demographic data including sex, age, clinical profession, years in clinical practice, disease duration and medication were collected from participants.

Each interview session was carefully recorded using a high-quality voice recorder, specifically the Sony IC recorder- ICD-PX470. The transcription process began with the transfer of audio files into a Word document, making use of the built-in transcription tool complete with time stamps to ensure accuracy. The transcribed content was integrated into the Word document, and audio playback was employed for reference and verification purposes. Rigourous quality control measures were implemented, involving a comprehensive cross-validation process with the original audio recordings to rectify any discrepancies or omissions. To uphold participant confidentiality, all transcripts underwent a thorough anonymisation procedure. Importantly, continuous member checking of the transcripts was carried out to guarantee clarity and comprehensibility, thereby significantly enhancing the reliability and trustworthiness of the study findings. To ensure the accuracy of data interpretation, the interview transcripts were meticulously reviewed by the researcher. Furthermore, the application of member checking was incorporated to enhance the methodological rigour of the collected data. Participants were invited to review and verify their interview transcripts. This technique added an additional layer of validation to the study, thereby augmenting the trustworthiness and confirmability of the research findings (Nowell et al., 2017).

3.2.7 Data analysis:

IPA data analysis was employed as the procedure is rigourous, adaptable, and multi-directional (Finlay, 2014). Table 6 provides an overview of the data analysis steps employed in the present study, which were guided by a framework proposed by Smith et al., (2009).

The median values for age, years of clinical profession, and disease duration were determined using SPSS version 26. The data analysis process began with the transcription of each interview, capturing both verbal and nonverbal cues such as laughter, nodding, facial expressions, and eye contact. Accuracy was ensured by cross-referencing the transcripts with the audio recordings. Familiarity with the data was established through multiple thorough readings of the transcripts. Nvivo 12, a non-numerical data analysis software, was utilised to systematically explore the data and assign initial descriptive codes. These codes were generated based on the lowest order themes identified in the data and were subsequently organised into groups, forming emerging themes. This stage aimed to condense the data while maintaining the integrity of the participants' experiences. A detailed outline of the stages of IPA employed can be found in Appendix G.

The emergent themes were then subjected to an iterative process of grouping and regrouping, aiming to identify connections among seemingly related emerging themes. This process was repeated for each transcript, bracketing the themes identified in earlier transcripts to allow for the emergence of new themes specific to each participant. Finally, after developing themes for all sixteen transcripts, they were compared and contrasted. The result was a set of themes that captured the essence of the entire dataset, exhibiting varying degrees of interpretation and induction.

TABLE 6: IPA DATA ANALYSIS PROCESS (ADAPTED FROM SMITH ET AL., 2009)

Stage:	Process:
1.	To establish familiarity with the data, the researcher engaged in a process of deep immersion by repeatedly listening to the initial audio-recorded interview. Concurrently, the researcher carefully read the corresponding written transcription. This approach allowed for a comprehensive understanding of the data, enabling the identification of nuanced details and insights into the participants' perspectives through the integration of auditory and textual information.
2.	During the iterative review process, detailed and comprehensive notes were made while reviewing the data and listening to the audio recordings multiple times. These initial notes encompassed descriptive observations, linguistic analyses, and conceptual insights. This approach ensured a thorough examination of the transcript, facilitating a deeper understanding of the data and the emergence of significant patterns and themes.
3.	The codes generated in Nvivo were further organised into groups to form themes that were consistently supported by the entirety of the data. This process involved identifying emergent themes that encompassed and highlighted the underlying patterns and shared characteristics in the dataset.

4.	Themes were examined and reviewed, considering the adequacy of supporting data and potential overlaps in the data. Similar themes were combined, and connections were established to develop subordinate themes, reflecting the interrelated nature of the participants' experiences and perspectives.
5.	Repeat Steps 1-4 for all participants
6.	Superordinate themes were developed through an examination of patterns across the sixteen cases. The analysis was presented in a coherent and logical order, ensuring a systematic flow of information. Data extracts were included as supporting evidence to substantiate the findings within each topic/theme both in text and in tables 8 and 9

To enhance the credibility, trustworthiness and validity of the findings and minimise the risk of bias, consensus of overall themes was sought by the supervisory team (Renz et al., 2018; Guion et al., 2011). The supervisory team (GH, DD, and MS) independently analysed the transcripts of two clinicians (GC10 and GC12), while two members of the study team (GH, DD) independently analysed the transcripts of two RA participants (GG01 and GG02). In instances of disagreement, resolution and agreement on the overall emergent themes were reached through further discussion (see Appendix H).

3.2.8 Ethical considerations:

Ethical approval for the study was obtained from the Psychology, Social work, and Allied Health Sciences Research Ethics Committee at GCU (HLS/PSWAHS/20/096). To protect participant anonymity, identification (ID) codes consisting of a letter code and participant number were assigned (e.g., GC for clinicians and GG for RA participants). Given the online nature of the interviews and the challenges posed by the COVID-19 pandemic, special attention was given to addressing potential distress or anxiety among participants, reflecting a commitment to ethical considerations in remote data collection. A comprehensive plan was implemented, providing robust debriefing and ongoing support throughout and after the interviews. Participants were informed of the Versus Arthritis hotline for immediate assistance in case of distress. Notably, only one individual reported experiencing distress and disclosed having previous suicidal thoughts, exacerbated by the isolation of the global pandemic. Appropriate measures were taken to ensure the well-being of this individual, including referrals to the Good Samaritans and SOS Silence of Suicide helpline. Furthermore, the participant was encouraged to engage in support groups tailored for individuals with RA, such as those offered by Versus Arthritis.

3.2.9 Rigour:

To uphold rigour and dependability in the study, various measures were employed. Dr. Karen Lorimer, a research with extensive qualitative experience, was consulted for guidance, offering individual support, and reviewing the interview topic guide. This collaboration contributed to refining and aligning the interview topic guide with established qualitative research practices.

Additionally, practice interviews were conducted with two podiatrists and two PhD students from GCU. These practice sessions identified potential challenges and enabled necessary adjustments to be made prior to participant interviews. To mitigate biases, the interviewer was introduced as a PhD student rather than as a podiatrist, aligning with the findings of Van de Mortel (2008) regarding the influence of disclosing one's professional background on participants' responses. This approach aimed to establish a neutral and unbiased environment that fostered participants' openness in sharing their experiences. Furthermore, a reflexive journal was maintained throughout the research process, serving as a tool for documenting thoughts, feelings, and reflections, facilitating critical self-reflection, and providing a resource for introspection during data analysis. These steps provided increased credibility and trustworthiness of the study findings.

3.3 Results

3.3.1: Participant characteristics

Interviews were conducted from 9th March to 9th July 2021. Initially, 12 individuals with RA and 11 clinicians were approached to participate in the study. However, participants declined for various reasons: number (n)= 2 cited time constraints, n=1 reconsidered their participation, and n=4 did not respond after initial contact. As a result, the final sample consisted of 16 participants, including 8 individuals with RA and 8 clinicians. Among the RA participants, 7 were female, with a median age of 54 years and a median disease duration of 11 years. The 8 clinicians had a median age of 44.5 years and clinical experience of 20 years. RA participant and clinician demographic details can be found in Table 7 and Table 8, respectively.

TABLE 7: RA PARTICIPANT CHARACTERISTICS

Participant ID	Sex	Age (years)	Disease duration (Years)	Current medication
GG01	Female	61	27	Biologics
GG02	Female	40	15	Biologics
GG03	Male	68	9	DMARD, Biologics
GG04	Female	50	12	Biologics
GG05	Female	58	56	DMARD
GG06	Female	48	5	DMARDs
GG07	Female	57	10	DMARD, Biologics
GG08	Female	51	3	DMARDs

DMARDs: Disease-modifying anti-rheumatic drugs

TABLE 8: CLINICIAN PARTICIPANT CHARACTERISTICS

Participant ID	Sex	Age (years)	Profession	Years of clinical experience
GC10	Female	43	Podiatrist	21
GG11	Male	45	Rheumatologist	20
GC12	Male	44	Podiatrist	20
GC13	Female	56	Podiatrist	16
GC14	Male	49	Podiatrist	16
GC15	Male	44	Physiotherapist	20
GC16	Male	54	Rheumatologist	22
GC17	Female	39	Podiatrist	21

3.3.2: Overview of themes

The analysis identified three global themes: "Feet are a priority" (comprised of 80 codes), "Existing methods of measuring foot disease are inadequate" (comprised of 120 codes), and "Implementation" (comprised of 187 codes). The global theme of "Implementation" was further organised into two sub-themes: "Facilitators to RADAI-F5 implementation" and "Barriers to RADAI-F5 implementation." The relationships between participant views and final themes are depicted in Figure 4. To provide further transparancy of the study findings, illustrative RA participant and clinician quotes are presented in Tables 9 and 10, respectively.

Theme 1: Feet are a priority in RA

Foot disease is common

- Feet overlooked/ignored by clinicians
- Feet affect all participants

Foot disease impact

- Structural deformity
- Impacts mobility and function
- Early ill health retirement
- Footwear choices limited
- Burden on family
- Impact on social life

Theme 2: Existing methods for measuring foot disease activity are

Suboptimal foot care

- DAS under-represents foot disease
- Consultants have to find a way around DAS-28
- Lack of referral/access to podiatry
- Clinical assessment of feet only conducted when prompted by patient

Lack of PROM use in current practice

- PROMs are too wordy/long/time consuming
- PROMs are used for audit purposes
- Lack of PROM trust

Need for clinically feasible foot disease PROM

- Short
- Quick
- Simple
- Easy to understand

Patient and clinician views

Clinical barriers to RADAI-F5 implementation

Practical difficulties

- Administrative burden
- Time
- Competing priorities

Electronic database

- Access to patient data
- Electronic medical record integration
- Lack of a universal database

Lack of validity

- Lack of trust in PROMS
- Need for objective measures
- No added value
- Question similarity

Theme 3: Implementation

Clinical facilitator to RADAI-F5 implementation

Promoting communication

- Patient-clinician communication
- Multidisciplinary communication
- Referrals

Guiding management

- Monitor changes in symptoms
- Monitor treatment efficacy
- Screening tool
- Audit

Promoting patient education

- Self-involved with foot health.
- Awareness of symptom experiences
- Promote education

FIGURE 4: OVERVIEW OF FINAL THEMES

	GG01	GG02	GG03	GG04	GG05	GG06	GG07	GG08
Theme 1: Feet are a priority	I had to take early retirement due to ill health caused by my arthritis… Obviously, like most people with arthritis, I often get corns or you know you get slightly deformed toes, with one foot being worse than the other… That's been one of the hardest things (with her RA), replacing shoes and finding shoes that fit	My left ankle is fused; my right ankle is beginning to fuse… I now notice that I walk different… I am very restricted, I can't walk very far, I use a mobility scooter… I use the wheel chair in the house because, in the mornings, I cannot walk at all. I can't even stand in the mornings becaus	I had retired at the time of having RA… I have difficulty walking the distances that I could do previously, and I have fatigue … My feet have suffered overtime. …. I now have fallen arches. When I'm walking, there is considerable pain that's associated with the development of RA… In terms of distance, I used to be a runner. I don't	It's (RA) life changing. It's just limited my activity so much… The biggest change for me was that I did have a business that I ran for over 20 years, and because I was so poorly and couldn't cope with any kind of stress as it flares everything… My feet were so sore that I couldn't walk to the end of the street and had to turn back because my feet were so painful …	I have very limited and restrictive movement… Initially, when my rheumatoid started, it started apparently in my right ankle, and I still have problems with that. I feel my ankles are solid, I can get a wee bit to move it up and down, but my feet…… yeah, I can't stand now at all…	I think prior to changing into the job that I have now, which is much more of a kind of light touch consultancy job, I was very stressed and really suffering quite badly physically from the disease… You tend to get it (swelling) on the underside of the foot, typically under the big toe, basically in that joint that connects it to the body of the foot, it feels like it is crunching and stiff after walking a lot… To be honest standing for long periods of time can actually be really not good for me…	I would say that I tried to take my own life at the turn of the year because of the pain. I was in that much pain… The pain in my feet can be so acute that it is not unusual for me to sit in really bad winter months have my heating up at 27 degrees with socks on, and I spend days on the sofa. That is just not the person that I was but the first person I'm increasingly becoming… I am retired. I retired five years ago. I loved my job, my job loved me, but I just became a very unreliable employee because of my foot pain…	[My RA] has affected it[feet] hugely. I work in schools, so I was working full time and I couldn't cope with working. Then I reduced my hours to three days. I do get tired a lot… It [my feet] hugely impacts how I am and I think I'm still getting used to that because I still remember how I was and how I used to enjoy life. So it's now enjoying life in a very different way. It's hard, but it's getting easier as I get used to it more… My toes. I struggle a lot with my toes. I don't get a huge amount of swelling but I do get a lot of tenderness and stiffness.

	when you can't try them on….	e I am in that much pain with my feet… I gave up work after I had my daughter and medically retired because my feet has got so much damage now…	run now...	I feel that the things that I would say like "Let us go for a walk, and I feel better", some days I can't do that, so I don't feel better. Therefore, that reduces my social interactions, so let's say that I can't meet a friend for a walk or I just can't go into nature, which would be something that I would have done in the past.				I get a lot of pain going across the top of the foot and in my toes. My toes constantly just go into spasm and they just stick up and I can't do anything with them. Sometimes when walking, I will suddenly just won't be able to walk because it's stuck and really painful for it to actually move...
Theme 2: Existing methods for measuring foot disease are inadequate	Very confused (that feet are not included in the DAS-28), because I am affected by my feet but I seem to forget	No, but she does get you to take off your socks and shoes, and she will look at your	There is a commonly used tool, which you will know about called the DAS, which doesn't have feet in it. It's	I don't understand. It's a whole-body disease, so I don't understand why they wouldn't include the feet. I think it's really unfair that it's	I would have thought that it (the feet) should have been included (in the DAS-28) or at least in another form like the one you've got at the moment.	I would imagine the two main areas that people are affected with the most are feet and hands. I'm kind of really surprised to have to say that it isn't	Why doesn't the DAS-28 include the ankle, or why do I not know that it doesn't?... Is there something else that I should be having done because my ankles and my feet are very swollen all of the	My first consultant said that it couldn't possibly be RA because it wasn't part of the joints that are supposed to suffer from RA, but that is where it is…it affects my feet…

to mention it in appointments … The rheumatologist never really mentioned anything about my feet. But I think I am very knowledgeable about it now and like I said, he might only have 10 minutes so maybe cannot provide that much information… They always check my hands, or you know apply pressure in your hands and check your	ankle placement. I would say that the most time is actually spent on your upper body and your bigger joints … Considering the amount of damage that I have, it (the DAS-28) should definitely include [the feet]. I can cope with my elbow problems, and my fingers are swollen, but the feet	really very poor, but there is no measurement of feet… If you don't have your feet measured and they are terrible, yeah, you're not going to get the benefit of the more effective drugs and biologics… So I think it's an excellent idea to push for feet to be included …	not included in the DAS score… I mean, my toes were separating, like the disease was active because you can see my toes were swollen and spreading. But he said, "it is not hot, and your markers are coming back normal, so it's not active". I have to admit I haven't had a great experience lately… Well, I think it makes you feel less likely to want to tell them [rheumatologists about your foot	For me personally, it is my feet and ankles that need attention	included (in the DAS-28), so it probably should be a figure or in their measurement... They're (rheumatologists) not particularly proactive with the feet. So no, I suspect unless I said "I've got a gammy foot", then nobody would start looking at them…	time? Is there another test I should be getting, and why am I not getting that?	I do feel that the feet are very sort of underrated with the RA. It is all about "Oh, I want help with my hands", and I can see the OT. If I need help for another part of my body, I can see my physio but with the feet....No one seems to push how important the feet are, so I do believe that the feet should be included in the DAS-28…

	joints (in hands), but I can't say they ever really look at your feet to be perfectly honest ….	really restrict you because it restricts my life so much …		problems] because you feel really belittled. You're not taken seriously by the rheumatologist, you feel like a fraud and that you are going crazy in your head. You know, you come back home, and you doubt yourself and think that you are a hypochondriac making things up. You know it's horrible …				
Subordinate theme 3: Clinical facilitators to RADAI-F5	This tool can be used to explain where your foot pain is to help them make a better informed decision. I think there are a	If you are given this tool when you have an illness, it is always in your brain that you need to look	You can see if it is (The RADAI-F5 scores) in the same place or if it is increasing or decreasing. I could then reflect on what I did around	It would make me feel more in control if I was doing the self-assessment via a tool like this. Then I could go in and say, "These are the things that I	I would be happy to discuss whatever I put on the form with them (rheumatologists) as a starting point. If my feet had been sore in the last few days, I would probably	I think that it potentially prompts joint-specific discussions. It's almost like a tool to perhaps kind of just help the discussion be a bit more efficacious …… If you've got a question	I would hope that we would go through the tool and take a question at a time and talk it through thoroughly while an examination was being done…. Because the RADAI-F5 asks about the joint tenderness	There has to be open communication between the whole health team….. It (RADAI-F5) was definitely a good tool to have so you can monitor your feet, so you know whatever time you had your medication

lot of people out there who haven't been able to. If they have had a lot of foot pain, they will not have had a chance to speak to anybody about it…. I think it's (the RADAI-F5) quite good to make you more aware of your feet, because I think it's like all these things you're inclined to. You don't ignore it; you learn to live with it.	after that part of your body and talk about it to my rheumatologist…. I wish I would have known about my feet before so I could have pushed for more help… I went from 0-100; somebody like me should have been caught quicker and been told to get into these feet before they end up with all these	that the affected things…. Yeah, the five questions were pretty easy to understand. And you had it "thinking only of your feet", which I think is necessary because people will perhaps use it for other things…. Sadly, my experience is that there are too few rheumatologists to keep on track with the changes that are affecting the patients. It (The RADAI-F5) would give a consistent basis	want you to focus on now….	want to discuss that using the form (RADAI-F5) …. This could help the consultants focus on the feet if it was the more symptomatic part of the body. Consultants do not have a lot of time to go through every part of the body, so using this could help focus on the feet and help set a plan or treatment focused on the foot…. Well, it was easy to fill in. The questions are clear. You know, sometimes when	here with 500 questions on it, nobody fills it in. If you've got a questionnaire with five questions, everyone will at least have a go…..	and the pain and foot pain and my foot health, so I think it will help me focus on my feet and encourage more treatments that I could do myself…. It was succinct, it was very easily understood, it was just very black and white and short and to the point….	sort of. Well, it's three months really before it starts to kick in, isn't it? It could be a useful tool to then look back and think, "Actually, that was actually really mild compared to what I am now…. I thought it was really easy, really simple. You know it does exactly what it says. The things on there (questions) it's straightforward. It's self-explanatory. There's nothing on there that I think would confuse anybody. It's not long, it's everything you need, and it is there and quick in clinics…..

	When you sent the form, I started to look back at my feet and I am aware that when my arthritis isn't right, my feet are wrong ….	defor mities. That never happe ned to me. It wasn't just treated like the rest of my body. It would have been helpfu l to have this tool so that I could have been more self-involv ed with my manag ement ….	for the rheumat ologist, podiatris t and orthotist s to compare how you were before with how you are now		you get these forms, you think, "what does that mean?". But I understo od all the questions in the form that you provided ….			
	If you give too many questio ns people get lost in amongs t them all and maybe not able to be comple ted in the 10-minute appoint ment. This is nice and short….	This one was nice and short. It also takes no time to fill this in; it takes literall y a few second s. I						

		don't even think the kettle had boiled by the time I completed it (laughs).						
Subordinate theme 4: Clinical barriers to RADAI-F5	I mean, this will obviously go along with other tools. You know, the blood tests and things as well.	You don't actually get a great deal of time to talk (to your rheumatologist), although she does try her best to accommodate you most of the time you are referred to a surgeon, a physio or the podiatrist.	It might make it more acceptable to the clinicians for there to be an independent, evidence-based measure included in the RADAI-F5. That struck me as something which would present you with a difficulty in persuading rheumatologists that this is not just measured by the patient, but also as an independent source of information	N/A	They have got very limited time during an appointment; they might not always have the time to go over every single one of the question	I mean, it's just building up another pool of details that is significantly less accurate? You're still going to have all the DMARD and blood monitoring thing so you can have all the inflammation markers and everything, so they'll have some data.	If information isn't picked up by the nurses in the Rheumatology Day Ward, it is picked up by the secretary, but they are very busy. You just wonder if they have the time to hand you the form and collect it again. No, it's (mobile applications) just something else that I have to do that will be a constant reminder about how poorly I feel, and I don't want to do that. Also, with my mental health, an app would just be another thing to do.	There was some question similarity between question 2 and 3 and there was not a lot on walking and effects on daily activity.

TABLE 10: CONTRIBUTING QUOTES FROM CLINICIAN PARTICIPANTS TO OVERALL THEMES

	GC 10	GC 11	GC 12	GC 13	GC 14	GC 15	GC 16	GC 17
Theme 1: Feet are a priority	If they have other joints that are more painful at the moment in time on top of their feet, that one will take preference to another, and the feet will be overlooked …	It's (the feet) a frequent issue at consultations. It obviously depends on the extent of that person's disease, but certainly, you could imagine that the feet would be mentioned in up to 50% of our consultations …	My understanding is the impact of feet that it has on a patients' disability. It creates a disability that comes to their foot function everyday sort of like activities that it has a major impact on. I suppose functionally but also to take into account sort of the psychosocial model, it just impacts on their life as a whole… I have had lots of experience where the DAS-28 looks positive but the patient sitting in front of me hasn't given me that same level of feedback in relation to their feet…	N/A	I don't really see very much with the early in inflammatory arthritis, so the new patients and the flares and the synovitis and that part of rheumatology. I mainly see the referrals from rheumatology for those patients that might be new or have been with the rheumatology consultants for a while and any foot problems that come in are kind of sent my way. So primarily, it's the mechanical proble	I know that the feet are undertreated and probably under assessed area nationally for people with RA. Also, my understanding is there's a lot of potential overlap of the erosive disease causing secondary degenerative disease, so even in a theoretically well-controlled rheumatoid patient, there could well still be foot problems there. I suppose, as the physiotherapist, if there are problems with the feet that impacts	It's (foot inflammation) common and it's troublesome for patients because it can have a major impact on their mobility. Pain control can be an issue… It's particularly difficult with the DAS-28 because you do get some people who predominantly have foot and ankle disease and that won't be represented really at all in their DAS score… I would spend much more time on the upper limb that I would on the lower limb with students as well, never	N/A

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					ms with the foot that I tend to see rather than the inflammatory issues …	on everything else, like our patients' ability to do cardiovascular fitness and that kind of thing…. So it's a crucial part, I think, of the overall package of care and management.	mind trainees…	
Theme 2: Existing methods for measuring foot disease are inadequate	I think in the DAS-28, it (the feet) is measured very poorly, actually. We often find that the disease looks as though it is in remission according to the DAS, but they have still got problems with their feet. So current measures in terms of just clinical measures ….as in the	Well, this (the feet) is under-represented in the clinical tools for assessing disease activity, and clinicians don't look at feet enough … People often have substantial foot disease and not	We don't routinely use any PROMS other than the traditional VAS scores. We do count joints and document joint involvement, but it's more of a kind of a written X bar detailing clinical history rather than using any structured PROMS… We've tried numerous PROMS. Historically, I think	Foot disease is currently not measured or represented by current measures of disease activity because it doesn't really. There's nothing that's specific to focus just on the feet…so it makes	You've already said about the DAS-28, which doesn't involve the feet at all, so there isn't any real sort of outcome measures that are used. We use the Minemop Outcome measure which you measure yourself and is	I think it's a real missed opportunity, and I think we do the screening tools we are told to do and probably not much more. A well-informed MDT kind of positive clinician will consider foot problems every time they see a patient but	I think within practice it's something that we're all quite aware of, so we'll regularly ask patients about their feet but for scoring and eligibility, it does give a little bit of difficulty … If you're getting people who are on the cusp of maybe being eligible for more advanced	Foot disease is not represented. It is basically ankle up, and it's like the feet don't matter… I think it's (the feet are) just not at the forefront of their mind because of that (exclusion from the DAS-28), and because it's not on that checklist… I don't think my two (employees)

| | DAS-28 is just not reflective of any problems within the feet…

I mean, we don't use PROMS as much
It makes me feel that we're not providing the best service to the patient because we are completely omitting anything below the knee joint. I don't think it's reflective of the person as a whole; it's just a snapshot of what they are actually seeing at that time without including the feet… | so much in their hands, so it creates problems which we find ways around. But it's just irritating and frustrating for everybody…

There is sufficient time to discuss whatever their priority is. So if they mention that (feet) as their priority, we will talk about that. You know, I think if it's not a big issue, then they will not mention it… | probably it's time-consuming for our clinical consultations. It is hard to try and capture all of the aspects of history taking, assessment, treatment and then writing up, the kind of administration side of things. I think were constructed by time, I suppose…. | referrals more difficult….we need a tool like the RADAI-F5 | a medical outcome profile. It's a kind of a broad generalised outcome profile. It doesn't particularly pinpoint the feet as such…. Yeah, I do think there's something missing (in terms of patient-reported outcomes). We don't use any of the long-winded foot outcome profiles. We just don't have the time to use anything like that really … | perhaps those that are less experienced or maybe the nurse-led clinic will just do the DAS-28 because that's what they've been asked to do and foot problems don't come into that, so it's a missed opportunity.

We use the Health Assessment Questionnaire (HAQ). We have tried the MSK-HQ but we didn't progress with that. We have tried EQ-5D, again we didn't particularly progress with that. For RA…. Pain VAS as a part of the DAS- | therapies, and you are then having to make an estimation of how bad their foot disease. As I said, other members of staff may have to involve you because again they got the same problem. It is a minor barrier but we do get around it… | that do MSK do (use PROMs) currently. I don't think they have separate ones for RA… |

						28 is probably the two other things we use, embarrassingly...		
Subordinate theme 3: Clinical facilitators to RADAI-F5	I just like the ease of being able to fill it (The RADAI-F5) out, to be honest. It's just simple. They are all extremely quick questions, and it gives you a very quick overview of what's been happening … This (The RADAI-F5) should form part of your patient education because you are building a relationship with the patient where you are acknowledging their foot problems. You know...we will be offering	Well, it's (the RADAI-F5) simple. It is not complex in both the number question and the terminology is easy for folks and it's nice that it is a Likert scale or something similar to the Likert scale. Yep, it looks good as a PROM that could be quick in clinics … You may have to have it	I thought it was really simplistic, easy to use, and easy to calculate… I think it could also encourage patient communication with clinicians and make certain that we are facilitating outcome driven care… I think I would use it (The RADAI-F5) to try and measure the success of the treatments that we are implementing…	I think that is great and I love the fact it's (the RADAI-F5) very short. We've got sort of half an hour to 40 minutes to do everything else, so I can't spend 10 minutes on this. That's how I really appreciate that it is concise. It's the fact it's five questions and it's dead easy to score… it would be nice to (use RADAI	That there are only five questions, and it's a simple scale of 0-10 and quite easy for them and for me to understand… It (the RADAI-F5) will assist in referral decisions with regards to AHP services, or like I said, clinical psychology or anything else. It will assist in disease medication, modifying and general management plan review …	It's short. It's fairly easy to fill out. I think 5 questions, scoring zero to 10, it's quite clear what the bounds are at the 0 and 10. I think you probably could ask 1000 questions and still not know everything you need to know, but only get down to five is much appreciated… I think self-monitoring is very good for the patient… Do I make sure I get shoes and socks off	It was short. So it's only 5 questions. It's very straightforward. I think it's easy for patients to understand the scales and at least I don't need to get my ruler out to measure what the score is, which you do for other things. And yeah, those are the main things... Short and easy to score so quick to use in clinic… I think that could be quite useful because that's often where the conversation starts… I could see that (The RADAI-	I thought it looked quite easy to use. It was easy for a patient to understand... the patient would understand the wording of it and things as well. I think it is clinically feasible. It's not going to take a long time to do. I think that'll be quite easy to implement into a clinic, and it is at a level of consultant could understand … It is nice because it helped track your patterns and things as well. It sort of made the patterns for you, which was really good because it helps encourage self-

	treatment in response to that, but we are also offering advice and building that patient relationship… I think I would use it for new patients but also for existing patients just to monitor progress from one appointment to the next. I think with the new early RA patients; I think we would use this tool to just monitor them to see how they were going in terms of the global disease as well rather than rushing things…	as some type of internal comparative for the patient's own baseline and see whether it was going up or down …		-F5 as a monitoring tool) because it would be a quantifiable thing that you can actually sit and see improvement… Patient-related outcome measures are really important to my work and help guide management…		for all my patients? Probably not as much as I should do, but if they mention it subjectively, I'll assess it. Yeah, that (the RADAI-F5) could help with the conversation if we're looking at very specific treatment issues…	F5) being useful if you're doing an intervention, particularly aimed at the feet, then following it up with this (RADAI-F5). You know if you've got a pre and a post and then what level of improvement you're looking for. I could see that being useful…	management ... Let's say if it was an MSK appointment, I would be using this (The RADAI-F5) every appointment to monitor the changes to help treatment… I think it (the RADAI-F5) would really highlight the need for looking at feet because as soon as you've got an official test, but it puts on people radars
Subordinate theme 4: Clinical barriers to RADAI-F5	I think, to be honest, it is more the time restraints and what	I think there are some time issues	I think you suppose in terms of barriers, I think it's time that is	I don't have a waiting area and I don't	It would be so much easier for me	So I suppose it's not necessarily a lack of desire	Time. Time is the biggy. It's finding enough time in	They (podiatrists) don't see the point in that information being

	we would do with that information... It is hard because we are not all on the same electronic system… However, there may be some concerns that it needs to be compared to bloods or what we tend to do, which is ultrasound imaging of the joints. I think they (rheumatologists and specialised AHPs) would want to find out if this tool compares to labs first. I don't think it can be totally used on its own; I think it needs to be used as part of the clinical assessment as well…	with clinicians Clearly there would have to be some way in which clinicians would not be overburdened with various PROM scores, flagging up, and so on, it just causes more administrative work…	probably the big one that staff will probably try and push back on… Yeah they (Rheumatologists) don't have access to Trakcare, which could be an issue when reporting RADAI-F5 results...	have anybody to hand a copy out. I don't have any admin so I can't do that before they come to the room… Bear in mind, the consultants and the nurses are on a different note system than I'm on, so the two wouldn't be able to work together anyway, so that's a problem… I think it is important that you compare the RADAI-F5 so that we can	rather than writing everything out and reduces that administrative side of things or should I say that barrier aspect. I think the consultants were possibly a little bit apprehensive and you could see a few barriers and thinking this is going to take time and I think they're really pushed for time... It (An app) cuts out the intermediary of trying to get	to do them, but it's the realism of how much you can complete with a patient during a short consult and the administrative factor… So I think it could be useful as a patient tool, but the kind of integration into electronic patient records might be a stumbling block… We probably need to do bloods or imaging in the interim and just see if there is an overall disease activity score that matches with the RADAI-F5…	clinic appointments that are stretched … Now this (RADAI-F5) could obviously be done and scored before they came in to see me, but that means somebody has got to be doing this scoring and the interpreting of it…	disclosed and the admin time to get it all entered. We have got a 6 practitioner clinic, so that is hundreds of patients every week that would then have to find the admin resources to put that on… It is the patients' perspective; it can be difficult to trust. We have to still do clinical examinations…

				look at disease ratios, we can look at bloods, we can look at X-Rays…	through admin and that administrative burden			

3.3.3: Feet are a priority in RA

Foot problems are common:

All RA participants recognised the presence of foot-related issues as a result of their disease. Moreover, 7 individuals with RA reported that their initial symptoms appeared in their feet. Clinicians participating in the study also acknowledged that RA participants commonly reported foot symptoms and that the feet were of significant concern during clinical appointments.

"It's (Foot disease) common and it's troublesome for participants …it's one of those things that people often will complain of when they first present and when the disease becomes more active again, it's something that they will comment on not infrequently." (GC16)

"You could imagine that the feet would be mentioned in up to 50% of our consultations." (GC11)

"Well, initially, when my rheumatoid started, it apparently started in my right ankle...but I don't think the GP did anything………it took years to diagnose" (GG05)

Several RA participants reported experiencing a range of foot problems including pain, stiffness, swelling, numbness, and joint deformities. Furthermore, the participants also frequently mentioned the presence of cutaneous lesions such as corns and calluses.

"On the toe … I have noticed that corns are developing there." (GG02)

"I struggle a lot with my toes. I don't get a huge amount of swelling but I do get a lot of tenderness and stiffness." (GG08)

Impact of RA feet on daily activities

All RA participants discussed the impact of their foot problems on their ability to walk. The majority reported a significant decrease in walking distance due to their foot disease, resulting in limitations in engaging in activities they once enjoyed. These limitations had observable ramifications not only on their social interactions but also on their overall QoL.

"I am very restricted... I use the wheelchair in the house because in the mornings, I cannot walk at all" (GG02)

"I don't walk very much anymore, whereas I used to walk probably anywhere between 7 and 10 miles a day before my rheumatoid." (GG07)

<u>Psychosocial impact</u>

All participants with RA extensively discussed the implications of foot disorders and deformities on footwear choice, highlighting the difficulties in finding appropriate shoes that could accommodate their foot abnormalities. The aesthetic aspect of footwear was deemed important, particularly for female participants, as it influenced their clothing choices.

"I am not able to find shoes that fit with my clothes…. It's frustrating… It is difficult when you cannot wear nice shoes at weddings." (GG07)

All participants with RA acknowledged that their foot health significantly impeded their ability to work. Six individuals were required to take early ill-health retirement or reduce their working hours owing to their inability to endure prolonged periods of standing. Consequently, a substantial proportion of participants (n=5) endured financial hardship and experienced detrimental effects to their mental well-being.

"I went from being somebody that was quite dynamic and ran a business that employed 20 people, and I loved what I did …. I have had a massive drop in income and a massive drop in self-esteem." (GG04)

"I became a very unreliable employee because of my foot pain."(GG03)

The foot symptoms experienced by RA participants universally impeded their social lives, necessitating adjustments in their activities and resulting in feelings of isolation and substantial emotional and mental distress among certain individuals.

"I did use to be very sort of outgoing and very sociable with my friends… I can't even bear to think about it now because I know I just physically couldn't or mentally couldn't do that anymore…. It hugely impacts how I am …because I still remember how I was and how I used to enjoy life." (GG08)

"I would say that I tried to take my own life at the turn of the year because of the isolation. I couldn't see my friends because I was always so tired and in pain. It is very lonely." (GG07)

Three RA participants conveyed that their foot disease has created an additional burden on their family life, with reliance on family members to carry out daily tasks at home. This was found to diminish an individuals' sense of autonomy.

"It affects things at home because my husband tends to do a lot more around the house now…so it's had a huge effect on the family." (GG08)

"I have to always plan everything and see where I can go. My daughter is only 6, so she is really quick and can run like the wind, and the scooter cannot keep up with her…. I am lucky enough to have a big family where everyone will take a wee turn in taking her somewhere, where she has got a bit more freedom than being with me…" (GG02)

3.3.4 Existing methods of measuring foot disease are inadequate

The majority of clinicians and seven RA participants emphasised the frequent oversight or under-recognition of their feet during regular rheumatology and GP appointments. They expressed dissatisfaction with their general practitioners (GPs) and rheumatology consultants as their foot symptoms were often disregarded, even when explicitly mentioned during consultations. Moreover, they perceived a lack of understanding among their GPs regarding the significance of foot symptoms as potential indicators of RA. Several RA participants expressed the belief that their feet received less attention compared to their hands. This perspective was largely corroborated by the clinicians.

"Well, this (the feet) is under-represented in the clinical tools for assessing disease activity, and … clinicians don't look at feet enough." (GC11)

"They always check my hands or you know apply pressure in your hands and check your joints (in hands), but I can't say they ever really look at your feet to be perfectly honest." (GG01)

"My first consultant said that it couldn't be RA because it wasn't part of the joints that are supposed to suffer from RA" (GG08)

All RA participants were surprised that feet are not included in the DAS-28. Both clinicians and RA participants were frustrated at the exclusion of the foot and ankle from this index as it resulted in foot disease being missed and the lack of a holistic overview of the participants' disease.

"Really frustrated that it (the feet) doesn't form part of the overall picture.... It's a whole-body disease, so I don't understand why they wouldn't include the feet in it… I've seen quite a lot of on

the various chat lines that people are saying, you know, "my feet are bad, so why aren't they in the DAS (DAS-28)," so it's not just me by any manner." (GG03)

"No one seems to push how important the feet are, so I do believe it should be included in the DAS-28" (GG08)

"I do think that they are missing something with that (not including feet in DAS-28) because as the evidence shows, a huge proportion of participants do have issues with their feet and inflammatory issues with their feet when everything else is OK." (GC14)

Clinicians acknowledged the difficulty in justifying the need for additional medical management due to the omission of foot assessment in the DAS-28, hindering the escalation of RA pharmacological treatment. As a result, clinicians had to develop alternative methods to incorporate painful and swollen foot joints into their justification for medical escalation, potentially increasing the workload for rheumatologists.

"Well, it's frustrating. People often have substantial foot disease and not so much in their hands, so it creates problems, which we find ways around. But it's (exclusion of the feet from DAS-28) is just irritating and frustrating for everybody, I think." (GC11)

"I'm a bit frustrated... if you're getting people who are on the cusp of maybe being eligible for more advanced therapies, and you are then having to involve other members of staff (to concur with the escalation of medication) ... It is a minor barrier but we do get around it." (GC16)

Rheumatologists elucidated that the omission of foot assessments in routine practice was not a consequence of the DAS-28. Rather, this decision stemmed from participants' expressed concerns and symptom data. Furthermore, limited time for consultations and the presence of various competing domains acted as determining factors in the infrequent evaluation of feet during clinical practice.

"If somebody has no symptoms in their feet, I probably wouldn't take off their socks and shoes. I won't have decided what I'm examining before I speak to the patient." (GC16)

"I think firstly if someone declares it as a problem, then we are really obliged to have a look.... You ask them "How are your joints?" and leave it open for broad comments. Then it is really up

to individuals to then volunteer what the priority things are for them…. If they can't feel that they can volunteer that, I'm not sure that is something that I can help with." (GC11)

The aforementioned observation raises concerns regarding the potential difficulties faced by some RA participants in sharing their experiences related to foot disease, particularly if they have had negative experiences in the past. However, it is noteworthy that despite these challenges, seven participants with RA expressed feeling comfortable and confident in articulating their clinical needs to healthcare providers.

"I'm quite happy to stand up for myself …but I think there are a lot of people out there who haven't been able to. If they have had a lot of foot pain, they will not have had a chance to speak to anybody about it….I am affected by my feet but I seem to forget to mention it in appointments" (GG01)

"I feel less likely to want to tell them (about foot problems) because you feel belittled. You are not really taken seriously by the rheumatologist and you feel like a fraud….You know, it's horrible" (GG04)

Clinicians also attributed the lack of frequent foot assessments to the lack of accessibility of the feet and a lack of foot assessment training.

"Accessibility. It's very easy to examine the upper limb…It probably comes down to comfort as well. Because I'm much better at examining the upper limb, I'm much more comfortable teaching somebody how to examine the upper level." (GC16)

Clinicians generally did not incorporate PROMs as part of their regular practice due to time constraints and administrative challenges in distributing and collecting them. Additionally, limited promotion and support from NHS trusts hindered their implementation. Some clinicians utilised PROMs for auditing purposes to enhance healthcare quality rather than for monitoring patient progress or facilitating patient-clinician communication.

"I haven't used any PROMS at all. The person I took over from haven't used any (PROMs) either" (GC13)

"We've tried numerous PROMS. Historically, I think probably it's time-consuming for our clinical consultations… and then writing up, the kind of administration side of things. I think we're constructed by time" (GC12)

"Using the Mind map… we have to use that for audit processes." (GC14)

Rheumatologists highlighted that competing priorities pose a substantial barrier to the integration of PROMs into their current practice. The complex nature of managing patients with rheumatic diseases, along with the numerous responsibilities involved in their clinical practice often left limited time and resources for incorporating additional assessments like PROMs.

"I mean there are so many domains that you could be asking about within a consultation…it's simply not feasible to go through all the risk areas for RA within a consultation." (GC11)

3.3.5 Clinical facilitators to the RADAI-F5 implementation
Clinical feasibility of the RADAI-F5

All participants agreed that a new clinical PROM should be simple and efficient in collecting clinically meaningful data to reduce the aforementioned constraints on clinicians and participants. Most participants (n=15) found the RADAI-F5 to be suitable due to its ease of use and quick completion.

"If you give too many questions people get lost in amongst them all and maybe not able to be completed in the 10-minute appointment. This (RADAI-F5) is nice and short." (GG01)

"The (RADAI-F5) terminology is easy for folks"(GC11)

Five clinicians expressed that the tool was well-designed and expressed their satisfaction with the utilisation of a NRS within the RADAI-F5. They perceived it as an appropriate measurement tool that allowed participants to comprehend and respond to the questionnaire items easily.

"It's a simple scale of 0-10 and quite easy for them (participants) and for me (clinician) to understand" (GC14)

Promoting communication:

RA participants and clinicians expressed that implementing the RADAI-F5 could improve therapeutic collaboration by facilitating discussions surrounding foot health; while clinicians acknowledged that the RADAI-F5 could enhance clinician-patient relationships and shared decision-making by prioritising patient-centric aspects of the disease.

"You are building a relationship with the patient where you are acknowledging their foot problems." (GC10)

"If my feet had ben sore in the last few days, I would probably want to risucss that using the form" (GG05)

"(The RADAI-F5) will make that conversation easier for the advanced practitioner, but also make sure things aren't missed from a patient perspective. I think it improves the clinician-patient relationship" (GC15)

The prospective impact of completing the RADAI-F5 on patient-clinician communication was particularly noteworthy to clinicians who treated participants with early RA. Engaging this group of participants in their care was noted to be challenging, and the RADAI-F5 was regarded as a tool that may aid with communicating treatment programmes and facilitate conversations around the importance of the RA foot.

"I believe that compliance to treatment programmes is a big part of early RA treatment success. So, if we can find out how to create individualised treatment programmes (using the RADAI-F5)…. as well as identify and address the issues that folks care about." (GC05)

AHPs highlighted the presence of weak or ambiguous reporting of foot disease activity in referrals, primarily attributed to the lack of a previous quantification method. As a result, clinicians recognised the RADAI-F5 as a valuable tool to streamline referrals and improve access to podiatry care.

"Foot disease is currently not measured or represented by current measures of disease activity because it doesn't really. There's nothing that's specific to focus just on the feet…so it makes referrals more difficult….we need a tool like the RADAI-F5" (GC13)

"It (the RADAI-F5) will assist in referral decisions with regards to AHP services" (GC14)

<u>Guiding management:</u>

Three clinicians and two RA participants recognised the potential of the RADAI-F5 tool in emphasising the importance of foot examinations and facilitating the screening of RA participants for foot-related concerns. In agreement, all participants highlighted that the RADAI-F5 could address a vital aspect of clinical care by directing attention towards the significance of feet in the RA population.

"I think it (the RADAI-F5) would really highlight the need for looking at feet because as soon as you've got an official test, it puts it on people radars" (GC17)

"It (the RADAI-F5) acts as a screener to first of all get the feet examined. The big thing is getting the feet examined, so it (the RADAI-F5) would be doing that because it would flag up that there was a problem." (GC11)

"Using this (the RADAI-F5) could help focus on the feet and help set a plan or treatment focused on the foot...." (GG05)

All clinicians and seven RA participants recognised the potential of the RADAI-F5 as a valuable tool for monitoring foot disease activity and treatment effectiveness longitudinally. They highlighted that tracking RADAI-F5 results over time could enhance patient engagement and adherence to treatment plans by demonstrating measurable improvements.

"I suppose it (the RADAI-F5) could mark the progression of (foot disease) presentation and again record the disease activity....and it could help focus on tracking foot disease" (GC12)

"It (RADAI-F5) was definitely a good tool to have so you can monitor your feet..... and treatments...It could be a useful tool to then look back and think, "Actually, that was actually really mild compared to what I am now." (GG08)

"The RADAI-F5 would give a consistent basis for the rheumatologist, podiatrist and orthotist to compare how you were before with how you are now" (GG03)

Four clinicians suggested that the RADAI-F5 could help with auditing their clinical practice, highlighting how the incorporation of this new tool may guide management and improve patient outcomes.

"I suppose from the broader point of view, it's important to use it (RADAI-F5) to audit your services and compliance with NICE guidance and kind of demonstrating the efficacy of what you do (i.e. interventions you implement)." (GC15)

Patient education:

Participants expressed concerns about their limited understanding of the impact of RA on foot health, which resulted in challenges in implementing effective self-care practices. Among the eight RA participants, five acknowledged a lack of awareness regarding the relationship between RA and foot disease. Furthermore, five participants with RA reported becoming aware of foot abnormalities related to RA only after experiencing them personally. These participants expressed the view that the implementation of the RADAI-F5 could contribute to patient education by fostering self-awareness of their foot health. They believed that utilising the RADAI-F5 would

enable participants to recognise their symptoms more effectively and take a proactive role in self-management, thereby enhancing their autonomy.

"It was only really when things start to get bad for my feet that I understood the importance of the feet." (GG04)

"I wish I would have known about my feet before so I could have pushed for more help…It would have been helpful to have this tool so I could have been more self-involved with my management" (GG02)

3.3.6: Clinical barriers to RADAI-F5 implementation
<u>Practical burden:</u>

Clinicians and RA participants highlighted several limitations to the clinical utility of RADAI-F5. The limitations of RADAI-F5's pertained to logistical challenges, including the need for administrative support for tasks such as printing, distributing, collecting, and processing RADAI-F5 data. Time constraints associated with interpreting the PROM results also emerged as a significant barrier.

"I don't have a waiting area and I don't have anybody to hand a copy out... It would be difficult because as I said I don't have any admin." (GC13)

"I think it's time that is probably the big one that staff will probably try and push back on." (GC12)

RA participants acknowledged time constraints as a barrier but expressed their willingness to complete the RADAI-F5 in the waiting room before their appointments. Conversely, clinicians favored patients filling out the questionnaire at home, aiming to mitigate the stress associated with the clinical setting. This approach facilitated the collection of data over an extended period, as opposed to a single point-in-time assessment during a clinic visit. Such an approach was seen to reduce the potential risk of participants intentionally inflating their scores to influence the outcome of their clinical appointment.

"I think that (completing the RADAI-F5 in the waiting area) would be good. Because you are waiting around to be taken in anyways." (GG02)

"I think there are things about coming to clinics that people change the nature of the problem and it is not a deliberate thing….they just ramp up all the figures, everything is much worse…. Also

folks are a bit stressed, they have just turned up or they have gone uphill ..... I mean, sometimes a clinic is not really a useful time to get PROMS. It is an artificial event, you are already assessing them in other ways" (GC11)

Lack of validity:

Three clinicians raised concerns regarding the perceived similarities between items 2 and 3 of the RADAI-F5, implying the potential inability of participants to differentiate between joint tenderness, swelling, and pain. Nevertheless, it is noteworthy that a substantial number of RA participants noted joint swelling and tenderness as separate entities.

"Yeah, so (question) #2, "how active is your foot arthritis today in respect to joint tenderness and swelling" and then (question) #3, "how severe is your arthritis pain in your feet today". So it's hard to distinguish the tenderness and swelling rather than the joint pain.... So I think from a patient you know that could be like almost like you're asking the same question." (GC12)

"I don't get a huge amount of swelling but I do get a lot of tenderness" (GG08)

While the concise nature of the RADAI-F5 was viewed as advantageous for its clinical adoption, one RA participant and three clinicians expressed reservations regarding its brevity. They contended that the tool did not adequately capture the comprehensive impact of RA on foot function and disability.

"You don't have a lot of function. It's quite a bit of static assessment of pain, swelling, tenderness, stiffness and general. But arguably what matters to participants is, "can I walk?" (GC16)

Rheumatologists expressed concerns regarding the potential limitations of the RADAI-F5 in capturing comorbidities and changes in the fundamental characteristics of a patient's underlying condition. To address these concerns, three RA participants and six clinicians emphasised the importance of incorporating objective measures such as ultrasound imaging, clinical examinations, and inflammatory blood markers. They believed that the inclusion of these measures would enhance the validation process and improve the reliability of the RADAI-F5 in detecting RA-specific features. Notably, the one participant that was apprehensive regarding the clinical adoption of the RADAI-F5 attributed this to the lack of validation against objective measures.

"It might make it more acceptable to the clinicians for there to be an independent, evidence-based measure included in the RADAI-F5." (GG03)

"I mean, this (RADAI-F5) will obviously go along with other tools. You know, the blood tests and things as well." (GG01)

"Its (RADAI-F5) just building up another pool of details that is significantly less accurate… You are still going to have all the blood monitoring thing so you can have all the inflammation markers…so they (clinicians)have more data" (GG06)

Clinicians also stated the need for RADAI-F5 thresholds and proposed interpretation guidelines for specific participants and stressed the significance of recognising clinically meaningful score changes and action thresholds. They believed that this would be best-established using imaging such as ultrasound:

"It would be easier to have thresholds at which we should be changing medication like the DAS-28. Interpretation of PROMS is important, and we need to know that the RADAI-F5 is accurate and recognising synovitis. I think you can do this with ultrasound." (GC16)

IT barriers:

When asked about the potential for the RADAI-F5 to be an electronic PROM (ePROM), technology-related logistics, including the lack of a standardised database to report RADAI-F5 scores was identified as a challenge. This was attributed to rheumatologists, GPs and AHPs not being linked to the same electronic health record (EHR), which may result in access and reporting barriers of RADAI-F5 results.

"I need to think about how I'm going to record this (RADAI-F5 scores) …. but bear in mind, the consultants and the nurses are on a different note system than I'm on, so the two wouldn't be able to work together anyway, so that's a problem." (GC13)

In addition, three clinicians expressed concerns regarding the integration of PROMs data into the EHR, particularly if it involved the inclusion of diagrams of affected foot joints. They emphasised the need for a robust electronic healthcare system that can effectively display PROMs data in a comprehensible manner.

"I think it could be useful as a patient tool, but the kind of integration into electronic patient records might be a stumbling block." (GC15)

Mobile applications (apps) and EPROMs:

Clinicians suggested integrating a mobile app or ePROM into rheumatology services to enhance patient engagement and prioritise urgent foot care. However, RA participants emphasised that ePROMs should not replace face-to-face appointments, which they considered essential for comprehensive care.

"It (apps) cuts out the middleman of trying to get through admin and that administrative burden." *(GC12)*

"I think the app would be very good…and it would be great to flag up a problem a lot quicker than waiting on phone calls and post and things." (GG02)

Certain RA participants raised concerns regarding the regular use of a mobile app or ePROM for symptom reporting, fearing that it could potentially amplify negative aspects of their disease behaviour and influencing their mental health.

"No, it's just something else that I have to do that will be a constant reminder about how poorly I feel, and I don't want to do that. Also, with my mental health, an app would just be another thing to do." (GG07).

Furthermore, all participants acknowledged that access to digital technology and comfort with using technology served as a significant barrier to the utilisation of mobile apps. This was attributed to factors such as older age and disparities in technology access in low-income populations.

"I suppose it's just about accessibility… we're going to cover base with people that are not so tech-friendly or have tech poverty" (GC12).

3.4 Discussion:

To enhance patient-centred foot care and promote the collection of PROMs as part of a value-based healthcare initiative in rheumatology MDT clinics, it is crucial to comprehend how the RADAI-F5 can effectively address the needs of key stakeholders. This study represents, to the best of our knowledge, the first exploration of clinical facilitators and barriers to the implementation of a new foot PROM from the perspectives of RA patients, rheumatologists, and AHPs. The study findings can help inform the implementation the RADAI-F5 in rheumatology care by identifying key clinical barriers and facilitators to its utility. Table 11 offers a concise overview of the implementation strategies recommended by the study participants to overcome the identified barriers.

TABLE 11: RADAI-F5 IMPLEMENTATION STRATEGIES

Perceived barriers	Effective RADAI-F5 implementation strategies
Lack of shared electronic databases	• Integration of PROMs data into electronic health record • Mobile App
Practical implementation difficulties	• ePROMs • Mobile App • Administration of PROMs in waiting area or prior to the appointment • Patient keeping a diary of RADAI-F5 scores
Lack of PROM validity	• Education on PROM purpose and application • Promotion of PROMs by NHS trusts • Association of the RADAI-F5 with ultrasound • Association of the RADAI-F5 with clinical examination

Need for a clinically feasible foot PROM

The present study provides a comprehensive understanding of the impact of foot disease on the lives of individuals with RA. While prior investigations have established the impact of foot impairments on walking ability (Van der Leeden et al., 2008; Grondal et al., 2008), this study highlights that foot disease can impose a substantial psychosocial burden, encompassing social interactions and occupational capabilities, corroborating previous research findings (Wilson et al., 2017; Bullock et al., 2019). Furthermore, the findings indicate that rheumatologists often underestimate the significance of foot disease in comparison to hand-related concerns, thus aligning with established literature (Otter, 2008, Wilson et al., 2017). RA participants perceived that their consultations primarily revolved around DAS-28 assessments. This finding is disconcerting, as persistent active foot synovitis can be present in patients classified as achieving DAS-28 remission (Van der Leeden et al., 2010; Woodburn, Barker & Helliwell, 2002). Rheumatologists recognised the infrequent foot assessments during routine consultations, citing factors such as time constraints, limited foot access, and lack of confidence in evaluating foot joints despite specialised training.Although the DAS-44 has been employed for assessing RA patients, its time-intensive nature restricts its routine clinical application (Scott & Scott, 2014). Consequently, all clinicians and RA patients concurred that a validated and clinically feasible method for early evaluation of foot disease activity in RA is warranted. Therefore, a PROM such as the RADAI-F5 could serve as a valuable instrument for highlighting and screening foot issues in this patient population, if used as an adjunct to the DAS-28.

Improving communication

Systematic reviews examining the impact of PROMs have revealed that their utilisation enhances clinical diagnosis through improved patient-physician communication (Marshall et al., 2006; Chen et al., 2013). The majority of participants in this study expressed agreement with these findings and highlighted that the implementation of the RADAI-F5 PROM could foster a more comprehensive, patient-centred approach to healthcare by facilitating meaningful dialogue surrounding patient symptoms. The use of PROMs to strengthen patient-clinician trust has been well documented in various studies and has shown to correlate with improved patient outcomes and the promotion of personalised care (Valderas et al., 2008; Haskard et al., 2009),

Early referral to podiatry for RA patients is considered imperative to prevent irreversible foot damage. The Podiatry Rheumatic Care Association (PRCA, 2008) recommends foot examination by a podiatrist within three months of diagnosis for optimal disease management and improved QoL, which has been corroborated in previous studies (Deighton et al., 2009; Combe, 2007). However, only one patient in this study reported that their rheumatologist followed this recommendation, indicating a gap in adherence. AHPs also noted that although there were open referral mechanisms between consultants and AHPs, reporting foot disease activity in referrals were weak or ambiguous, as there was no previous method for quantifying foot disease activity. As such, clinicians viewed the RADAI-F5 as a means to enhance collaboration and facilitate appropriate referrals within the MDT (Santana and Feeny, 2015).

Guiding management

Participants in this study highlighted that reviewing RADAI-F5 scores offers an opportunity for shared decision-making between patients and clinicians, leading to increased treatment adherence. Findings by Chen et al., (2013), Palmer & Miedany, (2016) and Field, Holmes & Newell, (2019) support the notion that including PROM collection in care planning can help guide personalised management. Consistent with these findings, in this study, two RA participants and three clinicians expressed that the RADAI-F5 could effectively track symptom changes over time. The data obtained from the RADAI-F5 can function as informative indicators to identify deviations from anticipated treatment progress, prompting clinicians to initiate discussions on alternative management approaches. Consequently, action plans can be formulated to address treatment challenges, and the RADAI-F5 can be utilised to monitor the effectiveness of these interventions. Moreover, this approach can assist in making informed decisions regarding the need for additional tests and referrals, saving valuable clinician time. (Detmar, 2003; Santana & Feeny, 2015).

Promoting education and self-monitoring

Patient education plays a crucial role in RA management (Graham & Williams, 2017; Siddle et al., 2021). Therefore, enhancing patients' understanding of foot health is essential to enhance functional ability and QoL (Graham, Stephenson & Williams, 2017). However, it is important to complement PROMs with external resources to address the social and psychosocial aspects of the disease (Kendrick et al., 2016). Integrating PROMs like the RADAI-F5 can improve patient knowledge, promote self-involvement in foot health management, autonomy and enhance perceived control over health (Palmer & Ndosi, 2016). Although the evidence supports the potential of the RADAI-F5 in facilitating patient self-monitoring, further investigation is warranted to determine the optimal frequency of administering the RADAI-F5 and to explore strategies aimed at sustaining patient engagement in completing the RADAI-F5 within rheumatology care settings.

Practical difficulties

Despite acknowledging the potential advantages of integrating the RADAI-F5 into routine care, rheumatologists have identified several barriers to its clinical implementation. A significant obstacle includes the administrative burden associated with distributing, collecting, and scoring the RADAI-F5 within the limited appointment time. While time constraints are frequently cited as hindrances to PROMs adoption, studies have demonstrated that PROMs can, in fact, save time by streamlining patient history examinations (Howell et al., 2015; Baeksted et al., 2017). RA participants conveyed that the RADAI-F5 is a concise tool that may assist clinicians in identifying and prioritising patient needs, potentially reducing the number of questions asked during examinations. This could result in shorter examinations, more meaningful discussions, and better-personalised care. However, the implementation of PROMs, such as the RADAI-F5, should not entirely replace patient history or clinical examination; instead, it should complement and enhance the existing process.

Efficient and effective implementation of the RADAI-F5 necessitates the mitigation of additional workload burdens on clinicians. While the notion of patients completing PROMs in waiting areas prior to consultations received support from the RA participants, clinicians highlighted that it is essential to exercise caution in order to address potential biases that may arise. Notably, biases may stem from patients who have more frequent visits exhibiting poorer health outcomes, thereby resulting in PROM scores that disproportionately represent individuals with compromised health statuses. Furthermore, there exists a plausible risk of intentional manipulation of PROM scores. To mitigate these biases, the incorporation of objective measures alongside PROMs may be imperative for informed clinical decision-making.

IT barriers

The implementation of the RADAI-F5 in clinical practice is confronted with challenges pertaining to logistical and technological constraints. To address these issues, recommendations put forth by the majority of participants suggest the utilisation of mobile apps and ePROMs to enhance the accessibility of RADAI-F5 data within clinics, while concurrently reducing administrative burden on clinicians (Holmes, Stanescu & Bishop, 2019). A study conducted at the rheumatology department of the Royal Berkshire Foundation Trust found that paper-based PROMs were time-consuming and had low participation rates (Chan et al., 2017). In contrast, completing a disease-specific ePROM before the appointment proved beneficial by saving time, increasing completion rates, providing comprehensive patient data, optimising clinical interaction, and reducing unnecessary visits for patients in good health (Chan et al., 2017). As such, the development the RADAI-F5 as an ePROMs holds promise for enhancing its utilisation in rheumatology care settings, while saving valuable appointment time and addressing the aforementioned logistical and administrative constraints. Additionally, the implementation of a patient-initiated follow-up (PIFU) program, which incorporates the use of RADAI-F5, not only holds promise for enhancing patient satisfaction but also provides an opportunity for patient empowerment. Implementing this approach has the potential to enhance patient education and promote self-awareness regarding foot health, enabling individuals to take a more proactive role in self-management strategies

Despite initial concerns regarding the elderly population's technological capabilities, emerging research indicates that older adults can effectively utilise mobile apps and ePROMs (Engelhard et al., 2017; Walker et al., 2017). Specifically within the realm of RA, studies have demonstrated the feasibility and acceptance of ePROMs, with patients finding them user-friendly (Koevoets et al., 2013). Moreover, the collection and remote sharing of symptom data through ePROMs have gained particular relevance during times of the COVID-19 pandemic. The integration of ePROMs into EHRs improves information exchange, communication, and patient care, delivering benefits such as time-savings for healthcare providers and researchers, enhanced patient engagement, and improved patient outcomes (Ratwani, 2017).

In the context of the RADAI-F5, clinicians can receive timely alerts for significant disease activity by integrating RADAI-F5 scores into patients' EHR and implementing a notification system. This facilitates prioritisation and scheduling of urgent appointments for patients with high RADAI-F5 scores, ensuring prompt and appropriate healthcare delivery. However, the widespread adoption of ePROMs still faces challenges, including the integration within EHR (Reisman, 2017) and it is important to acknowledge that additional research is necessary to explore the facilitators and barriers specific to the implementation of a RADAI-F5 ePROM. The current study primarily

focused on the implementation of paper-based PROMs, thus not encompassing factors such as technological infrastructure and the integration of ePROMs into the clinical workflow, which are crucial considerations in the successful implementation of ePROMs (Holmes, Stanescu & Bishop, 2019). It is also important to acknowledge that while many patients support the utilisation of RADAI-F5, many individuals remain cautious about replacing face-to-face consultations with ePROMs.

Lack of PROM trust

Although logistical and practical difficulties were reported as barriers, the most significant barrier identified in this study was, clinicians' and one RA participants' lack of trust in PROMs. Morden et al., (2017) argued that relying solely on PROM-detected symptoms for referral decisions may overlook important clinical judgment and expertise, potentially leading to both under-referral and over-referral of patients. They suggested that a more comprehensive assessment, considering multiple factors beyond PROMs, is necessary to ensure appropriate and individualised referral decisions. Addressing these perceptions requires the careful selection of PROMs that clinicians perceive as reliable and meaningful (Nguyen et al., 2021). Findings from this study indicate that many clinicians acknowledged limited routine PROM use, citing factors such as scepticism towards tools, lack of PROM promotion from NHS trusts and insufficient knowledge on how to effectively utilise PROM results. Consequently, in order to address these limitations, it is crucial to provide clinicians with comprehensive training, education, and support that emphasises the purpose of the RADAI-F5, strategies for data interpretation, and the potential benefits derived from its implementation.

The absence of questions related to function and disability in the RADAI-F5 tool was identified as another limitation, as these constructs were deemed important to daily living for individuals living with RA. However, several foot-specific PROMs have previously been developed to measure foot impairments and disability in RA, such as the FIS, FFI, and SAFE (Helliwell et al., 2005; Budiman-Mak et al., 1991; Walsmley et al., 2012) (See section 2.5.1). While the RADAI-F5 primarily focuses on evaluating foot disease activity rather than function and disability, it offers valuable information that can inform pharmacological therapy decisions. However, the RADAI-F5 should not replace patient history or other PROMs that specifically address the psychosocial dimensions of the condition. Instead, it should serve as a complementary tool to augment the comprehensive evaluation of patients. Nevertheless, it remains crucial to recognise the critical significance of timely detection of foot disease in RA as chronic inflammation can potentially result in foot deformities and progressive disability (Rojas-Villarraga et al., 2009). Therefore, the integration of the RADAI-F5 tool in RA management is vital for early identification of foot

disease, enabling effective pharmacological interventions and potentially reducing the risk of long-term foot disability progression.

One significant barrier identified in the adoption of the RADAI-F5 tool was clinician apprehension regarding its ability to differentiate between foot manifestations of RA and non-RA foot pain from co-existing conditions, such as fibromyalgia or biomechanical pathologies. The DAS-28 incorporates both subjective elements like palpation of tender and swollen joints. Nevertheless, it also consists of objective markers such as ESR and CRP, contributing to its perceived validity among clinicians (Orr et al., 2018). Concerns were raised by four clinicians regarding the potential risks and costs associated with making therapeutic decisions solely based on the RADAI-F5, highlighting the need for additional objective measures to provide confidence in this tool. Despite some clinicians expressing scepticism towards 'subjective PROMs," and favouring "objective measurements" such as lab tests and further imaging, the literature has highlighted that PROMs are equally as valuable as objective measures. A study by Hahn et al., (2007) compared the degree of error in clinicians' measurements with the degree of error in validated PROMs, and interestingly, the PROMs demonstrated favourable comparability to the objective measures trusted by clinicians. Nonetheless, the concerns raised by clinicians and RA participants in the present study are consistent with the literature highlighting the challenges in assessing the validity of PROMs, as patients may have limited understanding in assessing disease severity (Basch et al., 2005; Campbell et al., 2022). As a result, a proposed cross-sectional study (Chapter 4) aims to investigate the association between self-reported foot disease, using the RADAI-F5, and MSUS and clinical examination.

3.5 Strengths and Limitations

This study demonstrates notable strengths in its systematic and comprehensive exploration of patient and clinician perspectives, contributing to practical recommendations for the implementation of foot-specific PROMs in RA clinics. A significant strength lies in the researcher's (AH) transparency and reflexivity throughout the data collection and analysis process, ensuring transparency, objectivity, and rigour. The researcher's non-involvement in the clinical care of RA patients also adds to the objectivity, quality, and rigour to the findings (Johnson, Adkins & Chauvin, 2020). Additionally, usilising member-chiecking and three recruitment sources offers increased credibility and transferability of the study findings.

However, several limitations should be acknowledged. Firstly, there is a potential for participant bias as n=3 clinicians were aware of the RADAI-F5 project aims, possibly influencing their responses to align with the research objectives. Efforts were made to encourage honest opinions

during interviews, by incorporating the following statement prior to the interview "Please be aware that there are no wrong answers – we want to hear things from your perspective, and we encourage your honest thoughts and opinions." Nonetheless, this bias cannot be entirely ruled out. Secondly, selection bias may exist, as RA participants who volunteered may have had more severe foot disease or negative experiences with rheumatology departments. Additionally recruitment through professional networks and social media could introduce self-selection bias. The absence of blinding in the consensus process conducted by the investigators, which had been influenced by prior presentations of the study findings within the GCU MSK Research Group, may have introduced investigator bias and compromised the credibility and trustworthiness of the final study themes. A key limitation of the study stems from the inherent constraint of remote data collection during the Covid-19 pandemic, precluding the observation of participants' body language and environmental cues. This poses a challenge to attaining the depth and nuance of data collection, especially within the framework of IPA. Concerns regarding potential sampling bias also emerge from the reliance on participants' access to technology. Nevertheless, it is essential to recognise the imperative for adaptability during the pandemic, acknowledging the option provided to participants for telephone data collection as an alternative to video data collection.

3.6 Conclusion

This study highlights RA patients and clinicians' views of the RADAI-F5 as a potential clinical tool for assessing foot disease activity, while identifying several actionable areas for effective implementation. Though clinicians acknowledged the possible barriers to the implementation of the RADAI-F5, they were largely optimistic about the ability of this instrument to enhance care and facilitate a T2T approach for the RA foot. Concerns persist regarding the RADAI-F5's ability to accurately assess pathophysiological RA features such as synovitis, tenosynovitis, and bursitis, hindering its widespread adoption in rheumatology care settings. This aspect will be addressed in Study 2, which aims to assess the association between self-reported foot disease activity, using the RADAI-F5, and objective measures (Chapter 4). These novel findings could not have been predicted in advance, demonstrating the importance of including the patient and clinician perspectives in PROM development and implementation. Moreover, this study establishes a foundation for the effective integration of foot-related PROMs into clinical practice, offering valuable insights for future implementation efforts.

Chapter 4. Assessing the construct validity of the RADAI-F5 in relation to MSUS and clinical examination: The FOOTRADIUS STUDY

Chapter 3 emphasised the need for further validation of the RADAI-F5 using objective measures of disease activity. To address this knowledge gap, the present study focuses on establishing the construct validity of the RADAI-F5 relative to MSUS and clinical examination. These insights contribute to a deeper understanding of the RADAI-F5's potential for use in early assessment and management of RA patients.

The work included in this chapter was published in *Rheumatology Advances in Practice* (Hoque et al., 2023a) (Appendix I).

4.1 Background

Composite disease activity measures, such as the DAS-28, SDAI, and CDAI, have been extensively used in the assessment of disease status and guiding medical management in patients with RA (Salaffi et al., 2018). However, these indices have faced significant criticisms, particularly the DAS-28, which is impaired by the subjectivity of joint evaluation (Salaffi et al., 2018), limitations with the PGA (Ferreira et al., 2021), and most notably, its exclusion of foot and ankle joints, thus failing to detect foot arthritis (Van der Leeden et al., 2010; Wechalekar et al., 2016). This exclusion is attributed to practical constraints, such as limited time during routine appointments, difficulties in accessing and examining the feet, and clinicians' lack of confidence in assessing foot structures (De Souza et al., 2016). Moreover, the adoption of the DAS-28 clinical practice is limited, primarily due to its dependency on laboratory investigations and the complex calculations involved compared to the CDAI (Solomon-Escoto et al., 2011; Dissanayake et al., 2022). This poses a significant challenge as research has demonstrated that approximately one-third of RA patients classified as being in disease remission exhibit foot synovitis (Wechalekar et al., 2016). Hattori et al., (2018) provided support for this notion by reporting that among individuals in DAS-28-CRP remission, 31.9% of patients exhibited foot synovitis. This places these individuals at risk of enduring ongoing foot complications, disability, and irreversible joint damage (Luqmani et al., 2009; Wakefield et al., 2008). This underscores the importance of comprehensive foot examinations in accurately assessing disease activity (Hattori et al., 2018; Hooper et al., 2012), and highlights the urgent need for a more inclusive outcome measure that incorporates these commonly affected joints.

The recognition of foot health evaluation through clinical assessments of tender and swollen joints is a crucial aspect of RA patient care and is reflected in recommendations by organisations such as the NICE and PRCA (PRCA, 2008; NICE, 2018). However, recent research has demonstrated that clinical examination alone may not capture the full extent of foot complaints in RA patients

(Simonsen et al., 2021). One of the main limitations of clinical examination is the subjectivity inherent in the assessment process. Different clinicians may have varying levels of expertise and experience in evaluating foot joints, which can lead to inconsistencies in identifying tender and swollen joints (Salaffi et al., 2018). Furthermore, the accessibility to foot joints during routine clinical examinations can be challenging. Factors such as oedema, deformity, and limited range of motion in the foot can impede the clinician's ability to adequately evaluate foot joints (Alazzawi et al., 2017), especially in deeper structures such as the STJ. Another important consideration is that foot involvement in RA often extends beyond the joints. Extra-articular manifestations, such as tenosynovitis, enthesitis, and bursitis, can significantly contribute to foot disease burden and functional impairment (Suh et al., 2021). However, these manifestations may not always be readily identifiable through clinical examination alone (Pan, Zhao & Wu, 2022). The limitation of clinical examination highlights the potential benefit of supplementary tools to enhance the assessment of foot involvement in RA.The integration of RA-specific foot PROMs, such as the RADAI-F5 in routine clinical practice offers a valuable modality to attain a comprehensive evaluation of foot disease activity (Hoque et al., 2021; Hoque et al., 2022).

In both clinical and research settings, MRI is considered the preferred imaging modality for assessing RA disease (Østergaard, Ejbjerg B& Szkudlarek, 2005; Pan, Zhao & Wu, 2022). MRI offers several advantages, including its ability to accurately detect BME along with changes in the synovial membranes and tendons particularly in the early stages of RA (Sudoł-Szopińska et al., 2017; Wang et al., 2016). However, this imaging modality has a number of disadvantages: it can be time-consuming, inaccessible and expensive, and the use of contrast agents carries the risk of renal side effects and allergic reactions (Mandl & Aletha, 2019; Dill, 2008). Another key limitation is that MRI is not typically available in podiatry clinics throughout the UK and most podiatrists are not trained in interpreting MRI images.

MSUS has been recommended as a more feasible imaging modality due to its wider availability, dynamic utility and lower costs (Ranganath, Hammer &McQueen, 2020). Studies by Dando et al., (2021) and Bowen et al., (2013) advocate the utilisation of MSUS in assessing foot involvement in RA, as it provides valuable information on pathological features associated with the disease (synovitis, tenosynovitis, bursitis and erosive changes). Additionally, studies have demonstrated that MSUS is superior to clinical examination in detecting these pathological features of RA, as evidenced by Naredo et al., (2019). MSUS has the capacity to detect hyperaemia, a marker of persistent inflammation (Epis et al., 2013), and can identify synovitis in individuals without evident clinical abnormalities, specifically those presenting with subclinical disease. Additionally, MSUS has the potential to differentiate between true inflammatory conditions and other non-inflammatory conditions, such as osteoarthritis. (Kaeley, Bakewell & Deodhar, 2020). Despite the

growing utilisation of MSUS in RA, its availability remains limited due to factors such as the requirement for specialised equipment, trained personnel, costs, logistical challenges, and uncertainties regarding the management of subclinical disease (Franklin et al., 2017; Barberi & Geldand, 2021). Consequently, while MSUS continues to be a valuable tool for assessing and monitoring RA, its widespread adoption is limited in rheumatology MDT clinics across the UK, particularly those not designated as Research Centres of Excellence.

Over the last decade, there has been a paradigm shift in the evaluation of clinical outcomes, with a greater focus on patient perspectives being promoted. This is attributed to their ability to capture patient priorities for therapies more accurately than clinician-determined outcomes, while also complementing the patient's medical history, imaging, and laboratory data (Barberi & Geldand, 2021; Hamilton, Giesinger & Giesinger, 2017). Ultimately, adopting this patient-centric approach facilitates better alignment between interventions and patient priorities, resulting in enhanced healthcare outcomes. Chapter 3 highlights the utility of the RADAI-F5 PROM for various purposes such as patient screening, guiding therapeutic management, improving patient-clinician communication, facilitating shared decision-making and monitoring foot outcomes (Hoque et al., 2021). Furthermore, although patient history may aid in understanding the impact of disease and prompt rheumatologists to assess feet, some RA patients may hesitate to express their foot problems, relying on clinicians to initiate the discussion as illustrated in the previous qualitative chapter.

Tele-monitoring by collecting repetitive ePROMs has also become a growing area of research, particularly in adults with inflammatory arthritis (Thura et al., 2022). ePROMs offer numerous advantages, including the ability to evaluate therapeutic outcomes more frequently in a standardised and validated manner (Shelton et al., 2021). This alignment with the T2T principle enables early recognition of disease deterioration, supports clinicians in setting benchmarks for medication escalation, and enhances patients' understanding of their disease by monitoring flare-ups (Shelton et al., 2021; Thura et al., 2022). The utilisation of ePROMs has gained traction in various rheumatology clinical contexts, including PIFU, where patients actively engage in their healthcare management based on their ePROM or PROM scores (Arumalla et al., 2023). However, challenges arise in accurately assessing disease activity in remote consultations, particularly in the absence of a physical examination. Due to the COVID-19 pandemic and reduced face-to-face appointments, the RADAI-F5 tool may support patient-initiated follow-ups, which could potentially allow efficient resource allocation during the era of telehealth medicine. Should the RADAI-F5 demonstrate satisfactory validation against objective measures, it could present a potential avenue for use in remote consultations.

In Chapter 3, clinicians expressed a strong preference for objective measurements to further validate the RADAI-F5. Their concerns revolved around the subjectivity of PROMs have been similarly reported in previous literature surrounding PROMs in healthcare settings (Chopra et al., 2015; Harreld et al., 2013; Hamilton, Giesinger & Giesinger., 2017). While the RADAI-F5 has demonstrated good measurement properties in accordance with COSMIN standards, concerns surrounding its subjectivity have been raised, thereby impeding its widespread clinical utility. Healthcare practitioners expressed apprehensions regarding patients' ability to accurately discern disease severity, leading to a proposal for validating the RADAI-F5 against objective measures (Hoque et al., 2022). While it may seem unconventional to compare a PROM with objective metrics, given the inherently subjective nature of PROMs, it is important to note that there is no 'gold standard' PROM for assessing foot disease activity in RA. Consequently, the comparison with objective measures serves, as a method to ascertain the strength of the correlation between the RADAI-F5 and objective indicators of RA-related inflammation. Therefore, the primary objective of this study was to evaluate the construct validity of the RADAI-F5 relative to MSUS and clinical examination of foot and ankle disease. In addition, the secondary objective of this research was to compare the efficacy of clinical examination in comparison to MSUS for identifying active foot disease.

4.2 Hypotheses

In addressing the primary objective of the study, *a-priori* hypotheses were formulated to examine the extent to which RADAI-F5 scores were associated with other measures in a theoretically compatible manner (Schober, Boer & Schwarte, 2018) (Table 13). Correlation statistics was utilised to determine linear relationships, and for the purposes of this study, the following definitions for the correlation coefficient (r) were adopted (Schober, Boer & Schwarte, 2018):

- 0.00-0.19: "Very weak"
- 0.20-0.39: "Weak"
- 0.40-0.59: "Moderate"
- 0.60-0.79: "Strong"
- 0.80-1.00: "Very strong"

TABLE 12: A-PRIORI HYPOTHESES FOR R WITH RADAI-F5

Measure	*a priori* (H1) expectation for *r* with RADAI-F5
Clinical swelling	Moderate
Clinical tenderness	Moderate
Synovial hypertrophy	Moderate
Synovitis	Moderate
Erosions	Weak

The absence of existing literature comparing RADAI-F5 to MSUS made formulating hypotheses challenging. Prior to ethical approval for this study, no articles were available that directly compared PROMs to MSUS imaging in the context of RA. Consequently, the hypotheses were developed through extensive discussions with rheumatologists and podiatrists during stakeholder meetings. Additionally, relevant literature has emerged that can lend support to the hypotheses. Notably, a study conducted by Mortada, Dawa, and Amer in 2021 examined 245 patients with knee pain compared PROM evaluations using the Western Ontario and McMaster Universities Index of Osteoarthritis (WOMAC) scale, global VAS, and Health Assessment Questionnaire-II (HAQ-II) for functional assessment and ultrasonographic assessments were performed to evaluate synovial effusion, synovitis, osteophytes, and Baker's cysts.

The study revealed findings indicating positive correlations between ultrasound measurements and PROM subscales, including pain, stiffness, and function. Specifically, there were strong correlations with VAS (r=0.73, p=0.001), HAQ-II (r=0.67, p=0.001), as well as the WOMAC pain subscale (r=0.3, p=0.03), stiffness subscale (r=0.23, p=0.00), function subscale (r=0.40, p=0.01), and the overall WOMAC score (r=0.70, p=0.00). These findings provide a basis for indicating the presence of moderate positive associations between PROMs and ultrasound measurements.

In another relevant study by Nawata in 2021, which focused on 300 patients with RA undergoing MSUS, the relationship between ultrasound scores, PROMs and clinical variables was investigated. The results revealed correlations between clinical variables, PROMs and ultrasound scores. Stratified analysis highlighted associations between a GS score of ≥2 and persistent symptoms, including morning stiffness, pain, fatigue, functional impairment, and reduced quality of life, all measured on PROMs. These findings helped inform the hypotheses for this study.

4.3 Methods

4.3.1 Study design

A cross-sectional observational study design was employed to address the study aims. This study was conducted between November 2021 and November 2022 at the GCU Human performance laboratory.

4.3.2 Stakeholder involvement

Healthcare professionals, including rheumatologists and podiatrists from NHS Lanarkshire Rheumatology Group and the Practice Development Group Rheumatology (PDGR), expressed unanimous support for the adoption of the RADAI-F5. Nonetheless, all healthcare professionals emphasised the need for further validation of RADAI-F5 against MSUS imaging before its implementation in clinical practice, supporting findings from the qualitative study (Hoque et al., 2022). Furthermore, a rheumatologist believed that if "The RADAI-F5 was validated against imaging would save the fibbing". This proposal was aimed to mitigate challenges in the current practice where rheumatologists within this health board may articficially inflate TJC and SJC to justify the prescription of stronger immunosuppressants.

Furthermore, patient representatives examined patient-facing documents to guarantee its clarity, and sensitivity to the diverse needs and preferences of individuals involved. Additionally, rheumatologists and podiatrists from NHS Lanarkshire Rheumatology Group and the PDGR group actively contributed to the decision-making process regarding which foot structures to include in the MSUS scanning protocol. This decision was grounded in their clinical experience and further supported by relevant literature, as highlighted in section 5.3.10. Moreover, the NHS Lanarkshire Rheumatology Group played a pivotal role in addressing ethical considerations, particularly in the context of the COVID-19 pandemic. They emphasised the importance of a well-ventilated room, considering the vulnerability of the patient group, and provided guidance on obtaining informed consent in the absence of face-to-face appointments.

4.3.3 Ethical approvals

All participants provided written informed consent and this study was conducted in accordance with the principles of the 2008 Declaration of Helsinki. For this cross-sectional study, ethical and Health Research Authority (HRA) approval was obtained from the North East - Newcastle & North Tyneside 2 Research Ethics Committee (21/NE/0130) (Appendix J) and the GCU Psychology, Social Work and Allied Health Sciences Ethics Subcommittee (HLS/PSWAHS/20/242).

4.3.4 Inclusion criteria

The inclusion criteria were as follows:

- Age ≥18 years
- Physician-confirmed diagnosis of RA using the 2010 American College of Rheumatology (ACR)/EULAR Diagnostic Criteria (Aletha et al., 2010)
- Were cognitively aware to a level where they could provide informed consent and understand the instructions required for this study.

4.3.5 Exclusion criteria

The exclusion criteria were as follows:

- Unable to provide informed consent.
- Severe hearing, and/or cognitive impairments/mental disorders that make participation not possible.
- Wheelchair user
- At high risk of RA-ulcerations or had an active ulcer
- Had recent foot surgical interventions within the previous 12 months.
- Had foot injections within the previous 6 months.
- Had been diagnosed with severe comorbid disease such as neuropathy, lower limb deep vein thrombosis, severe peripheral vascular disease, stroke, lymphedema, or any other disorder that could impact on normal pain perception.

4.3.6 Sample size

The sample size was determined using G* Power software. A minimum of 60 participants was required to detect a correlation of at least weak effect size (0.2), with a power of 80% and an alpha level set at 0.05. The deliberate selection of a weak effect size was based on capturing the hypothesised weak association between erosions and the RADAI-F5.

4.3.7 Recruitment

Participants with RA were enlisted through their respective referring clinicians in three rheumatology outpatient clinics located within the Greater Glasgow and Clyde and Lanarkshire NHS Health Boards. These clinics consisted of Gartnavel General Hospital, Wishaw University Hospital, and Royal Alexandria Hospital. Convenience sampling was employed, necessitated by the constraints imposed during the COVID-19 pandemic, where access to the GCU facility was limited, resulting in the selection of participants based on their availability and location.

To inform potential participants about the study, a participant information sheet was issued by the referring clinician (refer to Appendix K) in the waiting area before patients' clinical appointments. Given the constraints imposed by the Covid-19 pandemic, including restrictions on early attendance and the limited five-minute window before appointments, an opt-out form was implemented. This measure was introduced to uphold patient autonomy, providing participants with a one-week timeframe to submit the opt-out form if they desired to withdraw from the study. After one week, the principal investigator (AH) made contact with potential participants in order to address any inquiries, evaluate their eligibility based on the predefined criteria (4.3.4 & 4.3.5), and ascertain their willingness to take part in the study. If willing, participants were allocated an appointment time at the GCU Human performance lab. Participants' travel expenses to GCU were reimbursed.

4.3.8 Measurements

Data collection took place on a single day at the GCU Human Performance Lab. Demographic and clinical information, such as age, sex, disease duration, and current medication was collected. The administration of PROMs involved the utilisation of paper-based forms. Participants were provided detailed instructions on the completion of the required documentation, including a comprehensive explanation of the purpose of each PROM and the specific scoring system employed, notably the NRS.

4.3.9 Clinical variables

DAS-28-ESR

Patients' DAS-28-ESR scores encompassed the evaluation of TJC, SJC, ESR levels and a PGA. The PGA was conducted through a single question, asking patients, "How active do you consider your arthritis today?" with a response scale ranging from 0 to 10. Due to the Covid-19 pandemic, a significant number of participants lacked up-to-date DAS-28 scores within the past year. As a result, the most recent DAS-28-ESR scores of the participants were obtained from the rheumatologist and subsequently communicated to the principal investigator (AH) via email. Participants were classified into different disease activity categories, namely remission, mild, moderate, and severe, based on corresponding DAS-28-ESR scores of <2.6, ≥ 2.6 to <3.1, ≥ 3.1 to <5.1, and ≥ 5.1, respectively (Inoue et al., 2007).

The RADAI-F5

The RADAI-F5 (Appendix B) was employed to evaluate self-reported foot disease activity. The final score for each participant was computed as follows: (Q1+Q2+Q3+Q4+Q5)/5. To establish disease activity categories to facilitate easy interpretation of RADAI-F5 scores, participants were

classified according to mRADAI-5 thresholds for remission, mild, moderate, or high disease activity. Subsequently, aligning participants with mRADAI-5 reference categories (Rintelen et al., 2009), the third quartile of corresponding RADAI-F5 scores was calculated to establish thresholds for the respective RADAI-F5 categories. The disease activity categories based on the RADAI-F5 scores were defined as follows: *Foot disease remission state* was defined as a RADAI-F5 score of ≤1.4, while foot disease categories for mild, moderate, and high disease activity, were defined as: >1.4 to ≤ 3.45, >3.45 to ≤5.7, and >5.7, respectively (Hoque et al., 2021).

<u>The Modified RADAI-5</u>

The mRADAI-5, developed by Leeb et al. (2008), is a concise questionnaire designed to assess self-reported global disease activity in RA. It consists of five items: (1) global disease activity over the previous six months, (2) current swollen and tender joints, (3) arthritic pain, (4) general health, and (5) duration of morning stiffness (Appendix L) (Leeb et al., 2008). Each item is scored on a NRS ranging from 0 to 10. The mRADAI-5 score is calculated as the mean of the five questions, represented as $(Q1+Q2+Q3+Q4+Q5)/5$. The mRADAI-5 has demonstrated excellent construct validity for assessing RA disease activity, with established reliability, convergent validity, and responsiveness (Leeb et al., 2008; Rintelen et al., 2009). The mRADAI-5 thresholds for disease activity classification are as follows: ≤1.4 for a remission-like state, 1.6–3.0 for mild disease activity, 3.2–5.4 for moderate activity, and 5.6–10.0 for high disease activity (Rintelen et al., 2009).

<u>Physician assessments</u>

In both clinical research and practice, the number of tender and swollen joints has been utilised as an indicator of RA activity (Felson et al., 1993). To assess these indicators independently, a qualified podiatrist, who was blinded to the PROM and MSUS results, conducted a comprehensive evaluation of 34 foot and ankle structures for tenderness and swelling. The assessed structures included 2-5 MTPJs, the TNJ, the TTJ, the STJ and 1-5 intermetatarsal (IMT) and plantar bursae.

For TJC assessment, the examiner applied appropriate pressure to each joint to elicit tenderness, serving as an indication of localised inflammation. The STJ was evaluated through eversion and inversion movements, applying pressure to the sinus tarsi region to assess for tenderness. Palpation of the tibialis posterior tendon involved tracing from above the medial malleolus to its insertion on the navicular bone, while also evaluating for tenderness during plantar flexion and inversion of the foot against resistance. The presence of synovial fluid and/or soft tissue swelling, excluding bony overgrowth, was considered a positive finding for swelling. The clinical examiner assigned a grade of either presence or absence for swelling and tenderness, with a summated score

representing the cumulative assessment. As such, the total scores for each foot ranged from 0 to 17 (Figure 5).

4.3.10 MSUS scanning protocol

MSUS examinations were conducted using the Logiq S8 ultrasound system (GE Medical Systems Ultrasound and Rheumatology care Diagnostics) equipped with a multi-frequency linear transducer (8-15 MHz). The principal investigator (AH), who had obtained a Postgraduate Certificate (PgCert) in MSUS, received specific training in scanning foot and ankle joints prior to conducting this study. The B-mode and PD settings were optimised for all MSUS examinations, taking into consideration the specific structures under examination and aiming to achieve the optimal image quality. For the evaluation of superficial MSK structures, the PD factory configuration was adjusted to enhance Doppler sensitivity using the Rubin Method (Rubin, Tuthill & Fowlkes, 2001). To ensure standardised and consistent MSUS imaging practices, the FOOTRADIUS study adhered to the recommendations put forth by Czyrny (2017) (Table 13). These recommendations provided a standardised approach to image acquisition and documentation. The systematic MSUS examination and grading of 34 foot structures required approximately 30-40 minutes per participant.

The selected joints and soft tissue structures in the feet were determined based on the most commonly affected foot structures among the RA population, as reported in the literature. The MTPJs in the feet are among the first to show early RA symptoms (Brooks & Kariharan, 2013; Khan et al., 2021). Synovitis of 2-5 MTPJs is often one of the primary joint areas demonstrating radiographic changes, including erosions and bone decalcification (Khan et al., 2021). The exclusion of the 1st MTPJ was based on its association with other conditions such as gout and osteoarthritis (OA), which can exhibit inflammatory findings (Bowen et al., 2020) unrelated to the RA disease process. Other joints most commonly inflamed include the TTJ (Lee, Kim & Chang., 2019) and the STJ (Kaeley et al., 2019; Belt et al., 2001). Additionally, in a study by Dakkak et al., (2020) they reported increased frequency of IMT and plantar metatarsal bursitis in RA, which was also supported by Bowen et al., (2010). Although involvement in the forefoot and ankle are more common than midfoot involvement, radiographic changes attributed to RA have been demonstrated in these regions. TNJ joint involvement appears to be one of the earliest midfoot joints to result in foot deformity in RA (Popelka et al., 2010). Furthermore, significant contributors to the collapse of the medial longitudinal arch include the involvement of the tibialis posterior tendon (Popelka et al., 2010). Furthermore, the inclusion of the Tibialis posterior tendon was deemed necessary, as tibialis posterior tenosynovitis has reported prevalence rates ranging from 13% to 64% in RA, contingent upon the diagnostic criteria applied (Michelson et al., 1995; Barns

et al., 2013).These selected joints and soft tissue structures offer valuable insights into the foot pathology associated with RA.

TABLE 13: PRINCIPLES FOR STANDARDISED MSUS SCANNING (ADAPTED FROM CZYRNY, 2017)

Principle	Description
All structures and pathological abnormalities should be scanned in two perpendicular planes	Ensured comprehensive examination of all structures and abnormalities by scanning in two different planes (i.e., Longitudinal and transverse)
Foot scans should be performed from proximal to distal	Scanning occurred from the proximal regions and progressively moved towards the distal regions of the foot
Patients should be positioned supine for dorsal foot images and prone position for plantar scans	Patients were in a supine position for capturing MSUS foot images. Participants were not in a prone position for scanning of intermetatarsal or planar bursae due to better visualisation in a supine position
Participant identification should be included in all images	Ensured that each image contained a clear description of the participant identification for proper identification.
Confirm patient's date of birth prior to imaging	Verified the patient's date of birth before conducting the ultrasound scan to maintain accurate records.
Note the date of the examination	Recorded the date on which the ultrasound examination was performed for reference and documentation purposes.
Correctly label the examined region	Properly labelled the examined region on each image, indicating the specific foot region, scanning plane, and whether it is the right or left foot.

The examination of the feet in this study followed a standardised protocol using MSUS, which included a bilateral assessment of 7 joints (dorsal longitudinal and transverse views of the 2nd to 5th MTPJs, TNJ joint, TTJ, and STJ). The 5th MTPJ was also scanned from the lateral aspect. Additionally, soft tissue features associated with RA, such as bursae in the 1st to 5th IMT spaces and plantar metatarsals, were also examined. The tibialis posterior tendon was assessed in the transverse and longitudinal views at three regions (inframalleolar, supramalleolar, and insertion at navicular joint). To evaluate synovitis and erosion in the candidate joints, participants were assessed in a supine position with fully extended knees and ankles flexed at a 90-degree angle, achieving a straight leg position. For the assessment of tenosynovitis in the tibialis posterior tendon, participants were asked to extend their legs with the hip externally rotated and a pillow

was placed under the lateral malleoli to facilitate easy access to the medial ankle. The grading of MSUS features for the assessed structures is described in Table 14.

There is currently no established, valid or comprehensive MSUS scoring tool specifically designed for assessing RA in the foot and ankle. In order to address this gap, a novel composite total MSUS score combining GS and PD was developed for this study, guided by Hammer & Kvien, 2011. The MSUS scores were obtained by summating semi-quantitative grading for GS SH, PD synovitis, and GS and PD tenosynovitis. Each foot was assigned a score ranging from 0 to 39 points (78 bilaterally). Additionally, for the assessment of erosions and bursae (SH and PD), a summative rating was given for the presence or absence of these lesions in each foot, resulting in scores ranging from 0 to 7 (Figure 5).
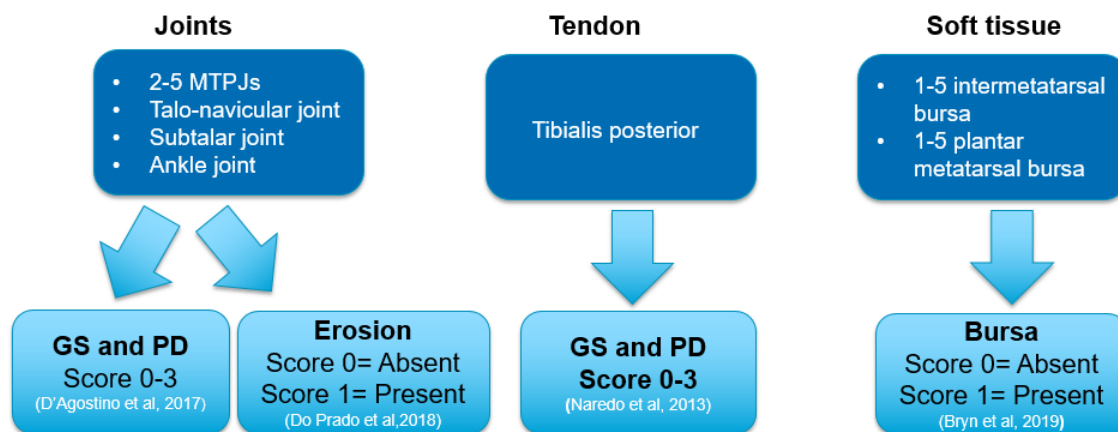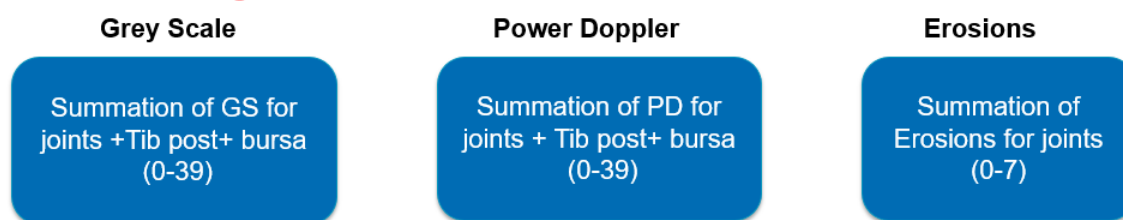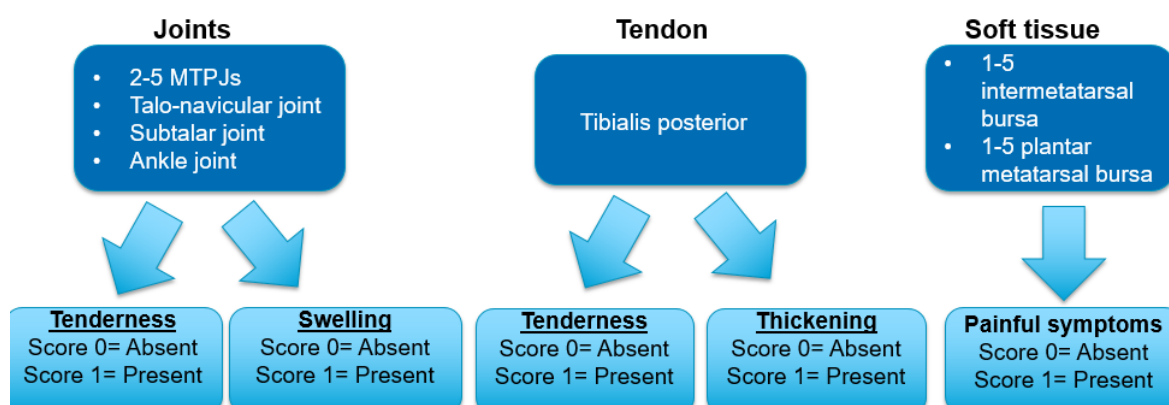
FIGURE 5: MSUS AND CLINICAL EXAMINATION SCORING METHOD

TABLE 14: MSUS GRADING FOR RA-RELATED FEATURES

Feature	Grading
Synovial Hypertrophy (D'Agostino et al., 2017)	• Score 0: No hypertrophy independent of presence of effusion. • Score 1: Minimal hypertrophy with or without effusion up to the level of horizontal line connecting bone surfaces. • Score 2: Moderate hypertrophy with or without effusion extending beyond the joint line, but with upper surface concave or hypertrophy extending beyond joint line, but with upper surface flat. • Score 3: Severe hypertrophy with or without effusion extending beyond the joint line, but with upper surface convex.
Erosions (Backhaus et al.,2009)	• Score 0: Absence of erosions • Score 1- Erosions present
Bursa/ bursitis (Fearon et al., 2014)	• Score 0: Absence of bursitis • Score 1- Bursitis present
Tenosynovitis (Alcalde et al., 2012)	• Score 0: Normal (i.e.,*8.4 mm (Schmidt et al., 2005)* • Score 1: Minimal thickening of tendon • Score 2: Moderate thickening of tendon • Score 3: Severe thickening of tendon
Power Doppler interrogation of synovial tissues (Schmidt et al., 2015)	• Score 0: No flow in the synovium • Score 1: Single vessel signals (*max 3 single)* • Score 2: Confluent vessel signals in less than half of the area of the synovium • Score 3: Vessel signals in more than half of the area of the synovium
Power Doppler interrogation of tibialis posterior (Alcalde et al., 2012)	• Score 0: No signals • Score 1: Signals in only one area of the tendon sheath • Score 2: Signals in more than one area of the widened tendon sheath • Score 3: Signals filling most of the widened tendon sheath

4.3.11 Study blinding

An independent investigator, who was unaware of the MSUS findings, conducted the clinical examination. However, due to the impact of the Covid-19 pandemic, it was not always feasible to have an independent assessor on site. In cases where an independent assessor was available (n=44), the principal investigator (AH), who performed the MSUS examination, remained blinded to the clinical examination and PROM results until after data collection. In instances where an independent assessor was not available, the principal investigator (AH) conducted the clinical examination while remaining blinded only to the PROM results. Participants were not blinded to any of the findings.

4.3.12 Statistical analysis:

All information from paper questionnaires was transferred to Microsoft Excel for data cleaning prior to analysis. All statistical tests were performed using a two-sided significance level of 5% using IBM SPSS Statistics version 28. Demographic and clinical data, including age, sex, disease duration, and DAS-28-ESR scores were expressed using descriptive, frequency, ratio, and interval statistics, including mean (standard deviation (SD)), female: male ratio, and percentage figures. Construct validity was demonstrated if 75% of the outcomes matched the *a-priori* hypotheses (Streiner & Norman , 2008; Kirshner & Guyatt 1985). Using Pearson's correlations, linear associations were estimated between the RADAI-F5 and objective measures. Associations between MSUS-detected SH and PD and the RADAI-F5 were further explored through cross tabulation according to RADAI-F5 disease categories. For each RADAI-F5 foot disease category, clinical joint evaluations and MSUS features were summarised using proportions the mean, median and interquartile range (IQR), as applicable. In order to investigate the factors contributing to persistent positive scores on the RADAI-F5, despite the absence of PD signals on MSUS, participants were classified into disease categories based on their RADAI-F5 scores. Subsequently, the associations between each RADAI-F5 item and MSUS and clinical examination was analysed.

Furthermore, in order to explore the correlations between RADAI-F5 scores and MSUS-detected foot disease activity at the item level, an analysis was conducted to evaluate the breakdown of each RADAI-F5 item across different foot disease categories. This approach provided further insights into the relationship between foot disease activity and individual RADAI-F5 items. To explore and describe subclinical foot synovitis, MSUS results were compared to clinical examinations results. Participants were grouped into categories based on their MSUS results. The percentage (%) of patients with MSUS features (GS, PD, erosions or bursae/bursitis) were compared to clinical swelling and tenderness data.

4.4 Results

4.4.1 Recruitment summary

81 patients were initially referred to the study from the three NHS sites. Among those, n=10 could not be contacted, n= 7 indicated a lack of availability to participate, and n=4 had to withdraw due to personal or familial long-term illness. The recruitment process resulted in the enrollment of 60 participants, with n=29 being recruited from Gartnavel General Hospital, n=28 from Wishaw General Hospital and n= 3 from Royal Alexandria Hospital (Figure 6). Additionally, 11 participants from the FOOTRADIUS study were specifically recruited for the embedded longitudinal study (Chapter 5) as they had recently initiated biologic therapy.
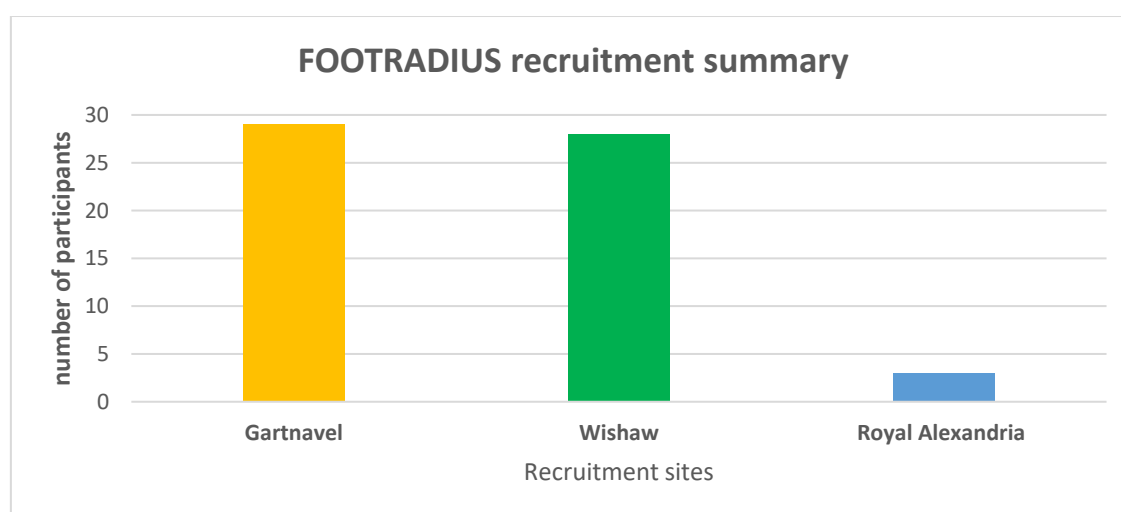
FIGURE 6: RECRUITMENT SUMMARY

4.4.2 Demographic and clinical data

A total of 60 participants, predominantly female (80%), with a mean age of 62.6 years and a median disease duration of 120 months participated in the study. 42 individuals were receiving DMARD therapy, 17 were receiving biologics, and 1 was not on any RA medication. Additionally, 12 individuals (20%) had previously received corticosteroid injections in the 6 to 12 months prior to their visit to GCU. Mean [±SD] scores for the DAS-28-ESR was 3.83 [±1.38], indicating that participants typically presented with a moderate level of disease activity. Based on the DAS-28-ESR, 18.3% of the participants were classified as being in remission, 28.3% had low disease activity, 25% had moderate disease activity, and 28.3% had high disease activity. The foot disease categories assessed by the RADAI-F5 showed the following distribution: 10% classified as in remission, 35% with low foot disease activity, 18.3% with moderate foot disease activity, and 36.7% with high foot disease activity. The mean [±SD] values for the PROMs were as follows: RADAI-F5 score was 4.39 [±2.69] and modified RADAI-F5 score was 4.79 [±2.05] (Table 16). These scores indicate that participants typically reported moderate foot-related and global disease.

The average [±SD] SJC in the assessed foot structures was 2.53 [±2.83], while TJC was 9.25 [±8.62]. GS SH was more prevalent than PD synovitis, with a mean [±SD] of 14.85 [±8.57] compared with 2.75 [±3.23]. Erosions were less frequently observed, with a mean [±SD] of 0.70 [±1.53]. Demographic data are presented in Table 15. It is important to highlight that a number of participants (n=6) reported having OA.

TABLE 15: PARTICIPANT DESCRIPTIVE DATA AND DISEASE CHARACTERISTICS

Characteristics	All participants (n=60)
Age (Years)	62.6 [±9.97]
Sex (F:M)	4:1
Disease duration (Years)	15.49 [±12.19]
DAS-28-ESR	3.83 [±1.38]
In remission (≤2.6)	11/60 (18.33%)
Low disease (>2.6 to < 3.1)	17/60 (28.33%)
Moderate disease (≥3.1 to <5.1)	15/60 (25%)
High disease (≥5.1)	17/60 (28.33%)
Therapy	
DMARDs	42/60 (70%)
Biologic therapy	17/60 (28.33%)
Glucocorticoids between 6months-1year	12/60 (20%)
None	1/60 (1.67%)
mRADAI-5	4.79 [±2.05]
In remission (≤1.4)	3/60 (5%)
Low disease (>1.6 to ≤ 3.0)	9/60 (15%)
Moderate disease (>3.2 to ≤5.4)	23/60 (38.3%)
High disease (>5.6)	25/60 (41.67%)
RADAI-F5	4.39 [±2.69]
In remission (≤1.4)	6/60 (10%)
Low disease (>1.4 to ≤ 3.45)	21/60 (35%)
Moderate disease (>3.45 to ≤5.7)	11/60 (18.3%)
High disease (>5.7)	22/60 (36.67%)
Clinical and MSUS assessments	
TJC	9.25 [±8.62]
SJC	2.53 [±2.83]
GS	14.85 [±8.57]
PD	2.75 [±3.23]
Erosions	0.70 [±1.53]

Results are shown as means [± standard deviation, SD], unless specified; DAS-28-ESR: Disease Activity Score-28 joints using erythrocyte sedimentation rate, DMARDS: Disease modifying anti-rheumatic drugs, mRADAI-5: modified version of the Rheumatoid Arthritis Disease Activity Index, RADAI-F5: Rheumatoid arthritis foot disease activity index, TJC: tender joint count, SJC: swollen joint count, GS: greyscale, PD: power Doppler, data based on n=60.

4.4.3 Affected foot structures and frequency of MSUS abnormalities

MSUS-detected SH and PD was most prevalent in the 2nd and 3rd MTPJs and TTJ. The frequency of MSUS abnormalities is highlighted in Table 16 and Figures 7 and 8. Structures that exhibited most swelling on clinical examination included the TTJ and STJ, while clinical tenderness was most evident along the tibialis posterior tendon, in the IMTs, the 2nd and 3rd MTPJ and the TTJ (Table 16). Figure 9 highlights the frequency of clinical swelling and tenderness of selected joints. It is important to note that n= 6 participants STJ could not be visualised adequately on MSUS due to oedema. In the present study, 96.7% (58/60) of participants' self- reported presence of foot disease. SH, defined as having a GS score of ≥1 was prevalent in 59/60 (98.33%) of participants, while overall synovitis, defined as having a PD score of ≥1 was evident in 38/60 (63.3%) of the participants (Table 17).

TABLE 16: PREVALENCE OF FOOT DISEASE BY SITE

	Synovial hypertrophy (%)	Power Doppler (%)	Clinical swelling (%)	Clinical tenderness (%)
MTPJ 2	88.33	33.33	1.67	43.33
MTPJ 3	81.7	31.67	20	48.33
MTPJ 4	45	8.33	13.33	31.67
MTPJ 5	10	1.67	5	15
TTJ	63.33	20	50	48.33
TNJ	50	13.33	25	31.67
STJ	30	6.67	31.67	38.33
Tibialis posterior	25	5.56	15	48.33
IMT bursa	33.33	10	N/A	58.33
Plantar metatarsal bursa	8.33	1.67	N/A	36.67

Results are shown as % based on n=60 for all structures except STJ (n=54); IMT: Intermetatarsal, MTPJ: Metatarsophalangeal joint, STJ: Subtalar joint, TNJ: Talonavicular joint, TTJ: Tibiotalar joint.

Affected structures (SH) n/120*
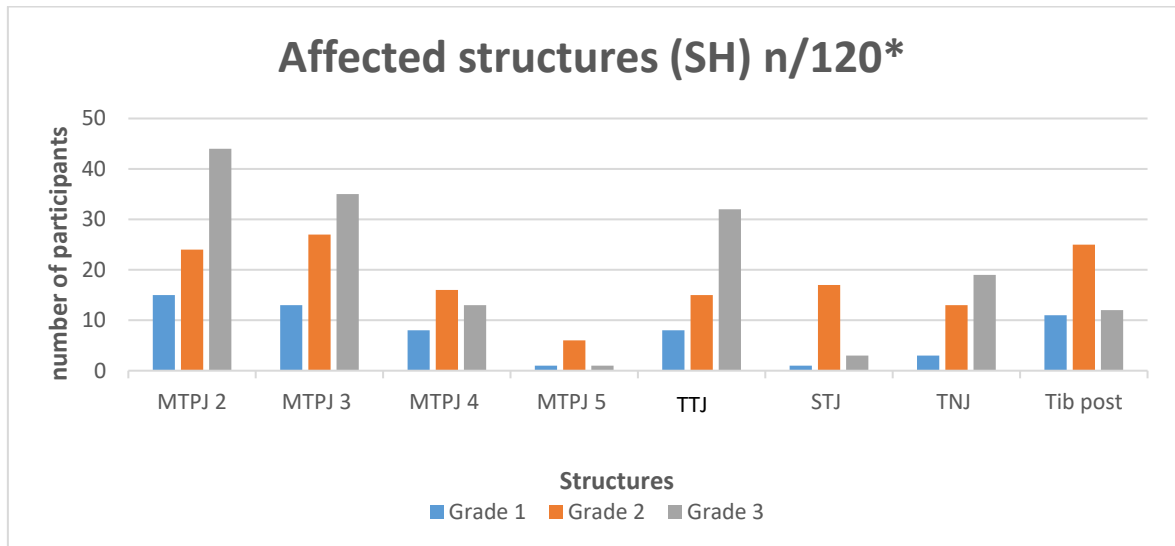
*n=120 for all except STJ, where n=108

FIGURE 7: SYNOVIAL HYPERTROPHY GS GRADE FREQUENCY IN SELECTED STRUCTURES

Affected structures (PD), n/120*
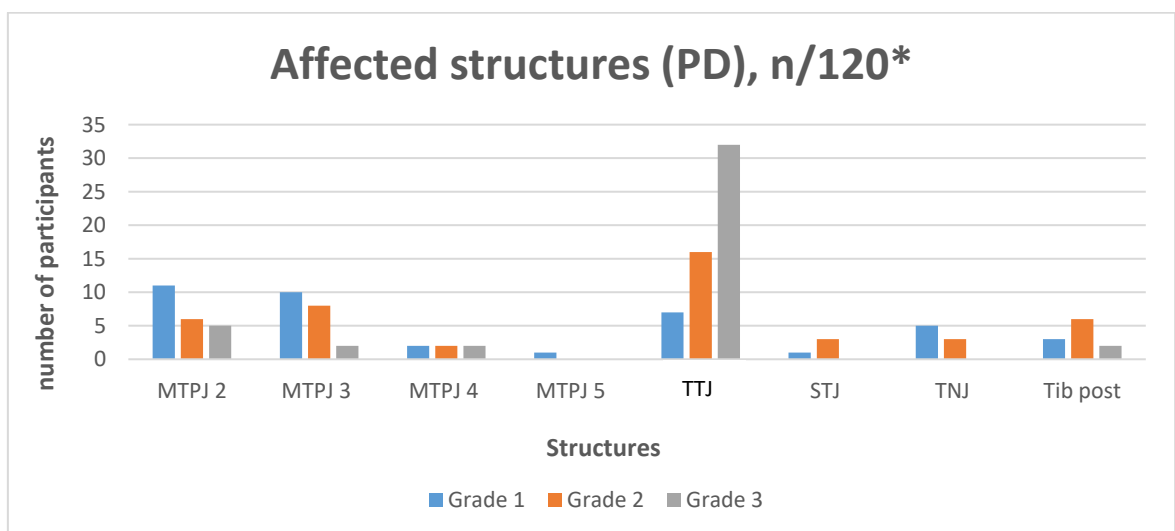
*n=120 for all except STJ, where n=108

FIGURE 8: SYNOVITIS PD GRADE FREQUENCY IN SELECTED STRUCTURES
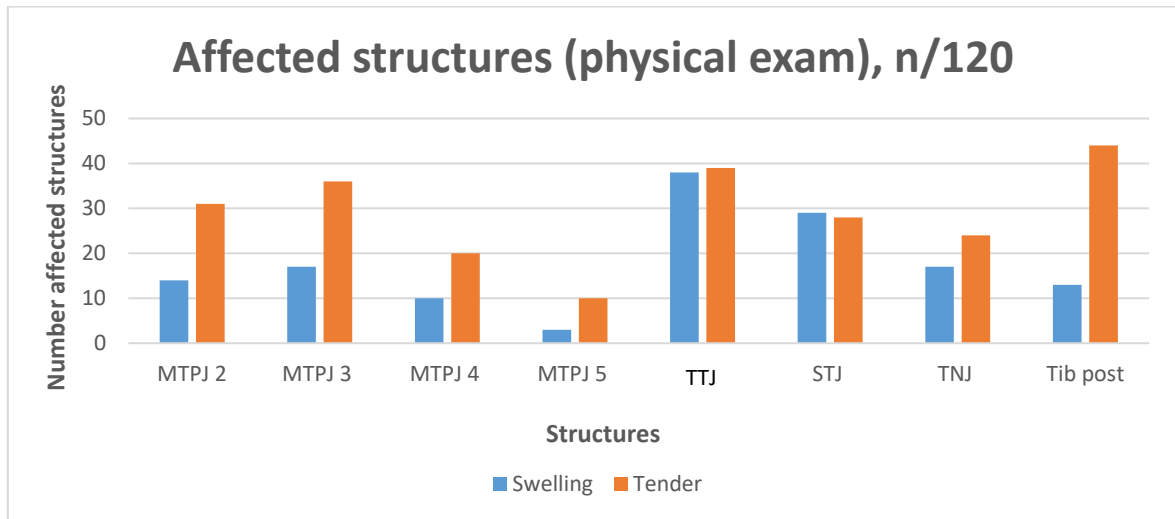
FIGURE 9: FREQUENCY OF TENDER AND SWOLLEN FOOT JOINTS

TABLE 17: FREQUENCIES OF US ABNORMALITIES ACROSS THE POPULATION

MSUS abnormality	Particpants affected % (n=60)
Overall synovitis (GS ≥ 2 and/or PD≥1)	65%
Total mild PD synovitis (PD, >0, ≤1)	10%
Total moderate-severe PD synovitis (PD≥1)	63.3%
Total mild GS (GS, >0, ≤1)	10%
Total moderate GS (GS≥1)	98.33%
Total moderate-severe GS (GS ≥2)	65%
Total mild tenosynovitis, (GS≤ 1, PD, >0, ≤1)	21.67%
Total moderate-severe tenosynovitis (GS ≥ 2 & PD≥1)	13.33%

*Q= quartile; GS, greyscale; PD, power Doppler

4.4.4 Associations between RADAI-F5 and clinical variables

The association between the RADAI-F5 and GS SH was stronger than expected (Pearson's © = 0.75 [95% CI 0.61, 0.84], p < 0.01) (Table 18 and Figure 10). As anticipated, a moderate positive association was observed with PD (r = 0.60 [95% CI 0.41, 0.74], p< 0.01) (Table 19 and Figure 10) and a weak association with erosions (r = 0.29 [95% CI 0.04, 0.51], p < 0.01). The RADAI-F5 had a weaker than anticipated association with clinical swelling (r = 0.37 [95% CI 0.13, 0.57], p < 0.05) and a moderate association with clinical tenderness, as expected (r = 0.44 [95% CI 0.21, 0.62], p < 0.01) (Table 18 and Figure 10). 80% of correlations for construct validity were in line with or better than the *a-priori* hypotheses, thus confirming construct validity.

TABLE 18: PEARSON'S CORRELATIONS OF RADAI-F5 WITH OBJECTIVE MEASURES OF FOOT DISEASE ACTIVITY FOR STRENGTH OF ASSOCIATION WITH A-PRIORI HYPOTHESES

Measure (n=60)	Correlation Coefficient (95 % CI)	Strength	*a-priori* hypothesis
Clinical swelling	0.37 (95% CI 0.13, 0.57)	Weak	Moderate
Clinical tenderness	0.44 (95% CI 0.21, 0.62)	Moderate	Moderate
Synovial hypertrophy	0.75 (95% CI 0.61, 0.84)	Strong	Moderate
Synovitis	0.60 (95% CI 0.41, 0.74)	Moderate	Moderate
Erosions	0.29 (95% CI 0.04, 0.51)	Weak	Weak

*Pearson's correlation, all significant at $p<0.05$
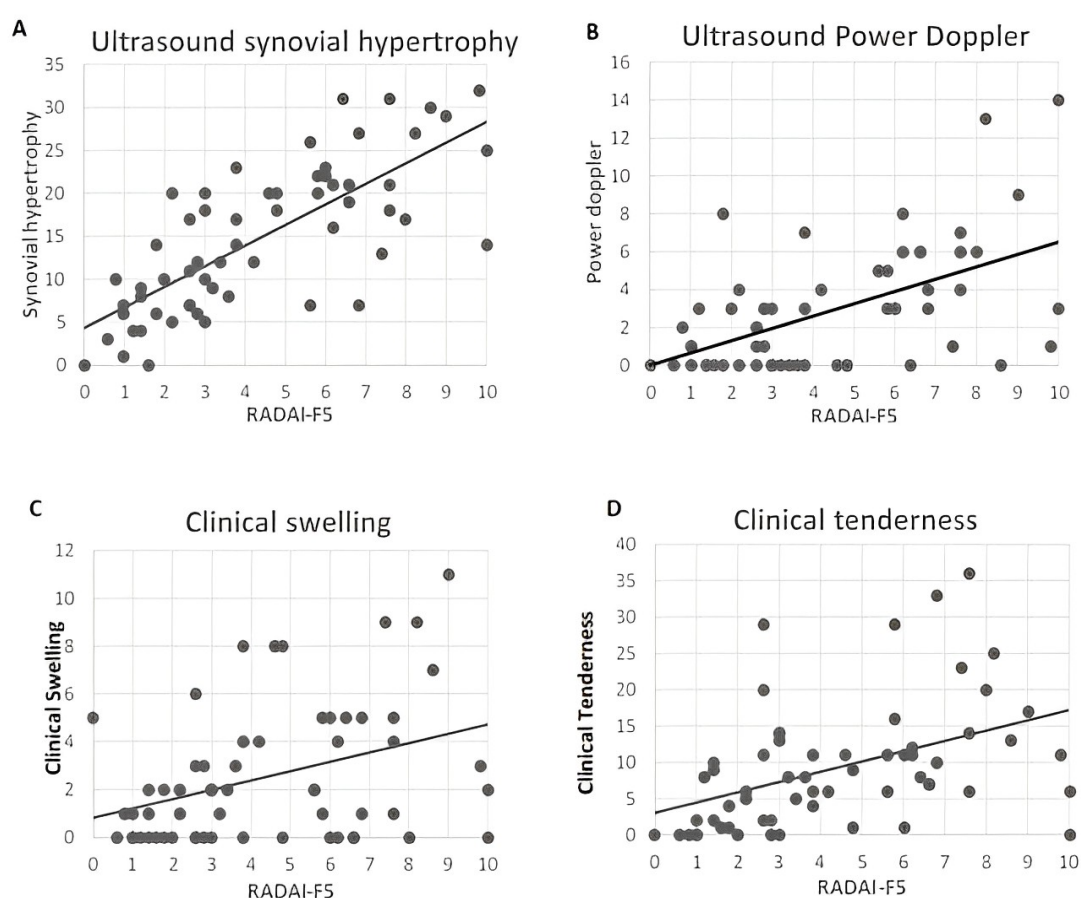
FIGURE 10: SCATTERPLOTS WITH LINE OF BEST FIT DEMONSTRATING CONVERGENT VALIDITY FOR RHEUMATOID ARTHRITIS FOOT DISEASE ACTIVITY INDEX (RADAI-F5) ASSOCIATIONS WITH (A)SYNOVIAL HYPERTROPHY (B) POWER DOPPLER (C) CLINICAL SWELLING AND D) CLINICAL TENDERNESS

Participants' data were analysed following classification into RADAI-F5 disease categories. When considering PD, there was not a significant difference in the mean and SD values compared to clinical examination for swelling. In the case of clinical tenderness, there was a greater disparity between the mean and SD values for MSUS PD compared to clinical examination. Furthermore, despite low clinical swelling (mean =1.17) and tenderness (mean= 0.33) scores, no erosions were observed (Table 19).

TABLE 19: RADAI-F5 DISEASE CATEGORY SUMMARY STATISTICS

RADAI-F5	Clinical swelling	Clinical tenderness	MSUS SH	MSUS PD	MSUS Erosions
In Remission (n=6)	1.17 [±1.77]	0.33 [±0.75]	4.5 [±3.5]	0.67 [±0.75]	0[±0]
Low (n=21)	1.33[±1.52]	7.10 [±7.30]	9.04 [±4.86]	1.05 [±1.29]	0.14 [±0.64]
Moderate (n=11)	3.56[±3.37]	6.67 [±3.86]	18.11 [±5.72]	3 [±2.40]	1.11 [±1.85]
High (n=22)	3.5 [±3.27]	14.36 [±9.52]	22.29 [±6.42]	5.04 [±3.59]	1.27 [±1.91]

Results are shown as means [± standard deviation, SD]; PD: Power Doppler, RADAI-F5: Rheumatoid arthritis foot disease activity index, SH: Synovial hypertrophy

MSUS features were analysed across different categories of DAS-28-ESR, and the corresponding RADAI-F5 classifications. Among the 11 patients in DAS-28-ESR remission, 4 remained in remission, 5 had low disease activity, and 2 had high levels of foot disease according to RADAI-F5. The analysis of the DAS-28 categories against MSUS features revealed that of those in DAS28-ESR remission or low disease activity states, 82% and 88.2% had signs of foot disease detected using MSUS, respectively (defined as having GS score of ≥1) , while 64% of individuals in the DAS-28 remission category had ≥ grade 2 GS SH at one or more sites of interest. In comparison, 88% of individuals in the DAS-28-ESR low disease category had ≥ grade 2 GS SH, while 100% of those in moderate to high DAS-28 categories ≥ grade 2 GS SH. Approximately 54% of individuals in the low DAS-28-ESR category and 53% in the remission DAS-28-ESR category exhibited PD signals in at least one of the assessed foot structures (Table 20).

TABLE 20: MSUS FINDINGS BY DAS-28-ESR DISEASE CATEGORY

DAS-28-ESR	GS MSUS ≥ grade 1 (n [% affected])	GS MSUS ≥ grade 2 (n [% affected])	PD MSUS ≥ grade 1 (n [% affected])	MSUS erosion more than 1 site (n [% affected])
In Remission (n=11)	9[82%]	7 [64%]	6 [54%]	0[0%]
Low (n=17)	15 [88%]	15 [88%]	9 [53%]	3[18%]
Moderate (n=15)	15 [100%]	15 [100%]	9[60%]	6 [40%]
High (n=17)	16 [94%]	17 [100%]	13 [77%]	11 [65%]

DAS-28-ESR: Disease activity score for 28 joints using erythrocyte sedimentation rate; GS, greyscale; PD, power Doppler

4.4.5 RADAI-F5 Item scores

17 individuals with RA continued to score on the RADAI-F5 (≥ 0) despite not having presence of PD signals. The RADAI-F5 item scores and MSUS GS SH and erosion findings of these 17 RA participants were analysed to investigate the factors contributing to their continued scoring on the RADAI-F5. Notably, the remission and low disease RADAI-F5 groups exhibited significantly higher scores for item 1, which pertains to foot disease activity within the previous 6 months compared to other items. The mean [±SD] scores for item 1 for these groups were 2.11 [±1.57] and 4.57 [±2.28], respectively. Table 22 summarises the statistics of the participants with no PD signals, including their mean [±SD] scores for each item as well as MSUS and clinical examinations. It is noteworthy that individuals classified in the RADAI-F5 remission category did not display any evidence of MSUS-detected SH or erosions. However, in all other RADAI-F5 disease groups, the presence of MSUS SH and erosions was observed (Table 21). The "in remission" group according to RADAI-F5 had a significantly shorter mean disease duration of around 4 years, compared to the "low", "moderate", and "high" disease groups, which had longer mean disease durations of 14.78, 15, and 24 years, respectively (Table 21). The findings indicate that RA patients may persistently encounter symptoms associated with foot disease activity, as assessed by RADAI-F5, despite the absence of MSUS-detected PD signals.

Correlation analyses between each RADAI-F5 item and PD indicated weak positive associations, particularly for questions concerning foot disease in the past 6 months (item 1) (r= 0.28 [95% CI 0.0-0.52], $p < 0.05$) and morning stiffness (item 5) (r= 0.26 [95% CI 0.00-0.50], $p < 0.05$) (Table 22). Conversely, GS SH scores demonstrated moderate associations for questions related to morning stiffness (item 5) (r= 0.50 [95% CI 0.27-0.68], $p < 0.05$) and strong associations for item 1(r= 0.62 [95% CI 0.42-0.77], $p < 0.05$) (Table 22). Notably, items associated with joint

tenderness/swelling (item 2), pain (item 3), and foot health (item 4) exhibited strong associations with GS SH and moderate associations with PD (Table 22).

TABLE 20: SUMMARY STATISTICS OF PARTICIPANTS WITH NO POWER DOPPLER SIGNALS

	RADAI-F5 Disease categories			
	In remission (n=2)	**Low (n=10)**	**Moderate (n=3)**	**High (n=2)**
Age (years)	66 [±8.49]	63.50 [±8.91]	67.67 [±4.92]	61.5 [±2.5]
Disease Duration (years)	4 [±3.20]	14.78 [±13.3]	15 [±10.03]	24[±6]
DAS-28-ESR	1.20 [±0.85]	2.38 [±0.89]	2.65 [±0.31]	3.59[±2.8]
mRADAI-5	2.50 [±0.71]	4.02 [±1.24]	4.33 [±0.52]	4.80[±3.80]
MSUS SH	0[±0]	7.80 [±4.42]	19.33 [±1.15]	30.5 [±0.5]
MSUS erosion	0 [±0]	0.30 [±0.95]	2.67 [±2.50]	1 [±1.10]
RADAI-F5 item 1	2.11 [±1.57]	4.57 [±2.28]	8 [±2.16]	8 [±0]
RADAI-F5 item 2	0 [±0]	2.40 [±1.74]	3.33 [±1.70]	8 [±2]
RADAI-F5 item 3	0.50 [±0.71]	1.60 [±1.11]	4 [±0.82]	7.5 [±1.50]
RADAI-F5 item 4	0.50 [±0.71]	1.90 [±1.04]	4.67 [±0.47]	5 [±1.10]
RADAI-F5 item 5	1 [±0]	2.10 [±2.51]	3.67 [±0.58]	9 [±1]

Results are shown as means [± standard deviation, SD]; mRADAI-5: Modified version of the Rheumatoid Arthritis Disease Activity Index, MSUS: Musculoskeletal ultrasound, RADAI-F5: Rheumatoid arthritis foot disease activity index.

TABLE 21: RADAI-F5 ITEM ASSOCIATIONS WITH MSUS

RADAI-F5 Item	**MSUS GS (Correlation coefficient (95% CI)***	**Strength**	**MSUS PD (Correlation coefficient (95% CI)***	**Strength**
Item 1	0.62 (0.42-0.77)	**Strong**	0.28 (0-0.52)	**Weak**
Item 2	0.72 (0.55-0.84)	**Strong**	0.44 (0.19-0.64)	**Moderate**
Item 3	0.68 (0.51-0.80)	**Strong**	0.40 (0.15-0.60)	**Moderate**
Item 4	0.62 (0.42-0.77)	**Strong**	0.41 (0.16-0.61)	**Moderate**
Item 5	0.50 (0.27-0.68)	**Moderate**	0.26 (0-0.50)	**Weak**

CI: Confidence interval, GS: Greyscale, MSUS: Musculoskeletal ultrasound, PD: Power Doppler.

*Pearsons, all significant at p<0.05

4.4.6 Subclinical foot synovitis

MSUS findings with clinical examination for tenderness and swelling were compared in order to assess the effectiveness of clinical examination in identifying active foot disease. Among the RA participants with self-reported foot disease (RADAI-F5 $\geq$ 0), a significant proportion (98.3%) showed MSUS features of inflammation (GS $\geq$ 1 and/or PD $\geq$ 1). In comparison, clinical evaluation of swelling and tenderness identified inflammation in 63.3% and 85% of patients, respectively. Based on these findings, three distinct groups were identified: (i) individuals with clinical synovitis, constituting 63.33% of participants who exhibited SJC/TJC joints and had MSUS-detected foot disease (GS $\geq$ 1 and/or PD $\geq$ 1); (ii) individuals with subclinical synovitis, accounting for 33.7% of individuals who displayed MSUS-detected abnormalities (GS $\geq$ 1 and/or PD $\geq$ 1) despite the absence of SJC/TJC; and (iii) individuals without clinical synovitis, representing 3.33% of participants who had no clinically confirmed synovitis (no SJC/TJC and no significant MSUS abnormalities). Figure 11 illustrates the distribution of these groups. Furthermore, Figure 12 provides a comparison between foot synovitis, tenosynovitis, and bursae detected using MSUS compared to clinical palpation. Erosions could not be reported as this cannot be determined using clinical examination alone.
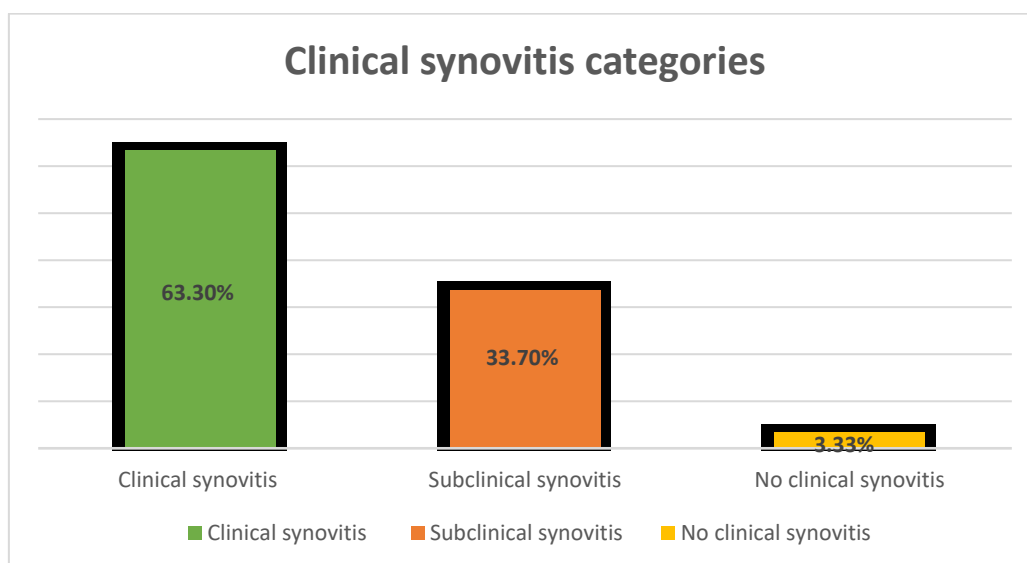
FIGURE 11: CLINICAL SYNOVITIS (%) BASED ON MSUS AND CLINICAL EXAMINATION
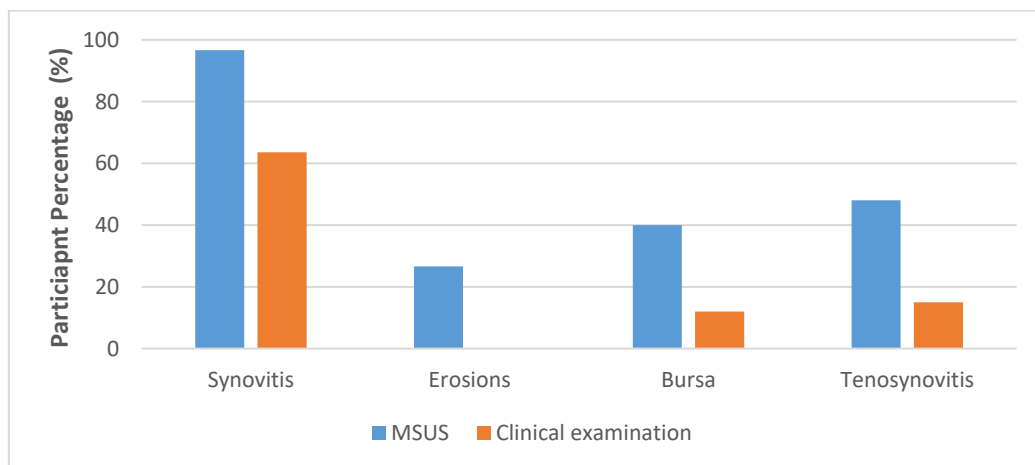
FIGURE 12: COMPARING FOOT SYNOVITIS, TENOSYNOVITIS, EROSIONS, AND BURSA: MSUS VS. CLINICAL EXAMINATION

4.5 Discussion

This is the first study to investigate the association between the RADAI-F5 and clinical and MSUS-detected foot disease in patients with RA. The results from this study demonstrate that the RADAI-F5 exhibits good construct validity as this novel tool displays moderate to strong associations with MSUS-detected foot disease, aligning with or exceeding the *a-priori* hypotheses. This study confirms and extends to existing evidence supporting the validity of the RADAI-F5 for assessing foot disease in individuals with RA (Hoque et al., 2021). In contrast to our previous study, which focused on an early RA cohort, the clinical utility of the RADAI-F5 in detecting inflammatory foot disease activity is now evident in both established and early RA patients (Hoque et al., 2021; Hoque et al., 2023a). These findings underscore the robust measurement attributes of this instrument, offering clinicians a sense of confidence regarding the tools construct validity.

Nevertheless, the RADAI-F5 demonstrated weaker associations with clinical swelling than anticipated. This observed discrepancy could be attributed to the potential presence of non-inflammatory causes of swelling (such as with individuals who have fibromyalgia or in obese patients) (Suresh, 2004) that are not captured by the RADAI-F5 questionnaire. Furthermore, clinical tenderness can be present in both inflamed and non-inflamed joints and may be influenced by factors such as individual pain thresholds (Zhang & Lee, 2018); so, may not always be accurate in assessing foot disease severity. Additionally, it is important to consider that clinical examination findings can be influenced by the expertise and experience of the examiner. In this study, the clinical examination was carried out by four independent assessors, all of whom were podiatrists with differing levels of experience. This variability in examiner experience may have played a role in the observed differences and fluctuations in the obtained results.

In the context of RA, foot examinations are recommended as a supplement to the DAS-28 (Simonsen et al., 2021; Van der Leeden et al., 2010; Hattori et al., 2018). However, it is important to note that such examinations are not consistently performed in routine rheumatology clinics (De Souza et al., 2016)). Furthermore, clinical examinations have limited sensitivity in detecting inflammatory RA features compared to MSUS (Brulhart et al., 2019; Borocco, Ansemli & Rossi-Semerano, 2023). This study's findings align with previous findings as evidenced by the presence of subclinical synovitis in 33.3% of individuals and weaker associations with clinical swelling than anticipated. A cross-sectional study by Dubash et al., (2021) in early psoriatic arthritis (PsA) patients suggests that swollen joints may serve as a better indicator of synovitis compared to tender joints. Simonsen et al.'s (2021) study demonstrated that a considerable percentage of rheumatoid patients (92.3% and 61.4%) who reported foot pain did not display signs of joint swelling or tenderness in the 1-5 MTPJ and ankle joints examined, respectively. In line with their findings, this current study also observed that swelling proved to be a less reliable indicator of foot disease than initially anticipated. This indicates that relying solely on clinical examination of foot joint and soft tissue structures may not be sufficient for identifying all individuals with active foot disease. Consequently, the incorporation of self-reported measures, like the RADAI-F5, may help indicate when physical examination of the foot is warranted.

An important observation in this study was that a subset of individuals ($n = 17$) scored above 0 on the RADAI-F5 questionnaire despite the absence of PD signals. Notably, participants classified as being in remission or having low RADAI-F5 disease scores exhibited higher scores on item 1, which pertains to foot disease activity over the past six months. These findings suggest three possibilities. Firstly, there may have been history of active foot disease that was not evident on the day of MSUS scan (i.e., they might have experienced disease activity within the six months prior). Secondly, foot symptoms stemming from BME could contribute to self-reported foot disease not discernible through MSUS. Lastly, patients' comprehension of active arthritis or their perception of active foot arthritis may be hindered by concurrent comorbidities that are not detectable by the RADAI-5 tool. It is crucial to acknowledge that the presence of BME, indicated by symptoms such as bone pain, and additional manifestations like swollen joints (joint effusion), holds significance (Wang et al., 2016). Notably, the pathologies of BME cannot be visualised through MSUS. In comparative assessments, MRI emerges as superior in detecting BME, whereas high-frequency MSUS demonstrates heightened sensitivity in identifying early joint effusion and synovial proliferation when juxtaposed with MRI (Backhaus et al., 2002; McQueen & Ostendorf, 2013). The limitations of MSUS in detecting BME may impact the accuracy of RADAI-F5 associations with MSUS. Patients with symptoms not visible on MSUS may still report significant foot disease activity, leading to potential discrepancies between PROM results and imaging results.

This emphasises the importance of using complementary diagnostic tools, such as MRI, for a comprehensive understanding of RADAI-F5 associations with inflammatory features of RA.

It is also important to note that individuals in low to high RADAI-F5 categories that scored > 0 on the RADAI-F5, despite no MSUS-detected PD, had longer duration of disease. These findings highlight a potential association between disease duration and self-reported foot disease, emphasising the potential influence of disease duration on foot-related outcomes in RA. The impact of disease duration on persistent foot or ankle pain in RA has been well established. Studies have indicated that longer disease duration is associated with higher levels of pain and reduced activity (Borman et al., 2012). Additionally, impaired foot function, characterised by altered pressure distribution and decreased walking speed, has been observed in patients with longer disease duration (Van der Leeden, 2007), suggesting a progressive nature of foot involvement and more radiographic damage in RA (Heinemann et al., 2018). Therefore, the implementation of early T2T strategies aiming for disease remission during a specific timeframe has been firmly established (Huang et al., 2022, Messelink et al., 2023). Consequently, incorporating instruments such as the RADAI-F5 to identify potential early foot disease and guide clinical interventions in the initial phases of the disease may be promising.

Interestingly, even in the absence of active Doppler signals, participants in the high RADAI-F5 disease group demonstrated GS SH scores typically corresponding to grade 2 or 3. This again indicates a strong relationship between the presence of SH and self-perceptions of foot disease and underscores the importance of addressing this aspect in clinical management. It is worth noting that pharmacological treatment for RA primarily focuses on addressing the inflammatory aspect of the disease, as identified by Doppler activity rather than SH (Bullock, 2019). Previous research by Witt et al., (2013) has shown that grade 1 SH can be observed in healthy individuals and remains unresponsive to therapy in both early and established RA. Similarly, Padovano et al., (2013) identified grade 1 SH in several healthy controls. However, Terslev et al., (2018) reported that grade 1 SH shows improvement with the initiation of biological treatment, regardless of the absence of Doppler activity. Similar findings have been observed for tenosynovitis, as grade 1 tenosynovitis without positive Doppler activity has been shown to improve with therapy (Ammitzbøll-Danielsen, 2016). Moreover, SH in RA patients has been associated with an early reoccurrence of DAS-28 relapse following remission, and it serves as a predictive factor for the progression of erosions (Brown et al., 2008). These findings suggest that SH remains clinically meaningful and responsive to change, and the eradication of Doppler signals should not always be the primary therapeutic objective in RA patients when considering therapy escalation. Consistent with the OMERACT guidelines, SH without Doppler activity is considered a characteristic that is assessed on MSUS of RA disease (Bruyn et al., 2019, D'Agostino et al., 2017), and should be

considered when assessing the activity of foot disease using MSUS. Therefore, the strong associations observed between GS and RADAI-F5 are thus encouraging, as they suggest that individuals with RA may be capable of detecting localised inflammatory changes associated with SHThis hints at the possible application of RADAI-F5 as a screening tool. However, the establishment of its effectiveness and broader applicability in this role necessitates further exploration through future studies. Future studies should evaluate the tools screening capabilities, assessing its sensitivity and specificity, and evaluating its integration into routine clinical practices. Additionally, examining the feasibility and cost-effectiveness of incorporating RADAI-F5 as a screening tool in various healthcare settings would contribute valuable insights for its potential implementation in preventive care strategies.

However, the management approach for patients presenting with grade 2 or 3 SH poses uncertainties. While current recommendations do not endorse pharmacological therapy or corticosteroid injections for SH in the absence of Doppler signals, emerging evidence suggests that SH alone may still serve as a predictor of future erosions (Bugatti et al., 2012). Consequently, it becomes pertinent to explore whether administering corticosteroid injections to patients with grade 2 or 3 SH accompanied by persistent pain could potentially mitigate the risk of future erosions. Presently, there is inadequate evidence to support the use of intra-articular corticosteroid injections as a treatment modality for SH in RA. Several pilot studies conducted in patients with OA involving the knee joint have reported no significant improvement in SH grades ≥ 2 following intra-articular corticosteroid injections compared to placebo injections (MacFarlane et al., 2023; Jüni et al., 2015). However, contradictory findings employing more advanced MRI techniques have demonstrated improvements and substantial reductions in mean synovial volume following intra-articular corticosteroid injections in OA knees (O'Neill et al., 2016). Moreover, in the management of OA, intra-articular corticosteroid injections have exhibited efficacy in providing short-term pain reduction and can be considered as an adjunct to core treatment for alleviating moderate to severe pain and improving functional outcomes (Ayhan et al., 2014). Considering these findings in OA, the question arises as to whether corticosteroid injections should be considered for RA individuals with grade 2 or 3 SH and persistent pain who have not achieved satisfactory outcomes with conservative treatments like physical therapy and analgesic medication. However, RA and OA have distinct pathophysiological mechanisms, making direct comparisons between them problematic. Nevertheless, the lack of practical guidelines for managing foot SH in RA underscores unmet clinical needs, highlighting the requirement for further research in the management of individuals with grade 2 or 3 SH and persistent pain.

Of those in DAS-28 remissions, 54% demonstrated ≥grade 1 PD signals affecting one or more sites of interest. Similarly, in low DAS-28 disease category, 53% exhibited ≥ grade 1 PD signals in the foot region. These findings were anticipated based on previous evidence indicating that composite disease activity indices, which fail to consider foot joints, inadequately capture foot synovitis (Wechalekar et al., 2016; Hattori et al., 2018), thereby resulting in suboptimal care for this specific patient group. However, in the studies, it was reported that approximately one-third of individuals in DAS-28 remission exhibited foot synovitis. Another study conducted on arecent-onset RA cohort examined synovitis in the MTPJs and revealed that 40% of those in DAS-28 remission displayed involvement of at least one MTPJ (Van der Leeden et al., 2010). This study's prevalence rates were higher; nevertheless, this may be attributed to the aforementioned studies utilised an early RA cohort, employed TJC and STJ and relied on radiographs to detect synovitis. These assessment approaches may not be the most sensitive or specific methods for assessing disease activity and fail to account for soft tissue structures that commonly exhibit signs of inflammation in the RA population.

Considering the robust positive correlation of the RADAI-F5 with SH and its moderate correlation with synovitis/tenosynovitis, integrating this tool as an adjunct to composite disease activity indices like the DAS-28 holds the potential to improve the detection and monitoring of local foot disease. This approach can pave the way for new foot care paradigms within the therapeutic 'window of opportunity', leading to improved patient outcomes (Woodburn et al., 2010). Nonetheless, it is important to note that the RADAI-F5 does not provide specific information about the affected areas within the foot; rather, it offers a comprehensive score for foot disease as a whole. Therefore, it does not eliminate the necessity of clinical examinations to localise foot symptoms. However, incorporating the RADAI-F5 into rheumatology MDT clinics may prompt clinical examination of the foot, enable early detection of foot disease, and guide therapeutic approaches based on the RADAI-F5 disease classification categories.

Based off discussions of this studies findings with key stakeholders, it is recommended that patients who are in RADAI-F5 remission or have low disease activity should receive verbal and written information about their condition. They should also be provided with guidance on appropriate footwear and, if necessary, recommendations for functional orthotics. For patients with RADAI-F5 scores falling in the moderate and high categories, it is recommended to further investigate through clinical examination of foot joints and soft tissues. If clinical examination confirms the presence of suspicious joints, the consideration of MSUS imaging to verify synovitis becomes crucial, potentially leading to the recommendation of steroid injections. Additionally, AHPs should consider referring patients to rheumatology for possible medication escalation if patients are in moderate or high RADAI-F5 categories and if there is presence of swelling or

tenderness on clinical examination of affected structures. Through the implementation of these strategies, healthcare professionals have the potential to proactively address foot-related issues in patients with RA. This approach may contribute to the enhancement of treatment outcomes and optimisation of overall foot disease management within the context of rheumatology care (Hoque et al., 2023a). It is important to underscore that the practical application of these recommendations within clinical settings is crucial to comprehensively evaluate their effectiveness.

Moreover, considering the RADAI-F5's construct validity demonstrated through objective measures, coupled with the rising prominence of remote consultations in the post-Covid-19 pandemic era, the RADAI-F5 exhibits potential for utilisation in this context (Hoque et al., 2022), allowing PIFU to be facilitated. By completing the RADAI-F5 questionnaire prior to appointments, patients can provide information on their foot disease activity during remote consultations, enabling healthcare providers to make better informed decisions regarding the requirement of a face-to-face appointment. Additionally, with the potential future integration of the RADAI-F5 as an ePROM or the development of a mobile app, patients can promptly contact the rheumatology MDT in the event of significant increases in RADAI-F5 scores, ensuring timely and appropriate interventions to address foot disease activity or highlight where additional imaging is required. This approach may potentially reduce the need for costly and time-consuming in-person visits, as suggested by Chan et al. (2017).

The current study demonstrated a notable prevalence of foot disease, with 98% of participants displaying MSUS-detected SH and 63% exhibiting PD signals in the foot or ankle. These findings emphasise the persistence of foot synovitis among the participants in the present study, despite advancements in pharmacological interventions. Previous literature extensively discusses the prevalence of foot involvement in RA, with earlier estimates ranging from 56% to 100% (Otter et al., 2010; Wilson et al., 2017; Simonsen et al., 2021; Grondal et al., 2008; Vainio, 1956; Vidigal et al., 1975; Michelson et al., 1994). However, a rigourous examination of the literature pertaining to the prevalence of foot disease in RA is important. Firstly, the potential influence of responder bias must be acknowledged, whereby individuals with existing foot pain in the RA population may exhibit a higher propensity to participate in surveys, thereby influencing prevalence estimates. Secondly, the challenge lies in accurately determining the prevalence of RA foot disease through surveys, particularly among patients with comorbidities that may influence their perception of foot-related disease. Furthermore, one significant limitation in these prevalence studies is the absence of a standardised, valid tool for quantifying foot disease activity. The lack of a valid and reliable scoring system tailored to RA foot involvement has led to studies relying on subjective constructs such as foot pain. The accuracy of prevalence estimates based solely on patient reports of foot pain in RA studies warrants scrutiny as pain can arise from biomechanical factors and may

not necessarily indicate systemic involvement. Consequently, the extent of foot disease may not have been adequately captured, especially in cases involving soft tissue involvement such as bursitis or tenosynovitis, which often necessitate incorporating imaging techniques like MSUS or MRI. The incorporation of a validated and reliable outcome measure, like the RADAI-F5, has the potential to enhance the precision and dependability of self-reported foot disease data in RA prevalence studies specifically concentrating on foot disease.

4.6 Study strengths and limitations

This study represents the first investigation into the relationship between a self-reported foot disease and objective measures for foot disease. The cross-sectional design of the study provides valuable insights that are applicable to rheumatology outpatient clinics, with most participants being consistent with the demographics of other large-scale RA studies (Kvien et al., 2006). However, it is important to acknowledge certain limitations of this study. There is a potential for self-selection bias, as individuals who chose to participate may have had a more severe degree of foot involvement. Nevertheless, the study sample encompassed an equal distribution of patients in both the low and high-foot disease groups. Additionally, the study only included participants who were fluent in English, limiting the generalisability of these findings. As such, future RADAI-F5 validation studies should seek to include participants from diverse ethnic backgrounds and individuals with varying levels of English language proficiency.

Another study constraint is that a small subset of participants (n=6, 10%) reported having concurrent conditions such as OA. Although the MSUS scan excluded the 1st MTPJ, the RADAI-F5 questionnaire inquired about symptoms throughout the entire foot and ankle, including the 1st MTPJ. This inclusion of the 1st MTPJ in the questionnaire may have influenced item 5 on the RADAI-F5, which pertains to morning stiffness. It is worth noting that while these patients with OA were not excluded from the study to enhance sample size and improve the clinical and research applicability of the questionnaire, this inclusion may limit the RADAI-F5's ability to differentiate between RA and other comorbidities or rheumatic diseases. Therefore, future validation studies should thoroughly investigate the tools' ability to distinguishing between RA and other conditions. Understanding these nuances will help determine the discriminative capabilities of the RADAI-F5 and provide further validity of the tool.

Another limitation of this study is that the MSUS examiner was not always blinded to clinical foot examinations due to the constraints imposed by the Covid-19 pandemic. Hence, the potential for investigator bias cannot be ruled out. However, it is important to note that any potential bias would primarily affect the clinical foot examinations and not the PROM scores, as the RADAI-F5 scores were always concealed from the principal investigator. Furthermore, it should be noted that the

reported DAS-28-ESR scores by the rheumatologist might not necessarily reflect the most recent scores due to the limitations imposed by Covid-19 and the lack of in-person appointments. Furthermore, the subjectivity inherent in the PGA introduces variability stemming from individual patient perceptions, potentially impacting the direct comparisons with other relevant literature. These limitations emphasise the significance of considering the contextual factors that might have influenced the results pertaining to the DAS-28 in this study.

A further limitation includes the development of a novel MSUS scoring system. When developing a novel scoring system, evaluating its reliability and validity, particularly inter-rater reliability, is imperative. However, the COVID-19 pandemic posed challenges as there was no MSUS trained staff available on site to perform scans on participants and subsequently score the images. Additionally, there was a need to minimise participant contact with multiple individuals due to the vulnerability of this patient group during the pandemic. As such, a future study is recommended to assess the intra and inter-rater reliability of the novel MSUS scoring system proposed in this study.

4.7 Conclusion

This study presents additional evidence supporting the good measurement properties of the RADAI-F5 when compared to MSUS and clinical examination, confirming the tools construct validity. Primarily, confidence in the tools construct validity highlights the potential of this tool to be used to raise foot disease awareness or highlight when to examine the feet in routine rheumatology MDT settings. Moreover, it holds promise as a valuable tool for identifying individuals who would benefit from referral to the rheumatology MDT for further imaging to confirm the diagnosis of active foot disease. By effectively stratifying patients based on their RADAI-F5 scores, clinicians can optimise resource allocation and ensure appropriate imaging, enabling early detection of synovitis and timely administration of suitable treatment to mitigate the risk of unfavorable radiographic outcomes. Aligning with the recommendations of the EULAR task force, the optimal management of RA involves striving for low disease activity by using validated instruments. With increased confidence in the construct validity of the RADAI-F5, its clinical implementation could aid in the early identification of individuals with RA who are at risk of experiencing poor functional and radiographic outcomes.

Chapter 5. Minimally important difference of the RADAI-F5

This chapter evaluates the MID of the RADAI-F5 using an anchor-based approach. These findings build upon the results of a previous validation study on the RADAI-F5, which employed a distribution-based method to determine the MID (Hoque et al., 2021). The significance of this chapter lies in its contribution to the understanding of the level of improvement necessary for patients to perceive a meaningful change in their RADAI-F5 scores. These insights have the potential to enhance the interpretability of RADAI-F5 and offer guidance for managing the RA foot.

5.1 Background

5.1.1 Challenges in the interpretation of patient-reported outcomes

According to Mokkink (2010), interpretability plays a pivotal role in attributing significance to the scores derived from PROMs within a clinical setting. In the context of the RADAI-F5, scores should be easily interpretable and meaningful to patients, clinicians, and researchers. In RA, rheumatologists possess extensive knowledge pertaining to important changes in clinical outcomes, including markers such as CRP, ESR and DAS-28 scores due to the well-established cut-off points for these measures (Ward et al., 2015). Furthermore, rheumatologists' clinical expertise enables them to evaluate physiological changes such as joint swelling. Nevertheless, PROMs, which aim to assess latent, unobservable constructs such as pain, present challenges in terms of interpretation.

The interpretation of PROM-derived data is faced with numerous challenges, such as its "subjective nature" and the complexities involved in interpreting the obtained scores. Subjectivity in the interpretation of a given notion arises due to individuals' varying personal experiences, perceptions, and values (Kluzek, Dean& Wartolowska, 2022). For instance, an individual's assessment of pain or fatigue levels may be influenced by various factors such as age, sex, cultural background, and prior encounters with these symptoms (Daste et al., 2022). Within the framework of the RADAI-F5, the construct of stiffness encompasses a subjective perception reported by patients, which is inherently distinct from objective measurements that characterise physiological parameters such as blood pressure or body temperature. Additionally, the perception of stiffness can be influenced by external factors including weather conditions (Qvarfordt, Andersson & Larsson, 2019). Consequently, this complexity adds to the challenge of accurately analysing PROM data, especially when comparing results across different patients or patient groups (Krogsgaard & Hansen, 2022).

Additionally, patients' comprehension of a concept of interest can experience temporal fluctuations attributable to contextual and perceptual changes, a phenomenon referred to as response shift (Vanier et al., 2021). For instance, parameters such as "How tough is it to climb a flight of stairs?" are highly prone to this shift in meaning over time if, for example, the patient develops a health condition that affects their ability to climb stairs or if they start to engage in more regular exercise, becoming accustomed to physical exertion. In the context of the RADAI-F5, response shift can influence the perception and reporting of stiffness levels. For instance, in the case of prolonged stiffness, there is a possibility of internal standard adjustment over time, leading to lower reported levels of stiffness. Additionally, if a patient starts a new medication, they may feel compelled to report lower levels of stiffness or pain even if their symptoms remain static. This would lead to an underestimation of their foot disease activity. Therefore, response shift can be a significant factor to consider when interpreting PROMs and understanding patients' perspective of their own health status (Vanier et al., 2021).

A substantive proportion of clinicians may exhibit a limited comprehension of the multifaceted influences, such as various external factors and measurement errors, on score alterations in PROMs. This is often attributed to the limited availability of interpretation manuals for PROMs (Gibbons et al., 2016). Nonetheless, different methods have been established to aid in comprehending and interpreting PROM score changes, including responsiveness and MID (Revicki et al., 2006). Responsiveness denotes the ability of an instrument to detect clinically significant changes in a patient's health status over time or in response to a specific intervention. It measures the instrument's ability to capture meaningful changes in the construct being evaluated, such as pain, QoL, or physical function (Mokkink et al., 2010). Conversely, MID is used to interpret whether the observed change is important from the patient's or clinician's perspective (Revicki et al., 2006).

5.1.2 Defining MID for PROMs

In 2010, the COSMIN panel defined the MID as "the smallest change in the construct being assessed by patients or clinicians that are considered significant" (Mokkink et al., 2010). This definition underscores the critical threshold of change necessary for a meaningful impact, serving as a foundational reference point for the evaluation of clinical and research outcomes. It is important to note that the MID is not a fixed characteristic and can vary depending on the population and context (Cook, 2008).

5.1.3: Uses of the MID

Understanding the MID is essential for informing treatment decisions at both individual and group levels (Johnston et al., 2015). By providing insights into the magnitude of change in PROM scores,

clinicians can determine appropriate treatment modifications, such as initiating new treatments, adjusting medication dosage, or discontinuing current medication or non-pharmacological interventions. Furthermore, knowledge of the MID aids patients in comprehending the potential benefits of specific treatments (Revicki et al., 2006). Additionally, the MID assists in calculating statistical power and determining sample sizes for future clinical trials (Serdar et al., 2021).

5.1.4: How is the MID determined?

Multiple methods are available for estimating the MID, each encompassing distinct strengths and limitations. Wells and colleagues (2001) conducted an extensive evaluation of these methodologies and identified nine strategies for assessing the MID, which are summarised in Table 23. Despite the diversity of frameworks employed, methods for determining the MID are typically categorised into two groups: distribution-based and anchor-based approaches (Van der Willik, 2021). Revicki et al., (2006) suggested that the anchor-based method should be employed as the primary approach for identifying the MID of a PROM, with the distribution-based method serving as supplementary or corroborative evidence.

Anchor-based techniques compare changes in a PROM with an external indicator, referred to as an anchor, to categorise individuals into groups based on the magnitude and direction of change (Lydick & Epstein, 1993). In anchor-based approaches, patient or clinician assessments are commonly used to categorise individuals as having experienced no change, a small change (positive or negative), or a substantial change (positive or negative), but it should be noted that using different anchors may result in variations in the estimated MID values (Cook, 2008). The anchor-based approach is valuable in determining the MID as it enables direct comparison to clinically relevant external criteria and facilitates the establishment of meaningful thresholds for change in PROM scores (Revicki et al., 2006). Limitations of this approach include inconsistencies based on prospective or retrospective data collection, the potential for the MID to fall within the instrument's random variation, and the susceptibility to recall bias (Sharma, 2021).

Contrary to suggestions by Revicki et al., (2006), there exists an argument for the preference of distribution-based methods in the identification of a meaningful change in scores, rather than relegating them to a secondary status. Distribution-based methods are estimated based on the natural distribution and variability of scores within a sample population (Sharma, 2021). Consequently, they can facilitate a more comprehensive understanding of what constitutes a significant group change in score, as opposed to relying exclusively on external anchors, which may not be generalisable to the entire population. Additionally, distribution-based methods are less susceptible to recall bias when compared to anchor-based methods (Wyrwich & Norman, 2022). As such, using both an anchor-based and distribution-based approach is recommended, as

it facilitates a more robust and nuanced determination of the MID, accounting for both external indicators and inherent characteristics of the PROM's score distribution (Ousmen et al., 2018).

5.1.5 The MID of the RADAI-F5 using a distribution-based approach

In the initial RADAI-F5 validation study (Hoque et al., 2021), since no anchor question was available, the MID was estimated using the data-driven approach. The MID was determined using a value of $0.5 \times$ the SD of RADAI-F5 change scores between baseline and 6 months. The MID value derived from the distribution approach was 1.16 over a 6-month period, indicating a medium-to-high degree of responsiveness for the RADAI-F5 (Hoque et al., 2021). While our previous validation work utilised a distribution-based approach to ascertain the MID of this instrument, the interpretability and clinical significance of change scores derived from an anchor-based approach have yet to be established. It is generally acknowledged that the anchor-based approach is important for estimating MID values, as they incorporate the patients' perspective. In light of this, the aim of the present study was to determine the MID of the RADAI-F5 using an anchor-based approach.

TABLE 22: METHODS FOR DETERMINING MID (ADAPTED FROM WELLS ET AL., 2001)

Indicator of Importance/Significance of Change	Type of Assessment	Data Level	Method Used to Determine Change	Minimum Important Change/Difference
Patient Perspective I	Change within (global ratings on change)	Surveyed patients	Patient global ratings on change in various domains of interest	Value of -3 to -1 or 1 to 3 on a 15-point scale
Patient Perspective II	Differences between (differences in patient conversation clinical outcome measures between patient groups based on subjective comparison ratings)	Patient conversation	Patient subjective comparison ratings	Differences in the mean of clinical outcome measures in which patients rated themselves as "somewhat better" and those that rated themselves as "about the same"
Clinical Perspective I	a. Differences between changes within	Consensus development (Delphi)	Clinician-examined differences between within-group change summary statistics	Minimum clinically important differences proposed by clinicians for a hypothetical randomised control trial comparing 2 treatments
Clinical Perspective I	b. Differences between end of study	Consensus development (Delphi)	Clinician-examined summary statistics compared at group level	Minimum clinically important differences proposed by clinicians for a hypothetical randomised control trial comparing 2 treatments
Clinician Perspective II	Changes within (patient scenario scoring)	Patient scenario	Clinicians indicate change in outcome measure needed before recommending it using both relative and absolute changes	Difference between the chosen option and the initial "average"

Clinician Perspective III	a. Differences between changes within (patient scenario)	Patient scenario	Clinicians contrast patients' change in outcome measure between adjacent scenarios	Minimum important difference determined using the difference in outcome measures for pairs rated "a little less" or "a little more"
Clinician Perspective III	b. Differences between (patient scenario)	Patient scenario	Clinicians contrast patients' outcome measure between adjacent scenarios	Minimum important difference determined using the difference in outcome measures for pairs rated "a little less" or "a little more"
Clinician Perspective IV	Changes within (prognostic rating scale)	Individual level (receiver operating characteristic analysis)	Patients given a prognostic rating by treating clinician on admission	Good or excellent prognosis used as an indicator of important improvement
Data Driven Approach	Changes within (SEM were longitudinal change scores)	Individual level	Standard error of measurement (defined as baseline SD $\times$ the square root of one minus Cronbach's alpha) considered a proxy for Minimal clinically important difference	Similar in magnitude to Jaeschke's approach using the same questionnaire
Discerning Important Improvement I	Changes within (improvement criteria)	Controlled randomised trials	Clinicians consider patient baseline and end of study data to discriminate efficacious intervention from placebo	Indicated by a "vast" majority
Discerning Important Improvement II	Changes within (achieving treatment goals)	Individual level (analysis)	Patients followed from admission to discharge from clinic	Best cut point for improvement in an individual patient determined using the best cut point to define an important improvement

5.2 Methods:

5.2.1 Study Design

This study is a retrospective longitudinal study using baseline and 3-month follow-up data. This study was conducted between November 2021 and March 2023.

5.2.2 Ethical approvals

This study was conducted in compliance with the principles of the 2008 Declaration of Helsinki and all participants provided written informed consent. Ethical and Health Research Authority (HRA) approval was obtained from the North East - Newcastle & North Tyneside 2 Research Ethics Committee (21/NE/0130) and the GCU Psychology, Social Work and Allied Health Sciences Ethics Subcommittee (HLS/PSWAHS/20/242).

5.2.3 Participants

The inclusion and exclusion criteria are detailed below.

Participants were included if they were/had:

- Age ≥18 years
- Cognitively aware to a level where they can provide informed consent and understand the instructions required for this study
- Physician-confirmed diagnosis of RA
- Commencing a new biologic therapy for the first time

    Participants were **excluded** if they had/ were:

- Severe hearing, and/or cognitive impairments/mental disorders that make participation not possible
- Unable to speak and comprehend English without assistance

5.2.4 Stakeholder involvement

The North West Clinical Effectiveness group, comprising of specialist podiatrists in rheumatology, played a crucial role in shaping the research aim for this study. Their valuable insights emphasised the need to consider the patient perspective when evaluating clinical treatment effectiveness. Their contribution was pivotal in steering the study towards a more patient-centred approach. They highlighted "The importance of MID to help demonstrate how various treatments such as steroid injections could improve foot disease activity."

To evaluate the MID of the RADAI-F5 using an anchor, it is necessary to incorporate individuals who have initiated a new therapeutic regimen. This approach enables the assessment of the instrument's responsiveness to temporal changes (Cook, 2008). RA patients who commenced new biologic therapy were recruited, a decision informed by discussions with rheumatologist stakeholders. Discussions with recruitment sites revealed that during the Covid-19 pandemic, a significant number of individuals obtaining appointments in rheumatology departments were commencing biologic therapy instead of DMARD therapy. As such, recruiting individuals initiating biologic therapy was considered optimal for meeting recruitment targets. Moreover, stakeholder discussions emphasised the importance of a 12-week follow-up period, aligning with the time needed to observe the effects of biologic drugs in this patient cohort.

5.2.5 Sample size

The selection of a sample size of 30 participants was guided by the recommendation of Hoggs, Tannis, and Zimmerman (2015) to achieve equal distribution across "small change" and "no change" groups. Nevertheless, practical limitations in participant recruitment, including limited escalations to biologic medications and reduced referrals during the Covid-19 pandemic, necessitated a sample size determined by practical considerations such as time, funding, and participant availability. Consultations with key stakeholders strongly influenced this decision. Stakeholders believed that, due to the pandemics impact on face-to-face appointments, extending recruitment would not significantly increase the sample size. This insight was crucial given the need to meet PhD timelines.

5.2.6 Recruitment

Participants for this longitudinal study were recruited through their referring clinicians from three NHS rheumatology outpatient clinics located in Greater Glasgow and Clyde and Lanarkshire, specifically Gartnavel General Hospital, Wishaw University Hospital, and Royal Alexandria Hospital. The procedure of recruitment is detailed in Section 4.3.7. For participants who did not participate in the FOOTRADIUS study, the referring rheumatologist disseminated both the initial and follow-up RADAI-F5 questionnaire, accompanied by a pre-addressed stamped envelope for convenient return.

5.2.7 Procedures

During the initial visit for the FOOTRADIUS study, participants were asked to provide demographic information and DAS28-ESR scores were collected by the rheumatologist and shared with primary investigator through e-mail. In cases where participants did not partake in the FOOTRADIUS study, the referring rheumatologist provided demographic data. All participants were invited to complete the RADAI-F5 at baseline. After three months, a text reminder was sent

to all participants to complete and return the RADAI-F5 questionnaire, which encompassed an additional question concerning their perception of change in foot disease status, as assessed on a 5-point patient global rating of change (GRC) scale.

5.2.8 Outcome Measures

Demographic and clinical data:

Demographic and clinical data, including age, sex, disease duration, and current biologic medication, were collected for all participants.

Clinical disease activity scoring:

The DAS-28-ESR was employed to assess disease activity in RA. Patients' DAS-28-ESR scores included assessments of TJC, SJC, ESR levels, and a PGA, which involved a single question: "How active do you consider your arthritis today?" with a response scale from 0 to 10. The referring rheumatologist electronically shared the participants' DAS28-ESR scores with the principal investigator (AH). As mentioned in the FOOTRADIUS study, the global pandemic hindered the availability of recent DAS28-ESR scores for all participants. Therefore, the most recent score that was accessible was provided, albeit solely for descriptive purposes.

Measures of foot disease activity:

The RADAI-F5 instrument (Appendix B) was employed to evaluate foot disease activity at baseline and 3 months. To ascertain the MID, summary scores of the instrument were utilised for analysis.

Anchor question

To evaluate the MID of the RADAI-F5, the patient's GRC was used as an external anchor (Landorf et al., 2010) to quantify improvement or deterioration in foot disease following the initiation of biologic therapy. The GRC question asked participants "With respect to your RA FOOT disease, how would you describe yourself now compared to the beginning of the study (3-months ago)?" The response options on a 5-point Likert scale ranged from "Much better" (+2) to "Much worse" (-2). Participants who indicated "Slightly better" (+1) or "Much better" (+2) scores were categorised as having "clinically important improvement", while those who selected the other response options (0, -1, and -2) were classified as "Not importantly improved."

5.2.9 Why a 5- point Likert scale?

The 5-point Likert scale, known for its good reproducibility and sensitivity to change, is commonly used to assess self-perceived clinical progress and to determine MID change scores (Mouelhi et

al., 2020; King, 2008). The use of the 5-point Likert scale in this study was advantageous as it provided a simple and efficient assessment method with minimal participant burden (Pouchot et al., 2008, Mouelhi et al., 2020).

5.2.10 Statistical analysis

Descriptive analyses of demographics and disease-related characteristics were summarised using means, SD and accompanying percentages for categorical variables. This was determined using SPSS version 28. Score distribution of the RADAI-F5 including baseline, follow-up and change scores were presented using mean and SD based upon the GRC scores. To calculate the MID value, the mean change in the RADAI-F5 score from baseline for all participants who indicated "no change" or "a small change" was determined. Subsequently, the mean change in outcome measures for participants who reported "a small change" was subtracted from the mean change for participants who reported "no change" (Figure 13). This method was adapted from Landorf and colleagues (2010). In order to evaluate the precision of the MID estimates, 95% CI were calculated.
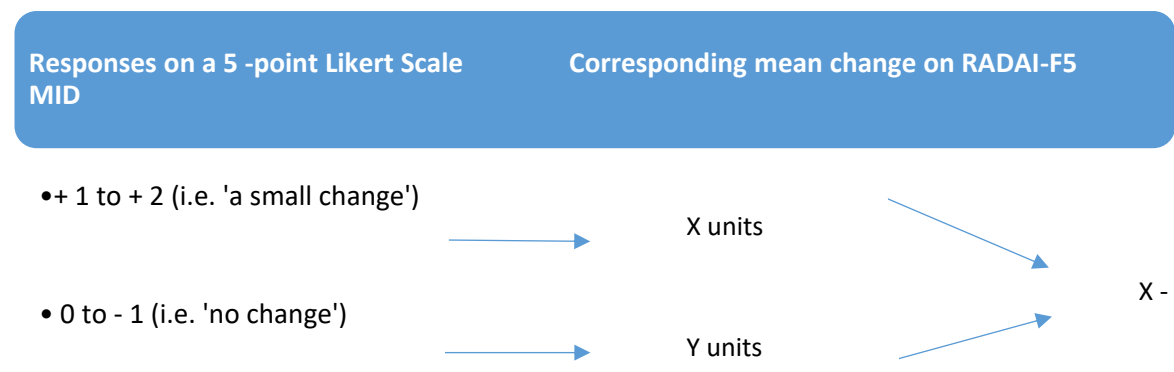
FIGURE 13: METHOD EMPLOYED TO CALCULATE THE MID OF THE RADAI-F5 USING THE ANCHOR-BASED APPROACH [ADAPTED FROM LANDORF ET AL, 2010]

The outcome data was checked to ensure that they satisfied the assumptions of normality. Variables that were found to have a non-normal distribution were evaluated for outliers using the empirical rule, defined as scores three SD away from the mean (Hayes, 2023). Participants identified as being outliers were excluded from the analysis to ensure the attainment of a normal distribution. Notably, one participant was identified as an outlier and consequently excluded from the calculation. Results including this outlier is included in Appendix M.

5.3 Results:

5.3.1 Descriptive characteristics

This embedded longitudinal study included 14 participants, with 10 (71.42%) being female. Their mean [±SD] age was 56.87 [±10.81] and mean [±SD] disease duration was 13.14 [±10.92] years.

Predominantly participants were recruited from Gartnavel General Hospital (n=10), followed by Wishaw General Hospital (n=4). No participants were recruited from Royal Alexandria Hospital. The mean DAS28-ESR score was 3.4 [±1.42], indicating moderate global disease activity. Participants categorised based off DAS-28-ESR scores were as follows: 0% in remission, 21.43% (n=3) with low disease activity, 35.71% (n=5) with moderate disease activity and 42.86% (n=6) with high disease activity. Four individuals were commencing on Adalimumab (Humira), six on Etanercept (Enbrel), two on rituximab (Rituxan), and two on Certolizumab (Cimzia). The mean RADAI-F5 scores at baseline and 3-months were 4.36 [±2.28] and 4.19 [±2.4], respectively, indicating moderate foot-related disease. Table 24 presents the demographic characteristics of these participants.

TABLE 23: DESCRIPTIVE DEMOGRAPHIC DATA

	Mean [±SD]
Age	56.87[±10.81]
Disease duration (years)	13.14[±10.92]
DAS-28	3.40[±1.42]
RADAIF5_0 *	4.36[±2.28]
RADAIF5_3 *	4.19[±2.4]
DAS-28: Disease activity score for 28 joints; RADAIF5_0: RADAI-F5 scores at baseline; RADAIF5_3: RADAI-F5 scores at 3-month follow-up	

Mean and SD of baseline, follow-up and change scores of the RADAI-F5 scores based upon the GRC are presented in Table 25. Overall, 5 (35.71%) participants reported deterioration [n= 1: Much worse; n= 4: slightly worse], 4 (28.57%) participants reported about the same score and 5 (35.71%) individuals reported improvement [n= 2: Much better; n= 3: slightly better], on the GRC.

TABLE 24: DESCRIPTIVE STATISTICS OF BASELINE, FOLLOW-UP, AND CHANGE SCORES OF THE RADAI-F5 BY RESPONSE CATEGORIES OF THE GLOBAL RATING OF CHANGE SCALE

Instrument	Baseline scores mean[±SD]	Follow-up scores mean[±SD]	Change scores mean [±SD]
RADAI-F5			
Much worse (n=1)	7.2 [±0]	10 [±0]	-2.8 [±0]
Slightly worse (n=4)	4.5 [±2.46]	4.4 [±2.29]	0.1 [±0.61]
No change (n=4)	3.78 [±1.95]	5.04 [±2.42]	-1.26 [±2.61]
Slightly better (n=3)	3.13 [±1.54]	2.09 [±1.48]	1.05 [±0.23]
Much better (n=2)	5.2 [±0.6]	4.2 [±1.2]	1 [±0.6]

The findings in Table 25 indicate that the average change scores for the "much worse" and "no change" groups were negative, signifying a deterioration in foot disease despite the initiation of biologic drugs. Conversely, the "slightly worse" and "much better" groups demonstrated positive change scores, reflecting improvements in foot disease during the follow-up evaluation. Notably, the "slightly better" group exhibited the most substantial improvement with a change score of 1.05. However, it is worth noting that the SD values for each group indicated a considerable level of heterogeneity in individual responses.

5.3.2 MID Results

The MID value of the anchor-based approach for the RADAI-F5 is presented in Table 26. The calculated MID for the RADAI-F5 was 1.02 (95% CI: 0.45 - 1.42).

TABLE 25 : ANCHOR BASED CALCULATIONS FOR MID OF THE RADAI-F5

Outcome	0 to -1	+1 to +2	MID value	95% CI
RADAI-F5	0.01	1.03	1.02	0.45 to 1.42

5.4. Discussion:

This study is the first to establish the MID value for the RADAI-F5 tool, using an anchor-based approach. Establishing the anchor-based MID holds importance in evaluating treatment effectiveness of foot interventions within this specific patient population. Additionally, this knowledge holds promise to facilitate shared clinical decision-making by providing preliminary guidance on when changes in management may be warranted (Rai et al., 2015). A comprehensive understanding of the MID of the RADAI-F5 may facilitate the implementation of effective treatment interventions during the therapeutic 'window of opportunity'. For example, if there were an improvement of at least 1.02 points in a patient's RADAI-F5 score, this would suggest that the current intervention exhibits a beneficial effect on foot disease. Conversely, if the RADAI-F5 score worsens or fails to improve by at least 1.02 points, it suggests the potential ineffectiveness of the prescribed treatment, necessitating the consideration of alternative treatment options. As such, clinicians can effectively determine whether patients have attained or not attained substantial clinical improvement using this MID value. Consequently, health care providers can facilitate prompt referrals to rheumatologists or for further imaging, thus providing a more comprehensive approach to patient care, rather than solely relying on predefined RADAI-F5 disease category thresholds.

Our prior validation study using a distribution method yielded a MID score of 1.16 (Hoque et al., 2021). The slight disparity between the distribution and anchor-based scores arises primarily from differences in the methodologies employed. Distribution-based scores relied on statistical analysis of the score distribution in a substantial RA patient cohort (n=150), assuming a normal distribution and a uniform MID for all patients. In contrast, the anchor-based method was based on patients' personal perceptions of a meaningful change by only 14 participants. Therefore, the variation in scores can be attributed to differences in underlying assumptions and statistical methods employed (Mouelhi et al., 2020), and the sample size of each study. Nonetheless, both provide valuable in assisting the interpretability of the tool. However, it is crucial to consider the small sample size in this study and its potential limitation in generalising the findings to the broader RA population.

Differentiating between group-level and individual-level differences is essential when considering the MID in PROM research. While group-level MID values provides a useful measure for evaluating interventions at a population level, it may not accurately reflect meaningful changes for individual patients (Hays & Peipert, 2021). Individual-level differences, on the other hand, capture changes within a single patient and often involve smaller MID values. To provide further insight into the MID of the RADAI-F5, it is important to differentiate between group-level and individual-level changes. In a hypothetical scenario of a randomised controlled trial (RCT) with 100 participants diagnosed with RA, randomly assigned to receive either Cimzia or a placebo, and baseline measurements of foot disease activity assessed using the RADAI-F5, comparing the post-intervention RADAI-F5 scores to baseline scores after a 12-week intervention period could reveal valuable insights into the efficacy of Cimzia as a treatment modality for RA-related foot disease. If the statistical analysis demonstrates a significant reduction in RADAI-F5 scores among the participants receiving Cimzia, exceeding the MID, while the placebo group exhibits no significant change, these group-level findings would provide valuable insights into the broader effectiveness of Cimzia as a treatment modality for RA-related foot disease.

Nevertheless, it is important to note that group-level analysis may not capture individual meaningful changes. The MID is a measurement property influenced by various factors such as a person's starting score, external factors, and psychological well-being (Franceschini et al., 2023). Furthermore, the diverse methods used for calculating MID result in highly heterogeneous values, significantly impacting the percentage of patients achieving MID in a given population. The considerable variability in thresholds obtained through different methodologies raises challenges in assessing the true effectiveness of a given treatment, casting doubt on the practical utility of MID in clinical research (Franceschini et al., 2023; Revicki et al., 2008). Moreover, as highlighted by Revicki et al. (2008), the notion of MID is not a fixed characteristic but may vary by population and context. To enhance the robustness of RADAI-F5 MID estimates, future efforts should involve

employing multiple approaches and triangulation of methods. Establishing what constitutes a small but meaningful change in foot disease activity should further be informed through focus group discussions with both RA patients and clinicians managing the RA foot, thereby contributing to a more nuanced understanding of this measurement property. Future research should investigate these alternative approaches to determining the MID and compare the efficacy of different interventions at both the group and individual level (Dettori et al., 2022; Hays & Peipert, 2021). A thorough understanding of these distinctions could enhance the utilisation of the RADAI-F5 in routine care settings.

5.5 Strengths and Limitations

This study has several notable strengths. The primary strength lies in its originality as the first study to establish the MID value for the RADAI-F5 tool, incorporating the patients view. This contribution holds promise for guiding clinical decision-making, understanding treatment effectiveness, and enabling timely interventions within the 'window of opportunity' for RA individuals with foot disease. However, there are limitations to acknowledge. The sample size for both the "no change" and "small change" groups was relatively small, consisting of 8 and 5 participants, respectively. This limited number of participants in each group underscores the difficulty in reaching robust and widely applicable conclusions, while also introducing a potential risk of Type 2 errors. Consequently, caution is advised in extrapolating the study's outcomes to the larger context of individuals with RA and future studies with a larger sample size are required for greater confidence in the MID value. Nonetheless, the notable proximity between the anchor-based and distribution-based MID scores (1.02 and 1.16) suggests a degree of consistency, despite the small sample size in this study.

Furthermore, it is noteworthy that the study cohort consisted of patients displaying moderate levels of foot disease activity. As a result, the MID value for RADAI-F5 in the RA population across high and low foot disease categories, including asymptomatic cases, may not be adequately represented. Additionally, the data used in this study only evaluated biologic medication escalation in three tertiary rheumatology centres in Scotland, potentially limiting the generalisability of these RADAI-F5 MID values on an international scale or to conservative treatments and DMARDs. Ideally, future research using a larger sample size should investigate MID values for the RADAI-F5 across a range of treatments and foot disease categories.

5.6: Conclusion

The present study helps establish the MID value for the RADAI-F5 using the patient perspective. The distribution and anchor-based MID values serve as preliminary benchmarks for evaluating meaningful changes in foot disease activity, aiding in the interpretability of the RADAI-F5 scores.

These MID values serve as an initial reference for healthcare providers, potentially aiding in clinical decision-making and patient-centered evaluations of interventions for managing foot disease in RA. Additionally, these MID values hold promise in contributingto a deeper understanding of the disease categories defined by RADAI-F5, potentially enabling more precise and tailored management strategies. Nonetheless, it is important to note the study's limitations, including the small sample size, when considering these findings.

Chapter 6. Tibiotalar and subtalar involvement in the RADAI-F5

To address the lack of a standardised approach for assessing the ankle in RA, this chapter explores the RADAI-F5's ability to measure TTJ and STJ disease. These findings emphasise the potential of integrating the RADAI-F5 into clinical practice to enhance the accuracy of detecting RA ankle and subtalar disease, thereby improving foot disease management and treatment outcomes in these structures.

6.1 Background:

The tibiotalar complex plays an essential role in providing stability and support during daily movement (Snedeker & Wirth, 2012). According to a study by Kiely and Lloyd (2021), the prevalence of tibiotalar pain in the early stages of RA is estimated to be 17%, and rises to 52% in patients with established disease. Although TTJ involvement is more prevalent in this patient population, studies have suggested that STJ involvement can also occur in up to 10-32% of individuals (Krähenbühl et al., 2019). Notably, STJ disease is often observed before changes in the TTJ, indicating that changes in the subtalar may represent an early manifestation of RA-related joint damage (Wakabayashi et al., 2022). Furthermore, untreated inflammation of the STJ in RA can lead to joint deformity, increased stress on the posterior tibial tendon, tibiotalar tenosynovitis, and subsequent collapse of the medial longitudinal arch (Zhang et al., 2021). This can result in limited range of motion, and impaired gait, leading to functional limitations, reduced mobility, and loss of independence (Rao et al., 2012; Noguchi et al., 2021). Consequently, physical and social activities, including work-related tasks, become restricted, contributing to a decline in mental health characterised by symptoms such as depression and anxiety (Gikaro, Xiong &Lin, 2022).

Clinicians consider the ankle and STJ to be essential components in facilitating healthy foot function and mobility (Sammarco, 2012). These joints enable various movements of the foot, and they transmit forces that provide stability during weight-bearing activities, while contributing to normal gait function. Muscles and tendons surrounding the ankle are conventionally regarded as the primary generators of mechanical power during human gait (Zelik & Honert, 2018). Therefore, when evaluating and treating foot-related conditions, it is imperative to assess and address any issues pertaining to the ankle and STJ due to their interconnected anatomy to the mid and forefoot.

The evaluation of the ankle holds considerable significance in RA due to its frequent involvement in the disease process (Kiely & Lloyd, 2021). The DAS-28 has been subject to criticism due to its failure to incorporate the ankle and hindfoot in assessing disease activity, resulting in an inability to identify tibiotalar and subtalar synovitis adequately (Thomson, 2009; Inamo et al., 2019). Furthermore, existing methods for assessing the ankle and subtalar in rheumatology MDT clinics

encompass approaches, including clinical examinations, imaging techniques, and PROMs (Abdelzaher et al., 2022). However, clinical examination of the hindfoot, including the TTJ and STJ is often fragmented, leading to the potential oversight and mismanagement of active disease in this region. Several factors may contribute to these challenges. Firstly, the intricate anatomical complexity of the ankle and STJ, characterised by multiple bones, ligaments, and tendons, presents difficulties in isolating and evaluating adjacent structures accurately. Secondly, the minimal presence of inflammatory tissue in certain regions, particularly those prone to osteophyte formation, further complicates the detection of pathological changes (Wakabayashi et al., 2022). Lastly, the deep-seated location of the STJ within the foot poses challenges in its evaluation compared to the more accessible TTJ (Abdelzeher et al., 2022). Consequently, the STJ is often overlooked in favour of the TTJ, potentially resulting in missed diagnoses and inadequate management of this structure (Pereira et al., 2021).

Furthermore, it can be argued that this limitation can also extend to clinical practice, where podiatrists may have limited expertise in identifying synovitis in the hindfoot, without imaging modalities. Common clinical assessments used in podiatry to evaluate the ankle include examinations of joint swelling and tenderness, anterior drawer tests, gait observations, assessments of lower limb alignment, and specific tests such as the Ottawa Ankle Rules, Knee-to-Wall Test, and Balance Tests (Alazzawi et al., 2017). However, these assessments, along with static observations using semi-quantitative scoring methods like the Foot Posture Index (FPI), have limitations in effectively capturing inflammatory changes associated with RA. Additionally, X-rays may not adequately capture soft tissue involvement or the specific inflammatory characteristics associated with RA.

Additionally, the weight-bearing nature of the tibiotalar and subtalar presents challenges in distinguishing between structural changes induced by RA and those resulting from normal weight-bearing stresses (Abdelzaher et al., 2022). Although MSUS has shown comparability with MRI in assessing the ankle (Bruyn et al., 2018), it has limitations in evaluating the anteromedial and posteromedial aspects of the STJ (Serban et al., 2020). Furthermore, the assessment of joint erosions at the STJ using MSUS is challenging due to the depth of the structure. Moreover, the widespread adoption of MSUS as a routine imaging modality for assessing these structures in podiatry settings is often impeded by restricted accessibility and a shortage of podiatrists trained in this imaging modality. This underscores the necessity for the development of a reliable, feasible, and valid outcome measure that has the ability to assess RA disease in the tibiotalar and subtalar regions. Such an assessment tool should be accessible to all members of the MDT without requiring specialised training in advanced imaging technologies.

In Chapter 2, section 2.5.2 (Table 4 & 5), a comprehensive overview of various RA PROMs for foot-related outcomes was presented. It was observed that certain PROMs explicitly address the ankle in their titles and instructions, reflecting an understanding of the distinct nature of ankle-related issues and the need to capture ankle complaints in foot-related outcomes. Examples of such PROMs include the Foot and Ankle Outcome Score (FAOS), the Foot and Ankle Ability Measure (FAAM), and the Self-Reported Foot and Ankle Score (SEFAS). This acknowledgment provides confidence that these measures encompass the ankle, allowing healthcare professionals to better evaluate the specific impact of ankle issues on patients' QoL and function. It also offers patients more clarity regarding the inclusion of these joints when completing PROMs. Conversely, foot-related PROMs specifically designed for RA, such as the FFI and the FIS do not explicitly mention the ankle in their titles or instructions. This raises concerns regarding the extent to which individuals with RA consider their ankle joint while completing these PROMs. It is important to recognise that patients may have varying perspectives on whether the ankle and STJ should be considered part of the foot complex. These perspectives can be influenced by their knowledge, personal experiences, and contextual factors (McKeon & Hoch, 2019). Some individuals, particularly those who have experienced foot-related issues, may view the ankle and STJ as integral parts of the foot. Conversely, other patients may consider the ankle and STJ as separate entities from the foot. Given the significant prevalence of ankle and STJ disease in RA, further investigation is warranted regarding whether patients consider these regions when completing the RADAI-F5. To address this knowledge gap, this study aims to determine whether the RADAI-F5 questionnaire adequately captures disease activity in the tibiotalar and subtalar joints.

6.1.2: Stakeholder involvement:

Stakeholder engagement, particularly with rheumatologists, highlighted concerns about the clarity of instructions in the RADAI-F5 questionnaire, specifically regarding the inclusion of the ankle. These concerns revolve around the questionnaire's effectiveness in accurately capturing active disease in the ankle region. The instruction to "THINK ONLY OF YOUR FEET" may introduce ambiguity for RA patients who perceive the TTJ and STJ as distinct from their feet. This ambiguity poses a threat to the precision of disease activity thresholds and could lead to under-referral or suboptimal treatment if patients fail to recognize the ankle's significance when completing the RADAI-F5 questionnaire. As such, addressing this knowledge gap is crucial to determining whether the RADAI-F5 captures disease at the TTJ and STJ disease in RA patients.

6.2 Methods:

The data utilised in this study was obtained from the FOOTRADIUS study (Chapter 4), which was a cross-sectional observational study conducted from November 2021 to November 2022. Section 4.3 of this thesis provides a comprehensive overview of the study protocol and participant criteria.

6.2.1 Measurements

<u>Demographic information:</u>

Relevant demographic and clinical information, such as age, sex and duration of disease were recorded.

<u>Foot disease activity:</u>

Foot disease activity was evaluated using the RADAI-F5 and scored by calculating an average summary score from the five items (Appendix B) (Hoque et al., 2021). *Foot disease remission state* was defined as a RADAI-F5 score of ≤1.4, while foot disease categories for mild, moderate, and high disease activity, were defined as >1.4 to ≤ 3.45, >3.45 to ≤5.7, and >5.7, respectively (Hoque et al., 2023a).

<u>MSUS:</u>

To detect foot disease at the TTJ and STJ, MSUS was employed. This assessment involved scanning and grading GS SH in 16 regions of each foot, including the TTJ, STJ, TNJ and MTPJs 2-5 and soft tissue sites (tibialis posterior tendon). The scanning protocol details can be found in Section 4.3.9. The TTJ was scanned from transverse and longitudinal views at the anterior, medial and lateral aspect. The STJ was imaged from inferior to the medial aspect of the TTJ and the sinus tarsi on the lateral scan. Grading for each region was performed using a semi-quantitative scale of 0–3 for GS SH (Table 27) (Figure 5). In six participants, the STJ could not be adequately visualised from both the medial and lateral aspects. As a result, these participants were excluded from the final STJ analysis.

The exclusion of PD signals and the inclusion of SH in the multiple regression analysis aligns with previous research findings. Prior studies have demonstrated that joints exhibiting SH but lacking Doppler activity still show considerable improvements during treatment, regardless of the SH grade (Terslev et al., 2018). Hence, it is essential to consider joints with SH when evaluating disease activity using MSUS, a recommendation also endorsed by the OMERACT group (Bruyn et al., 2019). This targeted approach allows for a comprehensive investigation of the correlation between the RADAI-F5 and disease activity in the TTJ and STJ.

TABLE 26: METHODS OF SCORING PATHOLOGY ON MSUS

Pathology	Definition	Scoring
Synovial hypertrophy (D'Agostino et al., 2017)	Abnormal hypoechoic, poorly compressible and non-displaceable intra-articular tissue that may exhibit Power Doppler signal.	**Score 0:** No hypertrophy independent of presence of effusion **Score 1:** Minimal hypertrophy with or without effusion up to level of horizontal line connecting bone surfaces **Score 2:** Moderate hypertrophy with or without effusion extending beyond joint line but with upper surface concave or hypertrophy extending beyond joint line but with upper surface flat. **Score 3**: Severe hypertrophy with or without effusion extending beyond joint line but with upper surface convex

6.2.2 Statistical analysis:

Data from paper questionnaires were transferred to Microsoft Excel for data cleaning prior to analysis. Data cleaning encompassed transferring paper-based data to an Excel spreadsheet, conducting multiple reviews for accuracy, identifying missing data and employing listwise pair deletion in SPSS for validation. All statistical tests were conducted using IMB SPSS version 28 with a two-sided significance level of 5%. Descriptive statistics, including mean (SD), median, IQR and percentages were used to summarise demographic and clinical data.

The scoring of SH at each anatomical structure, graded on a scale of 0-6, presented challenges as it deviated from the assumption of linear regression. This deviation arises from the complexity of the scoring system, particularly when aggregating SH scores from individual ankles. For instance, a scenario where one ankle exhibits a grade 1 score while the other presents a grade 2 score would yield a cumulative score of grade 3. Such an aggregate score may inaccurately reflect a severity of SH, exceeding the participant's actual presentation. Therefore, if participants had a SH score of ≥ 2 in one or more joints, they were assigned a value of 1. Conversely, if they had a SH score of ≤ 1 in both joints, they were assigned a value of 0.

Multivariable linear regression analyses were conducted to examine the association between RADAI-F5 (dependent variable) and SH scores in the TTJ and STJ joints as the main covariates of interest. Selection of variables for the final models involved visually examining bar charts to assess the relationship between TTJ or STJ and each scanned structure. Descriptive statistics were calculated for each joint to guide model inclusion. Considering the normal distribution of the data, individual t-tests were employed to compare means across different groups, identifying significant contributors to RADAI-F5 scores. Bivariate analyses were conducted for each joint variable, with variables ≤ 0.05 p-value considered statistically significant (Muhlbache &Piringe, 2013). Unstandardized B values within the 10% interval were also included.

Model selection techniques, including forward stepwise regression, were employed to refine the final multivariable model. The inclusion or exclusion of variables in the final TTJ and STJ models was determined through an iterative procedure, adding or removing variables based on their individual contribution to the model's predictive power while considering alpha levels (Chowdhury & Turin, 2020). This stepwise approach, illustrated in Figure 14, ensured a rigourous and data-driven selection of variables.

Step 1: Initial regression analysis

Linear regression analysis of tibiotalar * and RADAI-F5 scores provides a Unstandardised B value

Step 2: Individual regression analysis

Conduct separate linear regression analyses with the RADAI-F5 as the dependent variable and the following as covariates and variables of interest:

- Tibiotalar* +Metatarsophalangeal joint 2*
- Tibiotalar* + Metatarsophalangeal joint 3*
- Tibiotalar* + Metatarsophalangeal joint 4*
- Tibiotalar* + Metatarsophalangeal joint 5*
- Tibiotalar* + Talonavicular joint*
- Tibiotalar* + Subtalar Joint*
- Tibiotalar* + Tibialis posterior tendon*

Step 3: Variable selection criterion

Is the difference in Unstandardised B values from each individual regression analysis in Step 2 ≤ 10% compared to the Unstandardized B in Step 1?

YES

NO

Include variables in final model with RADAI-F5 and tibiotalar*

Exclude variables from final model with RADAI-F5 and tibiotalar*

Key: *dichotomised scores

FIGURE 14: COMPREHENSIVE OVERVIEW OF MULTIVARIABLE REGRESSION ANALYSIS

6.3 Results:

60 participants, of which 80% were female with a mean age of 62.4 years (IQR 50–62) and median disease duration of 120 months, participated in the FOOTRADIUS study. Among the RADAI-F5 foot disease categories, 10% of participants were classified as being in remission, 35% exhibited low foot disease activity, 18% demonstrated moderate foot disease activity, and 37% displayed high foot disease activity. Participants typically presented with moderate self-reported foot-related disease according to the RADAI-F5 (mean=4.39). More information on the participant's demographic can be found in Table 15.

Based on the dichotomised TTJ SH variable, 28 participants (46.6 %) had at least one TTJ with a SH score of ≥2, while 32 (53.3%) of participants were assigned a value of 0, indicating they had both TTJ with a SH score of ≤1. Based on the dichotomised STJ SH variable, 16 (29.6%) participants had at least one STJ with a SH score of ≥2, and 3 (5.56%) participants had both STJ with a SH score of ≤1. 6.67% and 20% of individuals had ≥grade 1 PD at the STJ and TTJ, respectively (Table 16).

The TTJ model incorporated various predictor variables, specifically foot disease affecting the 2 and 5th MTPJ, STJ, and the tibialis posterior tendon. The SSJ model incorporated the TTJ and the tibialis posterior tendon as predictor variables. The results of the linear regression analysis demonstrated a significant association between the presence of active arthritis, indicated by SH≥2 at the TTJ or STJ, and higher RADAI-F5 scores, even after controlling for foot disease at other aforementioned MSUS scanned sites. More specifically, the TTJ SH scores, dichotomised as either 0 or 1, were significantly associated with higher RADAI-F5 scores (B=1.33, p=0.04) (Table 28), after adjusting for other foot joint covariates. Similarly, STJ SH scores, dichotomised as either ≥2 or ≤1, were also significantly associated with higher RADAI-F5 scores (B=2.47, p=0.00) (Table 29).

TABLE 27: TIBIOTALAR REGRESSION MODEL AS COVARIATES FOR RADAI-F5 (N=60)

Variable of interest + covariates	Unstandardised B	p-value	95% CI for B
Constant	1.69	0.01	0.50 - 2.87
TTJ_SH_dich	1.33	0.04	0.04 - 2.60
MTPJ_2_SH_dich	1.42	0.04	0.08 - 2.76
MTPJ_5_SH_dich	1.50	0.16	-0.63 - 3.61
STJ_SH_dich	2.14	0.00	0.84 - 3.44
tibpost_SH_dich	0.38	0.54	-0.87 - 1.63

Ankle_SH_dich: Ankle synovial hypertrophy scores dichotomised, MTPJ_2_SH_dich: 2nd Metatarsophalangeal joint synovial hypertrophy scores dichotomised, MTPJ_5_SH_dich: 5th Metatarsophalangeal joint synovial hypertrophy scores dichotomised, RADAI-F5: Rheumatoid Arthritis Foot Disease Activity Index, STJ_SH_dich: Subtalar joint synovial hypertrophy scores dichotomised values, TTJ: Tibiotalar joint synovial hypertrophy scores dichotomised, tibpost_SH_dich: Tibialis posterior tendon (at all 3 regions) synovial hypertrophy scores dichotomised..

Variable of interest + covariates	Unstandardised Coefficients (B)	p-value	95% CI for B
Constant	2.57	0.00	1.68-3.45
STJ_SH_dich	2.47	0.00	1.16 - 3.78
TTJ_SH_dich	1.87	0.00	0.63 - 3.10
tibpost_SH_dich	0.28	0.66	-0.98 - 1.54

RADAI-F5: Rheumatoid Arthritis Foot Disease Activity Index, STJ_SH_dich: Subtalar joint synovial hypertrophy scores dichotomised values, TTJ: Tibiotalar joint synovial hypertrophy scores dichotomised, tibpost_SH_dich: Tibialis posterior tendon (at all 3 regions) synovial hypertrophy scores dichotomised..

6.4 Discussion:

This study reveals a significant association between foot disease activity at the hindfoot and the RADAI-F5, as indicated by increases of 2.47 and 1.33 in RADAI-F5 scores if SH is present at the STJ and TTJ, respectively. After adjusting for active arthritis at other foot sites, the findings demonstrate a significant and independent association between the TTJ and STJ and elevated RADAI-F5 scores. This finding provides initial evidence of the tools ability to evaluate disease activity at the TTJ and STJ. Hence, the absence of specific instructions for patients, emphasising the inclusion of the ankle in other foot PROMs or clinical assessments may result in incomplete understanding of an individual's overall foot symptoms, potentially leading to missed opportunities for appropriate treatment.

Symptoms and disease in the STJ often communicates with the TTJ, making it difficult to isolate and diagnose (Gorbachova et al., 2021). Despite the prevalence of STJ disease in patients with RA, clinicians face challenges when evaluating the involvement of this joint in RA. The physical examination of the STJ is limited to assessing range of motion and determining presence of tenderness, which may not suffice for detecting early disease progression (Belt et al., 2001). Moreover, clinicians who lack specialised training in assessing the foot may encounter challenges in effectively isolating the STJ from the ankle joint when assessing for disease activity. Conventional radiography, although widely available and cost-effective, has limited value in evaluating and monitoring STJ disease due to delayed detection of bone erosions and its inability to detect synovitis (Wakefield et al., 2000; Anari et al., 2019). In contrast, MRI offers a more comprehensive evaluation of the STJ, providing information on synovitis, bone structure, and cartilage composition (Acanfora et al., 2020). However, this imaging modality can be expensive and poses logistical challenges such as time constraints and limited accessibility in rheumatology care settings (Lento & Primack, 2008). The acknowledgment that RADAI-F5 measures disease

activity in the STJ and TTJ raises the prospect of identifying potentially at-risk patients. This could potentially facilitate timely treatments or referrals for additional imaging, allowing for early intervention and potentially contributing to favorable radiological and functional outcomes.

According to Mann and Coughlin (1992) and Belt et al. (2001), the majority of alterations observed in the ankle region can be attributed to the mechanical strains arising from atypical alignment of the STJ. Therefore, it is crucial to consider both the ankle and STJ when evaluating foot disease activity and pathology. Interestingly, the association between disease severity and RADAI-F5 scores appears to be stronger for the STJ, which raises questions surrounding the underlying mechanisms contributing to this phenomenon. It suggests that there may be unique factors or pathophysiological processes specific to the STJ that contribute to the perceived severity of foot disease. Nevertheless, there are doubts regarding patients' proficiency in differentiating between the STJ and the ankle joint and accurately localising the presence of RA disease. Employing foot anatomy models as an educational tool may facilitate better understanding regarding if patients can distinguishing between the STJ and ankle joint. Further investigation is warranted to explore the potential anatomical, biomechanical, or functional factors that may contribute to this observed association and to deepen our understanding of the complex relationship between foot disease severity and the subtalar joint.

The stronger correlation observed between the RADAI-F5 and STJ disease may be attributed to various factors such as anatomical variations, biomechanical considerations, or distinct inflammatory processes specific to the STJ. It is plausible that alterations in STJ biomechanics resulting from abnormal alignment or pathological conditions could influence the load distribution and mechanics of the TTJ (Klenerman, 1995), potentially leading to a higher disease burden and symptomatology in the STJ. Due to its unique anatomical composition and heightened susceptibility to physiological strain, the STJ might be more susceptible to early disease compared to the ankle joint. The distinctive structure and function of the STJ have a significant impact on an individual's quality of life (Krähenbühl et al., 2017; Krähenbühl et al., 2019), potentially causing patients to perceive pathology in this joint as more severe. Therefore, an effective diagnosis and management approach for STJ and RA-related disease are crucial. The use of RADAI-F5, complemented with MSUS imaging, particularly during the critical "window of opportunity," can facilitate proactive management strategies to minimise further damage to these structures and inform ankle management strategies more effectively.

In the FOOTRADIUS study, the TTJ commonly exhibited a prevalence of MSUS-detected pathology at 63.3%, while the STJ presented with 30% MSUS-detected pathology which aligns with previous research (Enache et al., 2019; Alsuwaidi et al., 2016; Abdelzaher et al., 2022). Nonetheless, these joints also demonstrated a low frequency of positive PD signals (6.67% for STJ

and 20% for TTJ), consistent with previous studies (Gutierrez et al., 2016; Suzuki, 2014). The limited sensitivity of PD in larger joints and deep anatomical regions may account for this observation (Abdelzaher et al., 2022). To enhance PD sensitivity, scanning of the medial and lateral aspects of the TTJ and all three facets of the STJ is recommended (Abdelzaher et al., 2022). Nevertheless, it is imperative to acknowledge that accessing the STJ from the posterior aspect poses significant challenges due to the presence of other soft tissue structures in that region, making visualisation of this facet difficult. Therefore, utilising MRI as an imaging modality may offer enhanced accuracy in detecting disease within this facet of the STJ.

The study findings indicate a potential association between concurrent TTJ and STJ disease. It is noteworthy to acknowledge that among the 54 individuals who had their STJ scanned using MSUS, 15 (27.8%) individuals presented with concurrent TTJ and STJ disease, which potentially lends support to the notion that STJ disease can exert an influence on ankle pathology (Wakabayashi et al., 2022) and vice versa. Coexisting ankle joint and STJ disease may contribute to elevated RADAI-F5 scores compared to isolated ankle or STJ disease, reflecting the cumulative impact of multiple affected foot joints on disease burden and symptomatology. However, the existing literature lacks quantitative assessment of this phenomenon. Definitive conclusions should be approached cautiously, as the sequential manifestation of disease between the TTJ and STJ cannot be conclusively determined through MSUS alone. Nevertheless, accurately quantifying concurrent TTJ and STJ disease could provide valuable insights into the interplay between different foot joint involvements and their contributions to overall foot disease activity. Furthermore, incorporating additional outcome measures such as patient-reported pain levels, functional limitations, and quality of life assessments alongside the RADAI-F5 in future studies would facilitate a comprehensive evaluation of the broader impact of RA ankle and STJ disease activity on patients' foot function and QoL.

6.5 Strengths and limitations

During the course of this doctoral journey, the initial objective of this study was to evaluate the efficacy of infrared thermography (IRT) in detecting foot disease within the RA population. This interest was substantiated by recent research on the RA foot suggesting promise regarding the utility of IRT in discerning joint inflammation in RA compared to healthy controls (Schiavon et al., 2021; Gatt et al., 2020; Kow & Tan, 2023). The appeal of thermal imaging, recognised for its cost-effectiveness, easy accessiability and non-invasive attributes, offers an objective measure of joint surface temperature in the assessment of RA-related inflammation (Kow & Tan, 2023). Despite the growing body of literature on thermography in RA, a gap exists in the literature concerning the potential application of IRT for assessing active foot disease among RA patients and distinguishing between different levels of foot disease severity.

The initial thesis design encompassed a study on the evaluation of the construct validity of IRT against the RADAI-F5. An additional aim included establishing the construct validity of IRT in relation to MSUS-detected synovitis. Unfortunately, following an intensive 8-month period dedicated to data collection, a glitch within the IRT imaging software occurred in February 2023, resulting in the unintended deletion of all accumulated data. The unexpected technical failure during the course of this doctoral journey significantly altered the trajectory of the research, prompting a re-evaluation of the studies outlined in the initial thesis design. While the retrieval of lost data was deemed unfeasible at this stage due to ethical and timeline constraints, the setback became an opportunity to recalibrate and refocus the research objectives. Stakeholder discussions played a crucial role in reshaping the research trajectory. The ensuing focus shifted towards an evaluation of the RADAI-F5, particularly its inclusion of the ankle joint. These discussions not only mitigated challenges in the research process but also contributed essential insights that informed the content of this particular chapter in the thesis.

Nevertheless, this study has notable strengths, including its ability to quantify a significant association between foot arthritis at the TTJ and STJ, and higher foot disease scores. Additionally, this study shows promise of the RADAI-F5 being able to evaluate disease activity at the TTJ and STJ. However, several limitations should be acknowledged. It is important to recognise that this study only considered joint disease at the STJ and TTJ, excluding tendons such as the anterior tibial tendons and ligaments. These soft-tissue structures could have potentially displayed synovitis or tenosynovitis and influenced patients' evaluation of their overall foot disease. Additionally, challenges arose from using MSUS to scan the STJ, particularly in participants with oedema, leading to the exclusion of six participants and potential limitations in capturing adequate STJ data. As such, future research should explore alternative diagnostic tools such as MRI to better evaluate the impact of STJ disease in RA.

A major limitation is that given that RADAI-F5 is a PROM, the significance of incorporating patient perspectives cannot be overstated. Patient perception is pivotal in evaluating the efficacy of the tool in assessing disease activity at the TTJ and STJ. A data-driven approach, while promising, may not capture the nuanced experiences and priorities of individuals undergoing assessment. This challenge in incorporating patient perspectives stems from the loss of infrared thermography data, coupled with resource and time constraints hindering the collection of primary data. Therefore, to definitively establish the inclusion of the ankle joint complex in the RADAI-F5, incorporating an additional question or foot diagram specifically addressing the patients ability to locate disease in these structures may have been advantageous. Moreover, the inclusion of a qualitative focus group discussion, comprising a subgroup of RA participants, could have provided additional insights into the rationale behind individuals' varying perspectives on whether the ankle

is included the RADAI-F5. This would have increased clarity in determining whether patients incorporate these joints when completing the RADAI-F5, and thus the tools ability to assess disease at the hindfoot.

6.6 Conclusion

The relationship between TTJ and STJ disease and self-reported foot disease activity, assessed using the RADI-F5, has not been previously quantified in the RA population. The results highlight that concomitant TTJ and STJ disease, detected using MSUS, may lead to elevated RADAI-F5 scores. However, a notable limitation in this study is the absence of patient perception regarding whether they consider the ankle or STJ when self-reporting foot disease on the RADAI-F5. Addressing this limitation through future research integrating patient feedback is crucial for a comprehensive understanding of the RADAI-F5's ability to capture disease activity at the hindfoot.

Chapter 7. Predictive validity of RADAI-F5 in assessing foot-related disability

This chapter aims to assess the predictive validity of the RADAI-F5 in evaluating foot-related disability in an early RA cohort. This evaluation is based on data obtained from the Foot Orthoses-Customised vs Off-the-shelf in Rheumatoid Arthritis (FOCUS) RA trial. This study's findings offers preliminary evidence supporting the predictive validity of the RADAI-F5, potentially helping clinicians in identifying patients at risk of self-reported foot-related disability. This knowledge can aid in implementing appropriate interventions to prevent or delay the onset of such disability.

7.1 Background:

Extensive research consistently demonstrates that foot symptoms have a substantial impact on disability and functional limitations in individuals with RA (Wilson et al., 2017; Rutkowski et al., 2022; Stolt et al., 2021; Rojas-Villarraga et al., 2009). In the early stages of RA, foot inflammation can cause pain and subsequent complications, contributing to foot disability and impairment. A longitudinal study conducted by Hooper et al., (2012) demonstrated a high prevalence of foot-related disability among patients with RA, with the cohort consistently reported moderate to severe foot impairment in 75-82% of cases at baseline, one-year follow-up, and three-year follow-up using the FIS. Bergström et al., (2017) further established that foot impairments and disabilities significantly impact mobility and daily activities in individuals diagnosed with RA. Thus, it is crucial to promptly and accurately assess foot symptoms and implement appropriate interventions to optimise foot function in this patient population. Despite advancements in pharmacological disease management, patients continue to report disability associated with foot problems (Rojas-Villarraga et al., 2009). These foot impairments result in significant limitations in performing essential daily activities such as walking, dressing, and bathing, leading to reduced independence and increased reliance on caregivers and healthcare services (Bergström et al., 2017; Rojas-Villarraga et al., 2009). Consequently, both patients and healthcare systems face the financial burdens associated with these disabilities.

Rojas-Villarraga et al. (2009) conducted a study emphasising the predictive value of examining the feet of RA patients in determining poor functional outcomes. Their findings demonstrated a strong correlation between foot abnormalities, active disease (detected using the DAS-28), and disability among RA patients. Consequently, they proposed the integration of regular foot examinations into clinical practice to supplement disease activity assessments and enable early interventions within the therapeutic "window of opportunity". Hooper et al's., (2012) study concurred these findings by demonstrating significant correlation between higher levels of disease activity, as measured by the DAS-28, and increased foot-related disability. However, it is

important to critically evaluate the effectiveness of the DAS-28 as a tool for capturing foot-specific disease, considering its exclusion of foot and ankle joints from its assessment. Thus, while the DAS-28 may hold predictive potential for foot-specific disability outcomes, its utility in guiding foot-specific management strategies is limited. To enhance the precision of assessing foot disease activity, the utilisation of RADAI-F5 may provide enhanced accuracy in determining if foot disease serves as a prognostic indicator for foot-related disability and impairment in RA patients.

Despite the extensive body of research on the consequences of foot disability and impairment in individuals with RA, there exists a knowledge gap regarding the prognostic determinants contributing to RA-related foot disability. Notably, longitudinal investigations in this area have been limited since the seminal work conducted by Hooper and colleagues (2012). The substantial prevalence of foot disability and impairment among individuals with RA underscores the urgent need for the development of effective interventions that mitigate associated burdens. Moreover, while disease activity measured by the DAS-28 has demonstrated predictive capacity for foot-related disability, a research gap persists regarding whether foot disease activity alone can serve as a robust predictor of disabling foot complications in RA patients. Addressing these gaps in knowledge holds promise to optimise patient care and outcomes.

Our initial validation study provided strong evidence supporting the reliability and validity of the RADAI-F5 in line with COSMIN standards (Hoque et al., 2021). In addition, Chapter 4 demonstrated significant associations between the RADAI-F5, clinical examination and MSUS, confirming the tools construct validity in capturing RA-related foot disease (Hoque et al., 2023a). Nevertheless, the investigation of the remaining components in the COSMIN taxonomy, specifically the predictive validity of the RADAI-F5, is crucial for further enhancing the acceptance and clinical utility of this novel tool. Consequently, the aim of this study is to assess the predictive validity of the RADAI-F5 within the context of an early RA cohort, specifically focusing on the moderate-high RADAI-F5 disease category, in relation to self-reported foot-related disability and impairment.

7.2 Methods:

7.2.1 Stakeholder involvement

The NHS Lanarkshire Rheumatology group, along with feedback from individual sessions with AHPs and feedback from clinicians at conferences, played a pivotal role in shaping the focus of this research study. Stakeholder input highlighted the importance of evaluating the predictive validity of RADAI-F5 for assessing the risk of future walking disability. One notable insight from a podiatrist resonated within the stakeholder group: "Patients care about whether they can function and walk and carry out daily activities, so it is important to understand if this tool can predict if

people will have poor function." This perspective helped direct the course of the study but also underscored the significance of addressing patient concerns regarding functional ability. Notably, the RADAI-F5 lacks a question specifically addressing foot function or disability. By incorporating these insights, this research maintains a firm grounding in the practical needs and perspectives of the individuals it aims to benefit.

7.2.2 Participants

This study utilised data from the FOCOS trial, which was a larger RCT that has previously been described in detail (Gallagher et al., 2018). Briefly, the FOCOS trial was a multicentre, parallel group, RCT with 6- and 12-month follow-up periods, where participants were randomly assigned to receive either customised or prefabricated FOs. The recruitment took place at rheumatology outpatient clinics within NHS Grampian, Fife, Lanarkshire health boards, Lothian health boards, Dorset Healthcare University Trust, and the Homerton University Hospital Trust. The data from the FOCOS trial was made readily available to members of the MSK Health Group at GCU, facilitating its use in this study.

Participants were included if they:

- Were ≥ 18 years of age
- Had a diagnosis of RA for less than 2 years based on the 2010 ACR/EULAR classification criteria (Aletha et al., 2010)
- Had experienced localised foot pain of at least 20 mm on the VAS
- Had not worn FOs in the 6 weeks prior to their RA diagnosis

Participants were excluded if they:

- Had neurological or endocrine diseases, such as diabetes, that could potentially affect peripheral nerves, foot structure, function, and pain perception
- Had any trauma or injury affecting the MSK structures of the lower limb or foot.

Ethical approval for the study was obtained from the East of England Essex Research Ethics Committee (15/EE/0410), and all participants provided written consent. The outcome measures collected in the trial are described below.

7.2.3 Outcome Measures:

<u>Demographic and clinical information</u>

This included age, sex, disease duration, height and weight, which was collected as baseline in the FOCOS trial (Gallagher et al., 2018).

The FFI is a valid and reliable self-administered questionnaire comprising of 23 items is categorised into three domains: foot pain (9 items), disability (9 items), and activity limitation (5 items) (Budiman-Mak et al., 1991). In this study, the Foot Function Index Disability Subscale (FFI-Dis) was utilised to assess self-reported foot disability. Participants rated each item on a 100 mm VAS, and a composite score was obtained by summing the items and dividing by the total number of items in the subscale, with higher scores indicating greater disability (Budiman-Mak et al., 1991). Furthermore, the FIS- impairment/footwear and activity participation (FIS-IF and FIS-AP) were utilised to assess self-reported disability related to foot function. The FIS is a validated, RA-specific measure that assesses foot disability across two domains: impairment/footwear (21 items) and activity limitation/participation restriction (30 items) (Helliwell et al., 2005). The FIS was completed using a yes/no-dichotomous format, with higher scores indicating worse disability. For FIS-IF, scores ≤ 6 were considered mild, 7-13 were considered moderate, and ≥ 14 were considered severe (Hooper et al., 2012). For FIS-AP, scores ≤ 9 were considered mild, 10-19 were considered moderate, and ≥ 20 were considered severe (Hooper et al., 2012). These primary outcome measures were collected at baseline, 6 months and 12 months.

The RADAI-F5 was used to determine foot disease activity. *Foot disease remission state* was defined as a RADAI-F5 score of ≤ 1.4, while foot disease categories for mild, moderate, and high disease activity, were defined as >1.4 to ≤ 3.45, >3.45 to ≤ 5.7, and >5.7, respectively (Hoque et al., 2023a). This outcome was also collected at baseline, 6-months and 12-months. The participant journey is illustrated in Figure 15.
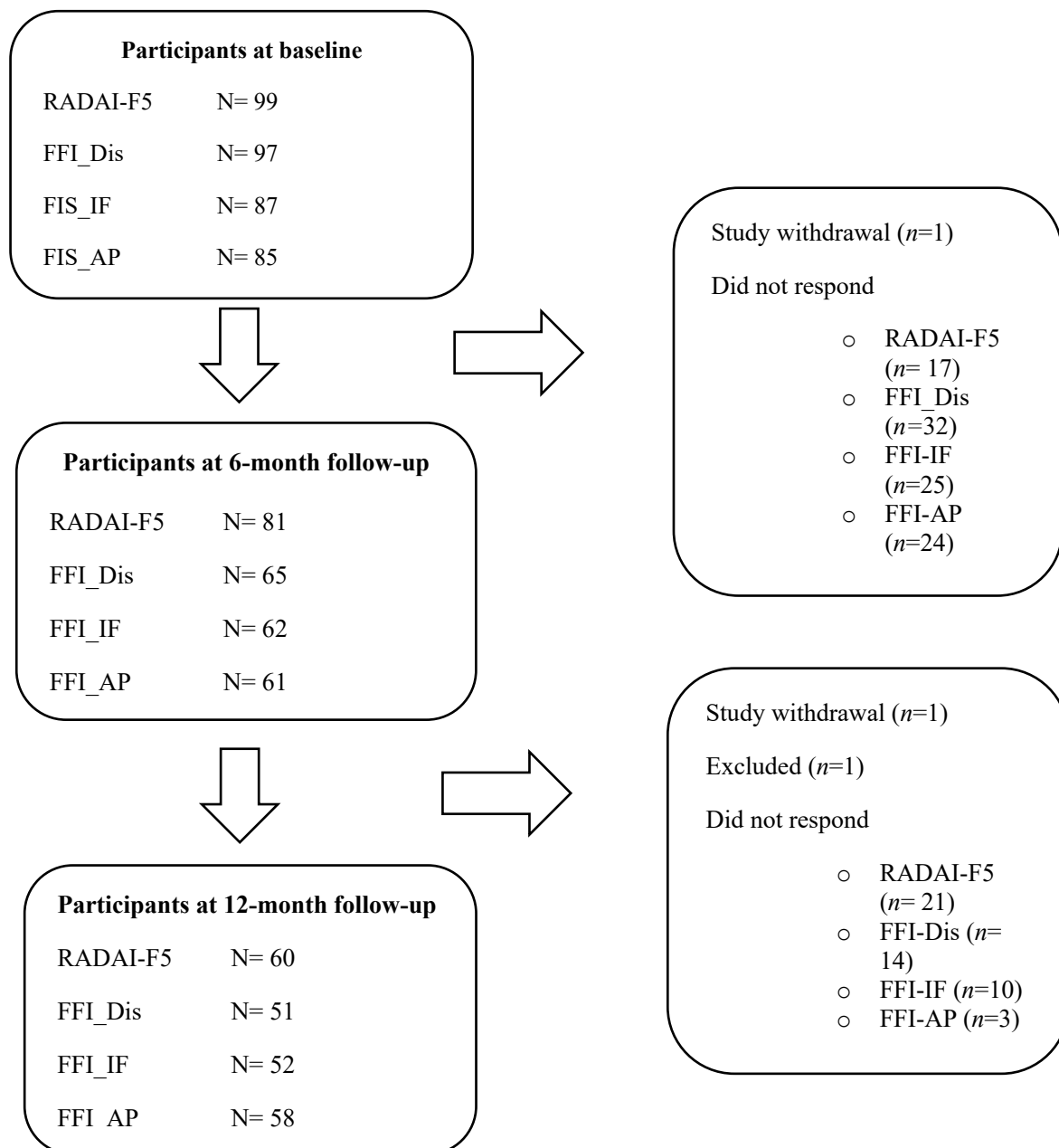
FFI_Dis: Foot function index disability subscale; FFI-AP: Foot Function Index - Activity and Participation Subscales; FFI-IF: Foot Function Index – Impairment and Footwear Subscales; N=Number; RADAI-F5: Rheumatoid Arthritis Foot Disease Activity Index.

FIGURE 15: FLOW-DIAGRAM OF PATIENT JOURNEY IN LONGITUDINAL STUDY

7.2.4 Statistical analysis:

All paper questionnaire data was transferred to Microsoft Excel for data cleaning. It is pertinent to acknowledge that this data cleaning procedure was performed by the authors of the FOCOS trial. IBM SPSS version 28 was employed to perform all statistical analyses using a two-sided significance level of 5%. Age, sex, disease duration and PROM scores were expressed using descriptive, frequency, ratio, and interval statistics, including mean, SD and percentage figures.

In the absence of comprehensive data or established benchmarks for determining the severity of foot disability using the FFI-Dis, a median split method was used as an alternative approach. The median split method is a statistical technique used to divide a set of data into two groups based on the median value of the dataset (Rucker et al., 2015). This approach allows for a relative comparison of individuals foot disability scores. Those with scores above the median are considered to have higher foot disability severity, while those below the median are considered to have lower foot disability severity. As such, the scores for FFI-Dis, FIS-IF, and FIS-AP measures were divided into two groups using the median split. This approach resulted in a dichotomisation of scores, with a value of 1 representing 'poor foot disability/impairment outcomes' and a value of 0 representing 'not-so-poor foot disability/impairment outcomes'.

To facilitate easier analysis and incorporate the new cut-offs for distinguishing remission-low from moderate-high foot disease, a cumulative element was introduced to the RADAI-F5. The RADAI-F5 score was dichotomised as follows: A score of 1 was assigned if a participant had two consecutive episodes of moderate-high foot disease (RADAI-F5 > 3.45) at baseline and 6-months. A score of 0 was assigned if individuals had only one episode of moderate-high disease and/or one to two episodes of remission/low foot disease at baseline and 6-months. For the analysis, the inclusion criteria was restricted to two consecutive episodes of moderate-high foot disease (RADAI-F5 > 3.45). This criterion was selected due to discussions with stakeholders, who supported the notion that the reoccurance of poor RADAI-F5 scores in two or more consecutive episodes would exert a greater influence on the progression of foot-related disability when compared to isolated or sporadic instances of a RADAI-F5 score of > 3.45. Cross-tabulations further supported this decision, revealing a statistically significant association between the inclusion of a cumulative element (two consecutive episodes of moderate to high RADAI-F5 scores) and "poor" foot disability and impairment outcomes.

Binary logistic regression was used to evaluate the predictive validity of RADAI-F5 scores with poor foot disability outcomes at 12-months. The dichotomised FFI-Dis, FIS-IF, and FIS-AP scores served as dependent variables, while the dichotomised RADAI-F5 scores were the independent variable. Baseline FFI-Dis and FIS AP and IF scores were included as covariates to control for

initial foot disability status. Coefficients (B) and their standard errors quantified relationships, and exponentiated coefficients (Exp (B)) represented odds ratios (OR). The selection of variables involved adjusting for potential confounding factors such as age, sex, disease duration, body mass index (BMI), and the presence of tender and swollen joints at baseline. Variables were considered for inclusion in the final model based on an exploratory bivariate logistic regression analysis to ascertain which variables correlated with the poor self-reported foot disability and impairment outcomes at 12 months. ORs were individually computed for each independent variable through bivariate logistic regression analyses, and the independence of these associations was subsequently confirmed via multiple binary logistic regression modelling. The significance of the relationship between each predictor and the odds of the outcome was evaluated using Wald tests. Furthermore, if the resulting Exp (B) value exceeded 10%, regardless of the p-value (Chowdhury & Turin, 2020), the variable was included in the binary logistic regression analysis. Figure 16 demonstrates an example of the analysis conducted using FIS-AP. The same procedure was replicated for FFI-Dis and FIS-IF.

Step 1: Initial binary regression analysis

Dependent variable: FIS-AP

Covariates: Two consecutive episodes of moderate-high RADAI-F5s scores and Baseline FIS-AP scores

Exp (B) value= 3.527

10% range = 3.174-3.879

Step 2: Individual binary regression analysis

Conduct separate binary regression analyses for each predictor variable with FIS-AP as dependent variables and two consecutive episodes of moderate-high RADAI-F5s scores and Baseline FIS-AP scores as covariates and included the following as predictor variables:

- Age
- Sex
- Disease duration
- BMI
- Swollen joint count
- Tender joint count

Step 3: Variable selection criterion

Is the Exp (B) values from Step 2 ≥ within the 10% range?

YES

NO

Include variables in final binary regression model for FIS-AP

Exclude variables from final binary regression model for FIS-AP

Key: FIS-AP: Foot impact scale- Activity Participation subscale; RADAI-F5: Rheumatoid Arthritis Foot Disease Activity Index-Foot Version; Exp(B): Exponentiated Coefficients (Odds Ratios); BMI: Body mass index.

FIGURE 16: OVERVIEW OF VARIABLE SELECTION FOR BINARY REGRESSION MODEL FOR FIS-AP

7.3 Results:

105 participants with a mean [±SD] age of 53.51 [±12.1] years and a median (IQR) disease duration of 6 (9) months took part in the FOCUS trail. 61% of the participants were females. The mean [±SD] BMI was 28.54 [±5.55]. The participant journey, as illustrated in Figure 15, revealed high levels of attrition, resulting in diminished participant numbers for each outcome measure at the 6-month and 12-month follow-ups. N=2 individuals withdrew from the study citing time-related issues, n=1 was excluded as they expressed a lack of willingness to continue with FOs. and n=27-39 individuals were lost to follow-up. Further demographic insights are presented in Table 30, comparing characteristics of individuals in the analysis and those lost to follow-up. The analysis group exhibited a slightly higher mean age (54.9 [± 9.37]) compared to the lost to follow-up group (51.83 [± 14.8]), and a lower mean BMI (26.31 [± 8.24] and 29.32 [± 5.59]), respectively. Moreover, the analysis group demonstrated a shorter disease duration (6.97 [± 6.30] months) in contrast to the lost to follow-up group (9.99 [± 6.59] months). Both groups displayed a higher proportion of females in terms of gender distribution (Table 30).

Concerning clinical characteristics, the analysis group presented with lower baseline mean RADAI-F5 scores (5.56 [± 2.06]) than the lost to follow-up group (6.11 [± 2.06]), indicating less severe foot disability, although they still exhibited high foot disease activity (Table 30). Similarly, the analysis group displayed lower mean FFI-Dis scores (53.45 [± 26.15]) compared to the lost to follow-up group (61.07 [± 22.21]), signifying reduced foot disability (Table 30). Mean FIS_IF and FIS_AP scores were relatively consistent between the groups, implying comparable levels of foot impairment and activity participation (Table 30). In summary, the analysis group presented with slightly more favourable demographic and clinical characteristics compared to the lost to follow-up group.

TABLE 30: COMPARISON OF DEMOGRAPHIC AND CLINICAL CHARACTERISTICS BETWEEN ANALYSIS AND LOST TO FOLLOW-UP GROUPS

Demographic variables	Analysis group	Lost to follow-up group
Age (Mean [±SD])	54.9 [± 9.37]	51.83 [± 14.8]
BMI (Mean [±SD])	26. 31 [± 8.24]	29.32 [± 5.59]
Disease duration (months) (Mean [±SD])	6. 97 [± 6.30]	9.99 [± 6.59]
Gender (female/male)	37/26	36/13
RADAI-F5 * (Mean [±SD])	5.56 [±2.06]	6.11 [± 2.06]
FFI_Dis* (Mean [±SD])	53.45 [±26.15]	61.07 [± 22.21]
FIS_IF* (Mean [±SD])	13.23 [±5.89]	13.70 [± 4.16]
FIS_AP* (Mean [±SD])	16.48 [±9.21]	17.67 [± 5.99]

BMI: Body mass index; FFI_Dis: Foot function index Disability subscale; FIS_AP: Foot impact subscale for activity limitation; FIS_IF: Foot impact scale using the impairment subscale; RADAIF5: Rheumatoid arthritis foot disease activity index

*baseline data

Of those in the final analysis, baseline, 6-months and 12-months, mean [±SD] RADAI-F5 scores were 5.56 [± 2.07], 4.12 [± 2.54], 4.13 [± 2.63] respectively. This indicates that participants typically presented with high self-reported foot disease activity at baseline and moderate at the follow-ups. The mean [±SD] baseline score for FFI-Dis, FIS-IF, and FIS-AP was 53.45 [±26.15], 13.23 [±5.89], and 16.48 [±9.21], respectively. This indicates that at baseline participants experienced moderate to severe levels of foot disability and foot impairment . At the 6-month follow-up, the FIS-IF mean [±SD] score of 10.79 [± 5.10] , FIS-AP score of 13.48 [± 9.31] and FFI-Dis scores of 37.63 [± 29.64] demonstrate a reduction in self-reported foot impairment and disability. At the 12-month follow-up, the FIS-IF score of 11.42 [± 5.75], indicate a mild deteriorating in self-reported impairment, while an FIS-AP score of 13.28 [± 9.96] indicatemild improvement in self-reported foot impairment. However, similar to the 6-month follow-up, the FFI-Dis score of 37.13 [± 30.92] reflects improvement in foot disability scores. These descriptive statistics are presented in Table 31. The preliminary data indicates that 43.3% (n=26/60) participants had poor foot disability outcomes at 12-months based on the FFI-dis subscale, and 53.8% (n=33/61) participants had two consecutive episodes of RADAI-F5 >3.45 within 0-6 months. It should be noted that the discrepancy in sample size numbers for the descriptive statistics is attributable to participants who were lost to follow-up.

Variable	Mean [±SD]
Age (n=105)	53.51[± 12.13]
Disease duration (months) (n= 86)	8.3 [± 6.57]
BMI (n=94)	28.27 [± 6.09]
BL_FFI_Dis (n=97)	53.45 [±26.15]
BL_ FIS_IF (n= 87)	13.23 [±5.89]
BL_FIS_AP (n= 85)	16.48 [±9.21]
BL_RADAIF5 (n=99)	5.56 [±2.06]
BL_SJC (n=99)*	3.15 [±5.00]
BL_TJC (n=99)*	5.83 [±6.76]
m6_FFI_Dis (n=65)	37.63 [± 29.64]
m6_FIS_IF (n=62)	10.79 [± 5.10]
m6_FIS_AP (n=61)	13.48 [± 9.31]
m6_RADAIF5 (n=81)	4.12 [± 2.54]
m6_SJC (n=67)	1.74 [± 3.94]
m6_TJC (n=68)	3.80 [± 6.09]
m6_FFI_Dis (n=51)	37.13 [± 30.92]
m12_FIS_IF (n=52)	11.42 [± 5.75]
m12_FIS_AP (n=58)	13.28 [± 9.96]
m12_RADAIF5 (n=60)	4.13 [± 2.63]
m12_SJC (n=53)	1.89 [± 3.70]
m12_TJC (n=53)	5.92 [± 8.06]

BMI: Body mass index; FFI_Dis: Foot function index Disability subscale; FIS_AP: Foot impact subscale for activity limitation; FIS_IF: Foot impact scale using the impairment subscale; RADAIF5: Rheumatoid arthritis foot disease activity index; Swollen joints: Number of swollen joints at baseline; Tender joints: Number of tender joints at baseline.

BL: baseline

m6: measurements taken at 6 months

m12: measurements taken at 12 months.

* BL-TJC and BL-SJC are in relation to the 28 joint count on DAS-28.

The logistic regression results for the predictive validity of the RADAI-F5 using the FFI-Dis, FIS-IF and FIS-AP are presented in Tables 32, 33, and 34, respectively. In Table 32, the bivariate binary logistic regression results indicate that individuals with two consecutive episodes of RADAI-F5 >3.45 have a significantly higher OR of 4.00 (p = 0.02) for foot disability compared to those without such episodes. The other independent variables, including sex, disease duration, BMI, baseline swollen and tender joints were not found to have a significant effect on poor foot disability.

In Table 33, the bivariate binary logistic regression analysis for predicting foot disability using the RADAI-F5 and FIS-IF, indicated that two consecutive episodes of RADAI-F5 >3.45 showed a positive association with foot disability outcomes, although the statistical significance was not reached (B = 1.18, p = 0.11, Exp (B)= 3.26, 95% CI: 0.76-14). Additionally, although BMI was included in the final model based on being within the 10% threshold as indicated in Figure 16, the findings were not significantly associated with foot disability outcomes (B = 0.17, p = 0.07, Exp(B)= 1.19, 95% CI: 0.99-1.43). Age, sex, disease duration and swollen and tender joints were not found to have a significant effect on poor foot impairment.

In Table 34, the OR of foot disability using the FIS-AP were 3.80 times higher for individuals with two consecutive episodes of RADAI-F5 scores > 3.45 compared to those below the threshold. However, these findings were not statistically significant and the wide confidence interval (95% CI: 0.83-17.27) indicated substantial uncertainty in this estimate. Furthermore sex and BMI was not significantly associated or predictive with foot disability (B = -0.21, p = 0.81, Exp(B) = 0.81, 95% CI: 0.15-4.47; B = 0.13, p = 0.16, Exp(B) = 1.13, 95% CI: 0.95-1.35). The other independent variables, including age, disease duration and baseline swollen and tender joints were not found to have a significant effect on the FIS-AP at 12 months.

TABLE 30: BIVARIATE BINARY LOGISTIC REGRESSION RESULTS FOR PREDICTING SELF-REPORTED FOOT DISABILITY USING THE FFI-DIS (N=51)

Variables	B	S.E	Wald	Sig	Exp (B)	95% C.I for Exp (B)
RADAI-F5 > 3.45	1.39	0.60	5.43	0.02	4.00	1.25-12.84
BL_FFI_DIS	0.06	0.02	9.42	0.00	1.06	0.64-1.07
Constant	-0.69	0.41	2.88	0.09	0.50	

B = coefficient; S.E. = standard error; Wald = Wald statistic; Sig. = significance level; Exp(B) = odds ratio; 95% C.I. for Exp(B) = 95% confidence interval for the odds ratio. BL_FFI_Dis: Baseline Foot function index disability; Predictor variable :"Two consecutive episodes (0to6m only) of RADAI-F5 >3.45", while the constant is FFI-dis

TABLE 31: BIVARIATE BINARY LOGISTIC REGRESSION RESULTS FOR PREDICTING SELF-REPORTED FOOT IMPAIRMENT USING THE FIS-IF (N=52)

Variables	B	S.E	Wald	Sig	Exp (B)	95% C.I for Exp (B)
Two consecutive episodes (0to6m only) of RADAI-F5 > 3.45	1.18	0.74	2.52	0.11	3.26	0.76-14
BL_FFI_IF	0.05	0.06	0.87	0.38	1.06	0.94-1.18
BMI	0.17	0.09	3.41	0.07	1.19	0.99-1.43
Constant	6.19	2.84	4.77	0.03	0.00	

B = coefficient, S.E. = standard error, Wald = Wald statistic, Sig. = significance level, Exp(B) = odds ratio, 95% C.I. for Exp(B) = 95% confidence interval for the odds ratio, BL_LFIS_IF: Baseline Leeds Foot Impact Scale impairment/footwear subscale scores, BMI: Body Mass Index, Predictor variable: "Two consecutive episodes (0 to 6 months only) of RADAI-F5 > 3.45", Constant: FIS-IF.

TABLE 32: BIVARIATE BINARY LOGISTIC REGRESSION RESULTS FOR PREDICTING SELF-REPORTED FOOT IMPAIRMENT USING THE FIS-AP (N=58).

Variables	B	S.E	Wald	Sig	Exp (B)	95% C.I for Exp (B)
Two consecutive episodes (0to6m only) of RADAI-F5 > 3.45	1.33	0.77	2.98	0.85	3.80	0.83-17.27
BL_LFIS_AP	0.03	0.03	0.84	0.36	1.04	0.97-1.10
Sex	-0.21	0.87	0.57	0.81	0.81	0.15-4.47
BMI	0.13	0.90	1.96	0.16	1.13	0.95-1.35
Constant	-4.13	2.70	2.33	0.2	0.44	

B = coefficient, BL_LFIS_AP: Baseline Leeds Foot Impact Score activity participation limitation subscale scores, Constant: FIS-AP, Exp(B) = odds ratio, Predictor variable: "Two consecutive episodes (0 to 6 months only) of RADAI-F5 > 3.45", S.E. = standard error, Sig. = significance level, Wald = Wald statistic; 95% C.I. for Exp(B) = 95% confidence interval for the odds ratio

7.4 Discussion

This study, necessitated as a secondary data analysis following the loss of IRT data, provides an initial assessment of the predictive validity of the RADAI-F5 concerning self-reported foot-related disability within a cohort of early RA participants over a 1-year period. The findings from this study demonstrated that two consecutive episodes of moderate-high foot disease activity, as determined by RADAI-F5 at baseline and six months, exhibited predictive validity for self-reported foot disability using the FFI-Dis outcome measure. Specifically, the OR of 4 indicates that individuals surpassing the >3.45 threshold on two occasions a four times higher odds of experiencing self-reported foot disability. Although the 95% CI for the OR ranges were wide, it is important to note that the p-value (0.02) indicates statistical significance, meaning that the association is unlikely to occur by chance. These results confirm the initial predictive validity of RADAI-F5 as a potentially useful tool for assessing risk of foot-related disability. Moreover, these findings contribute to the existing body of knowledge regarding the robust measurement properties of RADAI-F5 (Hoque et al., 2021; Hoque et al., 2023a). These findings simultaneously offer valuable insights for guiding subsequent research to further explore this measurement property, prompting potential future investigations based on preliminary evidence indicating this tools predictive validity.

Conversely, the findings regarding the potential association between the RADAI-F5 and foot impairment outcomes (FIS IF and AP) did not reach statistical significance and showed a degree of uncertainty, as indicated by the wide CI's. This suggests that the observed relationship between these variables and self-reported foot impairment may have occurred by chance (Van Rijn et al., 2017). Nonetheless, despite the lack of statistical significance, there was a slight trend towards significant association and this may warrant further investigation with larger samples over longer periods of follow-up. These findings align with the research conducted by Hooper et al., (2012), as they demonstrate that disease activity measured by the DAS-28 and disease duration are significant prognostic indicators of patient-reported foot disability, assessed using the FIS-IF and FIS-AP. However, their study incorporated a larger sample size and had a longer follow-up period, which may account for the discrepancy observed in the present study findings. Furthermore, while this study specifically examined localised disease activity, Hooper et al., (2012) explored overall disease activity. Importantly, the Hooper et al., (2012) study concluded that persistent foot disability remains a pertinent issue, despite advancements in disease management in this patient population. In this present study, even at the 1-year follow-up, the mean scores for FIS-IF and FIS-AP were 11.23 and 13.28, respectively, indicating moderate levels of foot-related impairment among participants. These findings provide support for the proposition that foot-related impairment continues to persist despite advancements in pharmacological management strategies

among the studied population. It is worth noting that although the RADAI-F5 did not demonstrate significant predictive validity for this particular outcome measure, the results highlight the ongoing challenges in effectively addressing foot-related impairment in this context.

One critical aspect to consider is the high RADAI-F5 scores throughout the study. Although these scores may be interpreted as an indication of the measure's effectiveness in capturing the impact of active foot disease on overall disability, it also raises concerns about the underlying factors driving the disability scores, particularly at the 12-month follow-up. The possibility that the disability scores at this specific time point are primarily influenced by the moderate to high prevalence of active foot disease in patients could undermine the ability of RADAI-F5 to accurately predict long-term disability outcomes. Nevertheless, the significant values for the FFI-Dis model still highlights the RADAI-F5s potential relevance in predicting long-term disability outcomes. Moreover, this observation can potentially be attributed to the fact that the studied cohort represents individuals in the early stages of RA, who may not have yet achieved optimal disease management through pharmacological interventions.

Various factors, including age, sex, BMI, and baseline pain and disability values, have been suggested as potential predictors of disability outcomes (De Croon et al., 2004; Sokka et al., 2009; Salaffi et al., 1992; Van Vollenhoven, 2009; Rydell et al., 2021). Existing studies indicate that sex may play a role, as women are more likely to develop RA and tend to experience more severe symptoms and disability (Van Vollenhoven, 2009). In this cohort, sex was only included in the FIS-AP model but the findings were not statistically significant. BMI has also been proposed as a potential predictor of foot disabilities, particularly in overweight individuals who have comorbidities like cardiovascular diseases that could contribute to such disabilities (De Croon et al., 2004; Sokka et al., 2009). BMI demonstrated a borderline significant relationship with FIS-IF (p = 0.065) but not in the FIS-AP model. These initial findings cautiously suggest that monitoring RADAI-F5 episodes and considering BMI may play a role in predicting foot impairment. However, further research is necessary to conduct longitudinal follow-ups to examine the impact of BMI on self-reported foot disease activity and foot impairments in patients with both early and established RA. Caution should be exercised when interpreting the non-significant effects of these variables in the current study, as their significance may vary across different contexts and stages of RA, necessitating further invistigation. However, within the scope of this preliminary study focusing on early RA patients and in relation to two episodes of moderate to high foot disease activity, these variables do not offer strong predictive value for assessing foot-related disability and impairment.

A study conducted by Rydell et al., (2021) demonstrated that patients with a longer duration of RA exhibited higher scores on the Health Assessment Questionnaire-Disability Index (HAQ-DI), indicating more significant functional limitations. Furthermore, the study revealed that as the duration of RA increased the impact of radiographic disease-related damage (Rydell et al., 2021). Additional research has corroborated the notion that foot disability and impairment worsens with longer disease duration (Turner et al., 2006; Van der Leeden et al., 2007). Moreover, a literature review by Radu & Bangau (2021) reported that longer disease duration can result in gradual and irreversible deterioration of the joints, deformities, and subsequent disability. This process not only detrimentally affects QoL, but also makes daily activities more challenging. Therefore, it is crucial to promptly identify and address foot symptoms in order to prevent or mitigate long-term disability (Rojas-Villarraga et al., 2019; Rydell et al., 2018). It should be noted that the current study specifically examined a cohort of individuals with early RA, and therefore, conclusive evidence regarding the association between longer disease duration and an increased risk of foot disability and impairment cannot be ascertained.

To date, no previous studies have investigated the association or predictive value of self-reported foot disease activity in relation to disabling foot complications in RA. However, it is noteworthy that the benefits of achieving early and sustained remission using a T2T approach in the context of RA have been extensively established (Taylor et al., 2022). Prior research consistently demonstrates that patients with inflammatory autoimmune conditions who attain minimal disease activity (MDA) within the first year of their disease experience improved HRQoL compared to those who do not (Snoeck Henkemans et al., 2022; Queiro et al., 2017; Wervers et al., 2019). Additionally, Kavanaugh et al., (2016) conducted a study showing that maintaining MDA, defined as consecutive visits with MDA over a period of ≥3-4 visits, is associated with fewer functional limitations and better overall health outcomes over a five-year timeframe. A recent investigation by Snoeck et al., (2022) revealed that individuals with PsA who failed to achieve MDA within the first year after diagnosis had significantly higher disease burden, characterised by elevated levels of pain, functional impairment, and disability over the subsequent two years. Consistent with these studies, the present findings emphasise the role of early attainment of MDA in the foot region for improving long-term patient outcomes, particularly concerning foot-related disability. As such, integrating the RADAI-F5 into rheumatology care settings could facilitate timely interventions to prevent or delay foot-related disability and impairment.

To further enhance our understanding of RA-related foot disability, it is worth considering the inclusion of PBMs in future studies. While PROMs provide valuable insights into patients' perceptions, PBMs offer distinct advantages by providing an objective assessment of a patient's

functional abilities. PBMs offer an objective measure compared to PROMs, as they are less influenced by external factors and demonstrate greater sensitivity to changes in a patient's condition over time (Beauchamp et al., 2015). Including PBMs in future studies could contribute to a more comprehensive evaluation of RA-related foot disease and its predictive validity relative to foot disability.

7.5 Strengths and limitations

This study has several strengths. Firstly, this is the first study to investigate whether self-reported foot disease activity can serve as a predictor of foot-related disability, offering initial confirmation of the predictive validity of RADAI-F5. The insights gained from this study can contribute to hypothesis generation for future research on the predictive validity of the RADAI-F5 in an early RA patient cohort. Secondly, the study-utilised data from the FOCOS trial, a large RCT known for its robust study design, allowing for a rigourous evaluation of cause-and-effect relationships and minimising bias. Moreover, participants with RA were recruited from various UK rheumatology outpatient clinics across different healthcare settings, enhancing the generalisability of the findings. Lastly, the study incorporated a 12-month follow-up period, allowing for the adequate longitudinal assessment of self-reported foot disability and impairment.

Nevertheless, several limitations should be acknowledged. Firstly, the cohort consisted exclusively of patients with early RA who exhibited moderate-high disease activity at baseline, 6-months, and 12-months. Consequently, the generalisability of the findings may be limited to patients with less severe disease or those with more established RA. Additionally, there is a risk that the higher levels of foot disease activity as reported at all three time points may have been the driver for self-reported disability. Secondly, participants might had higher baseline scores due to self-selection to the study based on greater foot pain severity, resulting in self-selection bias.

Furthermore, it is important to note that the final sample size of the foot-related disability and impairment measures study was relatively small, ranging from 50 to 52 participants, due to high levels of attrition during the follow-up period. As such, caution is required when interpreting the results. Demographic comparisons between the analysis group and those lost to follow-up, highlight potential differences in participant characteristics. These variations in demographic factors might have introduced confounding variables, influencing the internal validity of the study findings. For instance, the analysis group, with its lower baseline RADAI-F5 and FFI-Dis scores, indicates milder foot disability compared to the lost to follow-up group, potentially skewing the severity profile of the studied population. While efforts were made to provide a comprehensive analysis of the available data, it is crucial to acknowledge the impact of attrition on the robustness and generalisability of the study results. Further research addressing attrition-related challenges

and employing strategies to enhance participant retention is warranted to strengthen the validity of future investigations in this domain.

 Lastly, the influence of covariates on the association between RADAI-F5 and foot disability warrants consideration. While the logistic regression analysis accounted for age, sex, BMI, and disease duration, other comorbidities that may confound the relationship were not explored. The presence of comorbidities, such as central pain sensitisation or fibromyalgia, could potentially contribute to worse PROM scores and influence the relationship between RADAI-F5 and foot disability and impairment outcomes. Therefore, these preliminary findings should be considered as an initial step to establish the foundation for future research. Employing longitudinal studies of extended duration and larger sample sizes is imperative to further validate these findings and provide a more precise understanding of the predictive capability of the RADAI-F5.

7.6 Conclusion

This study demonstrates preliminary evidence that two consecutive episodes of moderate-high disease activity, as measured by the RADAI-F5, predicts self-reported foot disability in individuals with early RA. The findings support the reliable measurement properties of RADAI-F5, aligning with PROMs standards outlined by COSMIN (Gagnier et al., 2021). While caution is necessary due to study limitations, these results offer promising initial evidence for the predictive value of this novel tool in RA patients for self-reported foot-disability. However, it remains imperative to conduct longitudinal studies with larger sample sizes and longer study durations to explore the long-term impact of foot disease activity on disability in both early and established RA cohorts.

Chapter 8. Thesis Discussion

This chapter presents a comprehensive synthesis of the key findings derived from this thesis, with specific emphasis on the clinical implication of the RADAI-F5 in rheumatology care settings. Furthermore, the chapter addresses the limitations of the conducted studies and offers recommendations for future research using this tool within the field of rheumatology.

8.1 Thesis summary

This thesis comprises of five distinct studies that aimed to address specific knowledge gaps in the detection and management of foot disease in the RA population, using the RADAI-F5. Chapter 3 uncovered barriers and facilitators to the successful implementation of this novel tool. In the context of rheumatology settings, the tool was regarded as warranted and clinically feasible, offering potential advantages in early detection of foot disease, facilitating shared decision-making, promoting patient-clinician and MDT communication, and enabling remote consultations. However, the lack of validation against objective measures posed a perceived barrier to the RADAI-F5's adoption into routine care. Subsequently, Chapter 4 provided further evidence of the tools robust measurement properties, establishing its construct validity relative to clinical examination and MSUS. Chapter 5 provided anchor-based estimates of the MID value for the instrument, albeit using a small sample size. This preliminary value holds potential for guiding clinicians in the interpretation of RADAI-F5 scores and offering insights into patient management strategies.

Additionally, Chapter 6 confirmed the inclusion of the TTJ and STJ in the RADAI-F5 through a data-driven approach. Lastly, Chapter 7 contributed preliminary evidence suggesting that the RADAI-5 can predict self-reported foot-related disability in an early RA cohort, establishing preliminary predictive validity for this novel tool. Cumulatively, these chapters provide insights into the measurement properties and potential value of the RADAI-F5 in rheumatology care.

A key strength in this thesis includes the input from key stakeholders, involving RA patients, rheumatologists, and AHPs. By actively involving stakeholders who have first-hand experience and understanding of RA and disease activity assessment, the studies in this thesis generated scientifically rigourous evidence that is meaningful to RA patients and healthcare professionals involved in their care. Additionally, stakeholder discussions were integral in tackling practical challenges posed by the COVID-19 pandemic, including identifying alternative recruitment methods, comprehending the NHS recruitment process with the lack of face-to-face appointments, and and contributing to the formulation of research questions for this thesis.

8.2 RADAI-F5 validity and clinical implications

Clinical practice guidelines highlight the importance of integrating foot and ankle care within the overall management of RA (Hennessey, Woodburn & Steultjens, 2016; Woodburn et al., 2010; Williams et al., 2011). The incorporation of the RADAI-F5 in clinical practice provides an opportunity of an outcome-driven model of patient-centred foot care, enhancing collaboration between clinicians and patients (Hoque et al., 2022; Kwame & Petrucka, 2021). The RADAI-F5 offers an opportunity to effectively assess foot disease and track foot disease activity over time. Its integration in rheumatology care settings holds potential for increasing awareness of the RA foot, and holds the promise of optimising interventions, refining treatment strategies, and possibly improving foot health and QoL for individuals with RA. Moreover, the RADAI-F5 shows potential in delivering targeted foot care through referrals to extended scope practices like MSUS, whilst promoting collaboration within MDT clinics, aligning with recommendations proposed by Woodburn and colleagues for podiatry care in early RA (Woodburn et al., 2010).

The use of the RADAI-F5 in routine clinical practice may offer benefits for enhancing patient care (Hoque et al., 2023b) (Appendix N). With increased confidence in the RADAI-F5's validity against objective measures, the tool holds promise to enable early detection of foot disease related to RA and helps guide appropriate therapeutic interventions based on specific foot disease categories, as outlined in Table 35. These recommendations can empower clinicians to make decisions regarding treatment options and the necessity of referrals to the wider MDT. It is crucial to acknowledge that the recommendations presented in Table 35, derived from stakeholder discussions, and a literature review on current foot management in RA, lack field-testing. Consequently, these recommendations serve as a preliminary framework to steer treatment strategies. In order to determine how the RADAI-F5 can be used for guiding management in clinical settings, it is crucial to implement the tool in rheumatology care settings. This iterative process of implementation and evaluation has the potential to yield valuable insights into the feasibility, usefulness, and impact of integrating the RADAI-F5 into clinical practice. Additionally, it can lead to improved recommendations for managing different foot disease categories.

TABLE 33: FOOT DISEASE CATEGORIES TO AID IN INTERPRETABILITY AND MANAGEMENT OF RADAI-F5 SCORES

RADAI-F5 foot disease categories	In Remission	Low	Moderate	High
	≤1.4	>1.4-≤ 3.45	>3.45 to ≤5.7	>5.7
Management recommendation	Footwear recommendations MSK assessment Pain relief through NSAIDS Physical therapy if indicated Orthotics if indicated	✚	Justification for ultrasound for isolated suspect joints ✚	Ultrasound imaging Local inflammation control Onward referral to rheumatology

While the MID value of 1.02 offers insights into meaningful score changes for guiding management decisions, it is important to recognise the limitations associated with the small sample size in the study, which increases the risk of random variation and restricts the generalisability of the results (Indrayan & Mishra, 2021). Therefore, caution is advised when interpreting the anchor-based MID value, and further research utilising larger and more diverse samples is necessary to validate and enhance its reliability as a meaningful threshold for clinical decision-making. In the interim, the distribution-based analysis in the previous validation study (Hoque et al., 2021), which utilised a larger sample size (n=150), may present a more robust estimate of the MID. The distribution-based MID may also serve as a better reference point for researchers in determining the necessary sample size for future RADAI-F5 studies (Serdar et al., 2021). Nonetheless, it is valuable to highlight the importance of establishing the MID from the patient's perspective, given the significance of incorporating patient views in guiding management decisions (Devji et al., 2020).

While disease activity categories provide advantages in assessing disease status and guiding management, it is crucial to critically evaluate their limitations and consider alternative approaches. Relying solely on category boundaries may not accurately capture an individual's experiences or symptoms, undermining the goal of personalised care. In this context, the MID approach, which emphasises the magnitude of change, offers a patient-centric perspective that aligns with tailoring interventions to individual needs. Combining categorical disease classifications and MID indicators along with patient communication may provide a more

comprehensive evaluation of disease activity and guide tailored treatment strategies in RA foot care.

The RADAI-F5 holds clinical significance in the context of pharmacological management in rheumatology by addressing the challenge of accurately assessing foot disease, especially in cases where DAS-28 scores may be insufficient (Wechalekar et al., 2016; Hattori et al., 2018; Landewe et al., 2006). Employing the RADAI-F5 may contribute to a more comprehensive understanding of global disease in this patient population. Furthermore, the tool has the potential to eliminate the necessity of artificially inflating scores for drug escalation. However, it is important to note that the RADAI-F5 should not replace the DAS-28 but rather complement it to obtain a comprehensive disease assessment. While the FOOTRADIUS study provides confidence in the tools ability to accurately detect specific inflammatory features, such as synovitis, tenosynovitis, and bursitis, it should be used in conjunction with clinical examination and other objective measures, such as ESR/CRP. This combined approach may aid in the early detection of foot disease activity, allowing for timely interventions and reducing the risk of radiographic foot progression.

Traditionally, podiatry care for RA has primarily focused on biomechanics or cutaneous lesions (Woodburn et al., 2010; Hennessey, Woodburn & Steultjens, 2016). By offering insights into inflammatory RA foot disease involvement, the RADAI-F5 assists clinicians in tailoring care plans that go beyond isolated foot symptoms, and encompasses systemic disease. This integrated approach helps ensure that patients receive appropriate interventions that address the full spectrum of their disease, resulting in personalised patient care. Furthermore, Dando et al., (2020) highlighted the need for a transformative approach in rheumatology that ensures timely access to suitable clinicians for managing foot health issues. Healthcare professionals can gather patient-reported data on foot health using the RADAI-F5, enabling them to make informed decisions regarding when referrals to rheumatology MDT services, including podiatry are required. This proactive measure may help assure that patients receive comprehensive and coordinated care from various healthcare providers (NICE, 2018; Pickles et al., 2022).

Confirmation of the inclusion of the ankle and the STJ in the RADAI-F5 provides a more comprehensive understanding the tools ability to assess overall foot disease activity, potentially guiding healthcare providers on when hindfoot assessment may be relevant and allowing for tailored interventions. These include recommending specific exercises, orthotic devices, or footwear modifications to address the specific needs of the ankle joint.. Traditionally, the ankle and foot in RA have not been assessed separately, despite their functional differences. Considering if the ankle and foot are separate entities within the RADAI-F5 raises an interesting question regarding how patients may perceive these structures and allows for a deeper exploration of the

interconnectedness of ankle and foot pathology in RA. Future studies, incorporating mixed methods, could provide insights into interventions tailored to the needs of patients with ankle disease. Quantifying ankle disease in subsequent studies may offer data on the prevalence, severity, and progression of ankle-specific pathology, potentially informing clinical decision-making, resource allocation, and the development of evidence-based guidelines for managing the ankle joint complex in RA. Additionally, recognising individual perceptions of ankle and foot involvement may guide healthcare providers in adjusting communication and educational strategies to address patient needs. However, exploring this aspect necessitates patient feedback, particularly considering that the RADAI-F5 is a patient-reported measure.

Importantly, establishing the predictive capabilities of the RADAI-F5 tool offers preliminary insights into the tools potential ability to act as a screening tool for individuals at high risk of developing self-reported foot-related disabilities. By incorporating the RADAI-F5 as a screening tool in routine assessments at RA clinics, healthcare providers can implement preventive measures in a timely manner. However, it is crucial to acknowledge that the establishment of the tool's predictive validity is hindered by limitations in the sample size, significant attrition observed during the study, and participants being limited to an early RA cohort. These factors raise concerns regarding the generalisability and reliability of the findings (Indrayan & Mishra, 2021). Furthermore, there remains uncertainty regarding whether the high foot disability scores are driven by high foot disease activity scores. Additionally, the study did not demonstrate statistical significance for the FIS outcome measure, indicating that the predictive capabilities of the RADAI-F5 in relation to foot-related impairment are still undetermined. Although the RADAI-F5 may serve as a valuable tool for early identification of individuals 'at risk' of self-reported foot-related disability, it is imperative to conduct future longitudinal observational studies with a larger sample size to further validate the tools predictive validity among both early and established RA cohorts.

8.3: Alignment of the RADAI-F5 with current quality improvement frameworks for RA Care

Barber et al., (2021) conducted a nationally scoped research programme to develop, test, and implement a qualitative-based framework for RA care. The key themes identified in their research closely align with the findings of this thesis, encompassing rheumatology care access, timely initiation of appropriate treatments, individualised care plans, access to MDT healthcare, and provision of patient education (Figure 16). By utilising the RADAI-F5, healthcare professionals can assess and optimise foot care delivery in accordance with these identified themes and recommendations (NICE, 2018; Barber et al., 2021; Smolen et al., 2017). The integration of RADAI-F5 holds promise in supporting adherence to these recommendations by facilitating the evaluation of foot disease control, aiding in follow-up and monitoring processes, promoting

adequate referrals to advanced imaging and promoting patient self-education concerning foot disease (Laitenen et al., 2022). Consequently, the integration of the RADAI-F5 has the potential to facilitate and yield improved outcomes in the management of foot disease in individuals with RA.

FIGURE 17: STRATEGIC OBJECTIVES FOR QUALITY IMPROVEMENT FOR RA (BARBER ET AL., 2021)

The management of RA has primarily focused on achieving remission or low disease activity (Huange et al., 2022; Bowman & Guest, 2016). However, it is essential to acknowledge that RA is a multifaceted condition influenced by various psychosocial factors that significantly impact patients' QoL (Mucke, 2022; Espinoza et al., 2021). Although efforts have been made to evaluate and manage inflammation and disease activity, there is a growing recognition of the need to consider a broader range of factors beyond disease activity (Espinoza et al., 2021). The RADAI-F5 tool aligns with the medical narrative of enhancing early disease detection and facilitating T2T strategies within the 'window of opportunity.' Nevertheless, it is crucial to question whether this

tool adequately addresses the broader patient narrative, including the psychological and social factors contributing to understanding foot health and healthcare delivery. It is important to acknowledge that the RADAI-F5 tool, primarily focusing on foot disease activity, does not replace other components of the disease that patients may find equally important. Studies have identified suboptimal psychosocial well-being and negative disease perceptions as predictors of lower probability of sustained remission in early RA cohorts (Doumen et al., 2023; Hassan et al., 2019). Additionally, despite receiving adequate medical management in line with the EULAR guidelines, almost half of patients with mental health conditions still experience moderate to severe disease activity after 12-months, as highlighted by Lwin et al. (2020). These findings emphasise the need for a comprehensive approach to RA management that encompasses both foot disease activity and the psychological well-being of patients.

The integration of foot disease management within the framework of the psychosocial model of care presents an opportunity for holistic patient care. There are several arguments supporting the alignment between foot disease management and the principles of the psychosocial model. Firstly, foot disease manifestations in RA; including synovitis, tenosynovitis, and bursitis, can lead to pain, joint deformities, and functional limitations (Reina-Bueno et al., 2021; Tenten-Diepenmaat et al., 2018). By addressing foot disease, it is possible to reduce the burden of physical symptoms, such as joint pain, potentially improving patient mobility and overall physical well-being. Secondly, foot disease can have a significant psychological impact on individuals with RA, as evidenced in the qualitative research in Chapter 3. Chronic foot pain, loss of function, emotional distress, depression, and anxiety are among the psychological consequences and have been supported by numerous qualitative and quantitative studies (Cotchett et al., 2022; Sturgeon et al., 2016; Khan et al., 2021; Chapman et al., 2023; Wilson et al., 2017; Williams & Graham, 2012). By effectively managing foot disease, healthcare professionals can reduce joint pain, improve joint mobility, and enhance overall physical well-being. The RADAI-F5 offers an opportunity to reduce foot disease which may consequently result in reduction in psychological distress and burden, thus enhancing patients' mental health and well-being, as indicated by the qualitative study.

Furthermore, the integration of the RADAI-F5 into clinical practice may empower patients to actively engage in their own care and decision-making processes, as revealed by the qualitative study (Hoque et al., 2022). Involving patients in setting treatment goals, providing foot disease management education, and equipping them with self-management strategies holds the prospect of patient empowerment of their condition, leading to improved disease management (Laitenen et al., 2022). This patient-centred approach, utilising the RADAI-F5, promotes autonomy, self-efficacy, and patient empowerment. However, while the RADAI-F5 is a valuable tool for assessing

foot disease activity, it should be complemented with measures that capture the broader psychosocial aspects of the disease, such as the Short Form-36 or HAQ-DI (Küçükdeveci et al., 2021). By considering the interplay between physical symptoms, psychological well-being, and foot disease activity, healthcare providers have the opportunity to provide a more comprehensive and patient-centred approach to optimise foot outcomes for individuals with RA.

8.4 Dissemination of findings

Engaging stakeholders in disseminating the findings of this thesis played a crucial role in bridging the research-practice gap. It supported knowledge translation and empowered stakeholders to actively contribute to future RADAI-F5 research. Engagements with stakeholders were conducted with various local NHS services, including rheumatology clinics, podiatry services, and physiotherapy departments, as well as relevant RA patient groups. These engagements provided a platform to gather perspectives on the practical implications of the RADAI-F5 research. Additionally, the research findings were disseminated through presentations at podiatry and rheumatology conferences, enabling a wider audience that included researchers, healthcare professionals, policy-makers, and other stakeholders in the rheumatology field to be reached. Furthermore, a Knowledge Exchange (KE) event was organised specifically to disseminate the research findings to the wider RA community. Table 36 offers an overview of the various dissemination events conducted during the course of this doctoral journey.

TABLE 36: DISSEMINATION OF RADAI-F5 FINDINGS

Event	Date	Description
Musckoskeletal UK group- Glasgow Caledonian University	Thursday 15th August 2019	15 min oral presentation on the RADAI-F5 tool, including open discussions on implementing it in clinical practice.
Royal College of Podiatry annual conference	20-21 November 2019	5 min poster presentation and discussions with podiatrists about the significance of the RADAI-F5 tool.
Musckoskeletal Lanarkshire podiatry group presentation	5th November 2020	20 min oral presentation on the RADAI-F5 tool, including discussions on barriers and facilitators to its adoption in clinical practice.
North West Clinical Effectiveness Group Rheumatology Podiatry	2nd December 2020	20 min oral presentation and open discussion on the implementation of the RADAI-F5 tool in rheumatology care settings.
NHS Lanarkshire Rheumatology group	2nd March 2021	30 min oral presentation on the RADAI-F5 tool, with a forum for rheumatologists to share their views on clinical barriers and facilitators to its routine use.
Scottish Society of Rheumatology (autumn meeting)	25th October 2021	Qualitative study poster presentation
The Royal College of Podiatry annual conference	19th November 2021	Qualitative study poster presentation
British Society of Rheumatology Annual Conference 2022	25-27th April 2022	Qualitative study poster presentation

EULAR 2022 Annual conference	1-4th of June 2022	Qualitative study poster presentation
Royal College of Podiatry Annual conference and Exhibition	7th-9th July 2022	10 min oral presentation on the use of the RADAI-F5 tool in maintaining foot health in rheumatoid arthritis. Received high commendation award.
Scottish Society for Rheumatology autumn meeting-	28th October 2022	15 min oral presentation with feedback from rheumatologists and AHPs on the RADAI-F5 tool.
Podiatry Rheumatology Group	8th December 2022	20 min oral presentation and open discussions with specialist rheumatology podiatrists regarding the RADAI-F5 tool.
British Society of Rheumatology conference	23rd-26th April 2023	5 minute poster showcase
Knowledge Exchange event – Versus Arthritis- RA patients	19th July 2023	30 min oral presentation on the RADAI-F5 tool and current foot care methods in RA, facilitating focus group discussions with RA patients on their experiences of the RADAI-F5 and effective implementation of the tool.

8.5 Implications for future research

The findings of this study have highlighted several key areas for further investigation. Future studies using the RADAI-F5 are recommended in the following areas:

1. Feasibility Study of the RADAI-F5: Initiate a pivotal multi-center feasibility study to comprehensively evaluate the effectiveness of integrating the RADAI-F5 into clinical practice. As a foundational step, establish local steering groups for continuous planning, review, and refinement, employing the Plan, Do, Check, Act cycle. This process will build upon insights gathered from the current qualitative study.Cross-cultural validation of the RADAI-F5: Validate the RADAI-F5 tool in different cultural contexts and assess its reliability and validity in other rheumatic conditions.

2. Prognostic indicators for foot-related disability: Evaluate whether self-reported foot disease activity, as measured by the RADAI-F5, can predict foot-related disability and impairment in RA. This would involve a larger sample size and an extended study duration than the present preliminary predictive validity study.

3. Influence of foot disease on biomechanics and foot function: Investigate the impact of persistent and active foot disease on walking ability and foot function in individuals with early and established RA. Utilise PROMs (e.g. FFI, HAQ) and motion analysis systems to assess foot function, disability, overall health status, and objective biomechanical parameters during gait.

4. Tailored podiatry guidelines for RA patients: Develop or adapt existing foot guidelines for RA management, with a particular focus on incorporating the RADAI-F5 as a tool for evaluating foot disease. Additionally, create detailed instructions for the effective utilisation of the tool, accompanied by evidence-based and clinical recommendations of management strategies for each foot disease category.

5. Dedicated mobile app: Develop a mobile app for the RADAI-F5 and assess the usability and efficacy of such a tool in RA patients. This would provide a user-friendly platform for data collection, monitoring, and management of foot disease in RA, if it could be integrated within EHR.

8.6 Conclusion

The studies that form this thesis provide clear evidence of the recognition and support among key stakeholders for the implementation of the RADAI-F5 in rheumatology care settings, underscoring its importance in enhancing the quality of foot care for RA patients. However, challenges to its adoption were identified, particularly the need for validation against objective measures. Nonetheless, the RADAI-F5 exhibited moderate-strong correlations with MSUS, confirming its construct validity and good measurement properties. Additionally, the MID for the RADAI-F5 was determined to be a score change of 1.02, offering clinicians an initial threshold for considering treatment escalation or modification, which should be supplemented with patient perspectives gathered through discussions and history during clinical appointments. Moreover, preliminary evidence suggests the predictive value of the RADAI-F5 in assessing self-reported foot-related disability. In the realm of RA care, early detection and management of foot disease are paramount. The RADAI-F5 offers a potential avenue to improve foot disease detection and optimise management strategies within the 'window of opportunity,' potentially preventing poor radiographic and functional foot outcomes. Ultimately, the RADAI-F5 holds promise as a valuable tool that could improve foot care for individuals with RA.

Appendices:

Appendix A: Publication on measurement properties of the RADAI-F5

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Measuring Inflammatory Foot Disease in Rheumatoid Arthritis: Development and Validation of the Rheumatoid Arthritis Foot Disease Activity Index–5

Anika Hoque,[1] Kellie Gallagher,[2] Anne McEntegart,[3] Duncan Porter,[4] Martijn Steultjens,[5] James Woodburn,[5] and Gordon J. Hendry[5]

Objective. Omission of foot joints from composite global disease activity indices may lead to underestimation of foot and overall disease in rheumatoid arthritis (RA) and undertreatment. The aim of this study was to evaluate the measurement properties of the Rheumatoid Arthritis Foot Disease Activity Index–5 (RADAI-F5), a newly developed patient-reported outcome measure for capturing disease activity of the foot in people with RA.

Methods. Participants with RA self-completed the RADAI-F5, modified Rheumatoid Arthritis Disease Activity Index (mRADAI-5), Foot Function Index (FFI), and Foot Impact Scale (FIS) impairment/footwear and activity/participation subscales. The 28-joint count Disease Activity Score using the erythrocyte sedimentation rate (DAS28-ESR) was also recorded. Subgroups completed the RADAI-F5 at 1 week and 6 months. Psychometric properties, including construct, content and longitudinal validity, internal consistency, 1-week reproducibility, and responsiveness over 6 months were evaluated.

Results. Of 142 respondents, 103 were female, with a mean ± SD age of 55 ± 12.5 years and median RA disease duration of 10 months (interquartile range 3.6–20.8 months). Theoretically consistent associations confirming construct validity were observed with mRADAI-5 (0.789 [95% confidence interval (95% CI) 0.73, 0.85]), FFI (0.713 [95% CI 0.62, 0.79]), FIS impairment/footwear (0.695 [95% CI 0.66, 0.82], $P < 0.001$), FIS activity/participation (0.478 [95% CI 0.37, 0.63], $P < 0.001$), and the DAS28-ESR (0.379 [95% CI 0.26, 0.57], $P < 0.001$). The RADAI-F5 demonstrated high internal consistency (Cronbach's $\alpha = 0.90$) and good reproducibility (intraclass correlation coefficient = 0.868 [95% CI 0.80, 0.91], $P < 0.001$, smallest detectable change 2.69). Content validity was confirmed, with 82% rating the instrument relevant and easy to understand.

Conclusion. The RADAI-F5 is a valid, reliable, responsive, clinically feasible patient-reported outcome measure for measuring foot disease activity in RA.

INTRODUCTION

Foot pain and disability are common in people who have rheumatoid arthritis (RA), with up to 90% experiencing disease-related foot symptoms during the course of their disease (1–4). Synovitis in the small joints of the feet is present at the onset of RA in up to 70% of patients (5). With the implementation of pharmacologic management, the prevalence of forefoot disease stabilizes at 40–50% after 2 years, but the prevalence of radiographic joint damage increases from 20% to 50% (5). Approximately half of patients experience hindfoot joint problems (6), and clinically important soft tissue disease such as tibialis posterior tenosynovitis has a reported prevalence ranging from 13% to 64% (3).

The management of RA involves a treat-to-target strategy that comprises regular review, objective assessment of disease activity, and escalation of treatment if there is persistent disease activity. The aim is to achieve clinical remission (or low disease activity) (7,8). Evaluation of inflammatory disease activity in RA

involves the composite disease activity indices, of which the most widely used are the 28-joint count Disease Activity Score using the erythrocyte sedimentation rate (DAS28-ESR) (9), the Clinical Disease Activity Index (CDAI), and the Simplified Disease Activity Index (SDAI) (10). These include 28-joint counts for tenderness and swelling that omit the joints and soft tissues of the feet (11). Recent studies have demonstrated that approximately one-third of patients with RA classified by the DAS28, SDAI, and/or CDAI as in remission had clinically determined active foot synovitis (2,11,12). Although the examination of foot joints is recommended (13), patients treated solely according to disease activity indices may be at risk of ongoing foot joint damage (11,14).

Various self-reported measures of RA disease activity have been validated, including 2 versions of the Rheumatoid Arthritis Disease Activity Index (RADAI and modified RADAI-5 [mRADAI-5]) (15,16). While these tools are more likely to capture foot disease activity than composite indices that exclude examination of foot joints, they are not widely used in clinical practice. Several questionnaires have been developed for measuring RA-related foot problems, including the Foot Impact Scale (FIS), the Foot Function Index (FFI), and the Salford Rheumatoid Arthritis Foot Evaluation instrument (17–19). These largely focus on disability as opposed to disease activity, and so have limited value for informing medical management. In addition, these tools lack feasibility in clinical practice due to a high number of items and associated time burden, as well as the absence of clinically meaningful categories for ease of interpretation.

The current gold standard technique for measuring foot disease activity is magnetic resonance imaging (MRI) (20). The more widely used imaging alternative is musculoskeletal ultrasound, which is less sensitive than MRI and more specific than clinical examination of disease activity in RA (20–22). However, these methods are not routinely used due to impracticalities such as cost of scans/equipment, time to perform scans, training needs, and the risk of exposure to contrast agents. There is also a lack of consensus concerning how to

approach medical management of subclinical disease detected using musculoskeletal ultrasound (23).

Therefore, there is no widely used, validated, and clinically feasible method for the assessment of foot disease activity in RA. We propose that a patient-reported outcome measure designed to measure local foot disease activity may provide an opportunity for a treat-to-target medical approach that does not exclude foot disease activity. Accordingly, the purpose of this study was to develop and validate a new concise measure of foot disease activity for people with RA.

PATIENTS AND METHODS

Development of the questionnaire. The design and content of the Rheumatoid Arthritis Foot Disease Activity Index–5 (RADAI-F5) was derived from the mRADAI-5, a 5-item patient-reported outcome measure for the self-report of global disease activity, developed and evaluated by Leeb et al (16) and Rintelen et al (24). It is completed in a numerical rating scale format from 0 to 10 and scored by an average summary score ranging 0–10. The RADAI-F5 was developed by editing the mRADAI-5 with an opening statement: "Thinking only of your feet," and editing the original questions to subsequently read as follows: "How active was your arthritis in your feet over the last 6 months?" (0 = completely inactive to 10 = extremely active); "How active is your foot arthritis today with respect to joint tenderness and swelling?" (0 = completely inactive to 10 = extremely active); "How severe is your arthritis pain in your feet today?" (0 = no pain to 10 = unbearable pain); "How would you describe your general foot health today?" (0 = very good to 10 = very bad); "Did you experience foot joint stiffness on awakening yesterday morning? If yes, how long was this stiffness in your feet?" (0 = no stiffness to 10 = stiffness the whole day). The RADAI-F5 is scored by an average summary score ranging from 0 to 10.

Study setting and participants. The 2 data sources for this study were 1) a primary RADAI-F5 validation study, conducted at rheumatology outpatient clinics at Glasgow Royal Infirmary, Gartnavel General Hospital, and Stobhill Hospital within the Greater Glasgow and Clyde National Health Service Board, and 2) a larger randomized controlled trial, the details of which have been published previously (25). Briefly, the trial was a multicenter, parallel-group, randomized controlled trial with 6- and 12-month follow-up periods, with participants randomly allocated to either customized or prefabricated foot orthoses. Trial participants were recruited from rheumatology outpatient clinics within NHS Grampian, Fife, and Lanarkshire, Lothian Health Boards, Dorset Healthcare University Trust, and Homerton University Hospital Trust.

Participants were included if they were ages 18–75 years, with a definitive clinical diagnosis of RA. Patients were excluded if they were unable to read, write, and/or understand the English

language, or if they were diagnosed with other major medical conditions that could have diminished their ability to distinguish between RA-related foot problems and problems due to alternative disease mechanisms. Ethical approval was obtained from the West of Scotland Research Ethics Committee 5 (13/WS/0106) and the East of England Essex Research Ethics Committee (15/EE/0410). Participants were recruited consecutively, and written consent was obtained from all participants.

Data collection and measures. Demographic and clinical information was collected at baseline, including age, sex and disease duration. The newly developed RADAI-F5 was collected at baseline, 1 week from baseline, and 6 months from baseline. All other measurements were recorded at baseline and 6 months. The DAS28-ESR scores were recorded by rheumatologists as part of routine care and made available to researchers. The mRADAI-5 was collected as an additional self-reported measure of global disease activity (16). Foot-related impairments and disability were evaluated using the FFI (18), and the FIS (17). The FFI is a widely used and extensively validated 23-item patient-reported outcome measure, completed using a 100-mm visual analog scale format, providing a mean summary score from 0 to 100 (higher scores indicating worse disability) (18). The FIS is an extensively validated RA-specific 51-item measure with domains for impairment/footwear (21-items) and activity limitation/participation restriction (30-items). It is completed using a yes/no dichotomous format, and scores for domains are calculated by summing "yes" responses (higher scores indicating worse disability) (17).

To evaluate the content validity and practical burden of the RADAI-F5, 3 additional items were evaluated: a 5-point Likert scale regarding questionnaire relevance to participants (ranging from extremely irrelevant to extremely relevant), a 5-point Likert scale regarding participants' opinions on the readability/understanding of the new questionnaire (ranging from very difficult to very easy), and the time taken to complete the questionnaire (in minutes).

Statistical analysis. Data were analyzed using SPSS 25 and Excel 2016. Descriptive statistics for age (median [interquartile range (IQR)]) in years, sex (female:male ratio), and disease duration (median [IQR]) in months were generated for all participants at baseline. The RADAI-F5 was examined using factor analysis by principal component analysis to reveal the structure and item loading. The Kaiser-Meyer-Olkin test and Bartlett's test of sphericity were undertaken to determine data suitability for factor analysis. The number of factors extracted was decided by a combination of Kaiser's rule (eigenvalues >1), examination of the scree plot, and interpretation of items' contribution to the factor. To test internal consistency, we evaluated the inter-item correlation matrix and calculated Cronbach's alpha, a measure of consistency between items in a scale. A Cronbach's $\alpha = 0.7-0.9$ was considered acceptable (26,27).

Hypotheses were generated a priori to examine the extent to which baseline scores (construct validity) and 0–6-month change scores (longitudinal validity) on the RADAI-F5 were associated with baseline and 0-6-month change scores from other measures in a manner that was theoretically consistent (28). Hypotheses for construct validity, which focused on baseline scores, were specified as follows: moderate positive correlations between the RADAI-F5 score and mRADAI-5, FFI, and FIS domains, and a positive weak correlation between the RADAI-F5 score and the DAS28 score. Hypotheses for longitudinal validity, which focused on 0–6-month change scores, were identical except for the FIS subscales, where a weak positive correlation was anticipated, because the FIS is less responsive to change (29). Spearman's rank (r_s) correlation and 95% confidence intervals (95% CIs) were used to test these hypotheses, and coefficients were interpreted as follows: 0–0.09 = negligible, 0.1–0.39 = weak, 0.4–0.69 = moderate, 0.7–0.89 = strong, and 0.9–1.0 = very strong (30).

The 1-week (test–retest) reliability was examined using a 2-way mixed intraclass correlation coefficient (ICC) with corresponding 95% CIs for baseline and 1-week scores. Once preliminary foot disease categories were established (see below), Cohen's quadratic weighted kappa and corresponding 95% CI for foot disease categories (remission, low, moderate, high) were calculated, with values >0.61 indicating substantial reliability (31).

Absolute measurement error was evaluated using the standard error of measurement (SEm), derived by dividing the SD of the mean change between the 2 measurements ($SD_{change}/\sqrt{2}$); the 95% limits of agreement, derived by calculating the mean change between the 2 measurements, $\pm1.96 \times$ the SD of the changes ([$mean_{change}$] $\pm 1.96 \times$ [SD_{change}]); the 95% smallest detectable change (1.96 $\times \sqrt{2} \times$ SEm), and construction and examination of Bland-Altman plots (32–34).

Responsiveness was evaluated using 4 different effect size statistics: Wilcoxon's signed ranks test, Cohen's *d*, the standardized response mean, and Guyatt's Index (35). In the absence of an anchor question to calculate the minimum important difference (MID), the MID was calculated using a value of 0.5 $\times$ SD_{change} scores between baseline and 6 months. Guyatt's Index, representing the magnitude and variability in change scores relative to its MID, was calculated as $MID/\sqrt{(2 \times SD_{change})}$ (36). Effect sizes were interpreted as follows: <0.15 = negligible, ≥0.15 to <0.40 = small, ≥0.40 to <0.75 = medium, ≥0.75 to <1.10 = large, ≥1.10 to <1.45 = very large, and ≥1.45 = huge (35).

Participants were classified according to mRADAI-5 thresholds for remission, mild, moderate, or high disease activity. With participants assigned to the mRADAI-5 reference categories, the third quartile of corresponding RADAI-F5 scores was calculated to establish the thresholds for respective RADAI-F5 categories (24). Cohen's quadratic weighted kappa and 95% CI were used to evaluate agreement between disease activity categories between the mRADAI-5 and the RADAI-F5.

Table 1. Characteristics of the participants at baseline (n = 142)*

Characteristic	Value
Female, %	72.5
Age, years	55.5 (50–62)
Disease duration, months	10 (3.6–20.8)
RADAI-F5 (0–10)	5.2 (3.2–7.3)
mRADAI-5 (0–10)	5.4 (3.4–7.2)
DAS28-ESR (0–10)	4.1 (2.84–4.92)
FFI (0–100)	45.9 (23.2–58.03)
FIS IF (0–21)	13 (8.0–15.25)
FIS AP (0–30)	16.0 (6.5–22.0)

* Values are the median (interquartile range) unless indicated otherwise. DAS28-ESR = 28-joint count Disease Activity Score using the erythrocyte sedimentation rate; FFI = Foot Function Index; FIS AP = Foot Impact Scale activity/participation subscale; FIS IF = FIS impairment/footwear subscale; mRADAI-5 = modified Rheumatoid Arthritis Disease Activity Index; RADAI-F5 = Rheumatoid Arthritis Foot Disease Activity Index-5.

Median (IQR) values were obtained for readability and relevant Likert scores and completion time. For evaluation of floor and ceiling effects for the RADAI-F5 in the RA population, we adopted the conventional 15% threshold for patients achieving the highest and lowest scores to define ceiling and floor effect, respectively (32,37). To evaluate structural validity via factor analysis, a minimum sample size of n ≥100 at baseline was targeted a priori to achieve a participant-to-item ratio of 20 (38). For hypotheses testing for construct and longitudinal validity, between 61 and 123 participants were required to detect at least weak correlation coefficients from 0.25 to 0.35 at 80% power and 0.05 significance level (G*Power 3.1.9.2).

RESULTS

A total of 142 participants (72.5% female) with a median age of 55.5 years (IQR 50–62 years) and median disease duration of 10 months (IQR 3.6–20.8 months) took part, including 37 from the primary RADAI-F5 study and 105 from the randomized controlled trial. A total of 84 participants completed the RADAI-F5 at 1 week for reproducibility analyses, and 64 completed 6-month follow-ups for responsiveness analyses. Median (IQR) DAS28-ESR and mRADAI-5 scores indicated that participants were typically in a moderate disease activity state at study baseline (Table 1). For DAS28-ESR disease categories, 21.5% were in remission, 8.4% had low disease activity, 47.7% had moderate disease activity, and 22.4% had high disease activity. Median (IQR) FFI, FIS impairment/footwear, and FIS activity limitation/participation restriction subscale scores suggested that participants typically presented with moderate foot-related disability at baseline (Table 1).

Dimensionality. The Kaiser-Meyer-Olkin value of 0.83 and highly significant Bartlett's test ($P < 0.001$) indicated sampling adequacy and suitability for structure detection and factor analysis. Both Kaiser's "eigenvalue >1" rule and scree plot examination suggested a 1-factor solution, and this solution explained 73.18% of the common variance. Item loadings on the factor were uniformly >0.4, indicating that all items contributed significantly to the aggregate score.

Internal consistency. High inter-item correlations (>0.8) were observed for questions 2 and 3, 2 and 4, and 3 and 4 of the questionnaire. Moderate inter-item correlations (>0.6) were observed for questions 1 and 2, and 2 and 5. All other inter-item correlations were between 0.4 and 0.6. Cronbach's α = 0.90, indicating a high level of internal consistency.

Construct validity. The RADAI-F5 had a weak positive correlation with the DAS28 ($r_s = 0.38$ [95% CI 0.26, 0.57], $P < 0.001$) (Figure 1), and a moderate positive correlation with the FIS impairment/footwear ($r_s = 0.69$ [95% CI 0.66, 0.82], $P \le 0.001$) and FIS activity limitation/participation restriction subscales ($r_s = 0.48$ [95% CI 0.37, 0.63], $P < 0.001$). Stronger positive correlations than predicted were observed for the mRADAI-5 ($r_s = 0.79$ [95% CI 0.73, 0.85], $P < 0.001$), and the FFI ($r_s = 0.71$ [95% CI 0.62, 0.79], $P < 0.001$) (Figure 1). Sixty percent of associations for construct validity were in line with a priori hypotheses and therefore largely theoretically consistent. Construct and longitudinal validity analyses are shown in Table 2.
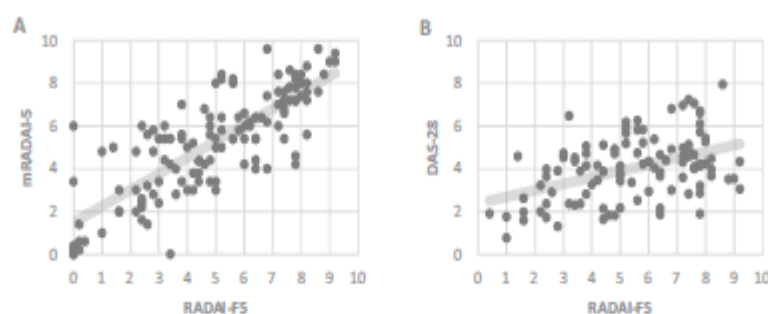
Figure 1. Scatterplots demonstrating convergent and divergent validity for Rheumatoid Arthritis Foot Disease Activity Index–5 (RADAI-F5) associations with the modified Rheumatoid Arthritis Disease Activity Index (mRADAI-5) (n = 133) (A) and the 28-joint count Disease Activity Score (DAS-28) scores (n = 106) (B). The gray lines show the best fit for the trend. Each circle illustrates a participant's RADAI-F5 score and corresponding modified RADAI (A) or DAS28 (B) score.

Table 2. RADAI-F5 construct and longitudinal validity correlations for a priori hypotheses testing for associations with alternative disease activity and foot disability measures*

Measure	Correlation coefficient (95% CI)	Strength of association	A priori hypothesis for association
Construct validity†			
mRADAI-5 (n = 133)	0.79 (0.73, 0.85)‡	Strong	Moderate
DAS28-ESR (n = 106)	0.38 (0.26, 0.57)‡	Weak	Weak
FFI (n = 132)	0.71 (0.62, 0.79)‡	Strong	Moderate
FIS IF (n = 125)	0.69 (0.66, 0.82)‡	Moderate	Moderate
FIS AP (n = 124)	0.48 (0.37, 0.63)‡	Moderate	Moderate
Longitudinal validity§			
mRADAI-5 (n = 63)	0.66 (0.41, 0.74)‡	Moderate	Moderate
DAS28-ESR (n = 60)	0.33 (0.04, 0.52)¶	Weak	Weak
FFI (n = 64)	0.60 (0.47, 0.77)‡	Moderate	Moderate
FIS IF (n = 63)	0.43 (0.01, 0.56)‡	Moderate	Weak
FIS AP (n = 63)	0.19 (−0.01, 0.49)	Weak	Weak

* 95% CI = 95% confidence interval; DAS28-ESR = 28-joint count Disease Activity Score using the erythrocyte sedimentation rate; FFI = Foot Function Index; FIS AP = Foot Impact Scale activity/participation subscale; FIS IF = FIS impairment/footwear subscale; mRADAI-5 = modified Rheumatoid Arthritis Disease Activity Index; RADAI-F5 = Rheumatoid Arthritis Foot Disease Activity Index-5.
† Using baseline scores.
‡ $P < 0.01$.
§ Using 0–6-month change scores.
¶ $P < 0.05$.

Longitudinal validity. The RADAI-F5 had a weak positive correlation with the DAS28-ESR ($r_s = 0.33$ [95% CI 0.04, 0.52], $P = 0.011$), and a moderate positive correlation with the mRADAI-5 ($r_s = 0.66$ [95% CI 0.41, 0.74], $P < 0.01$), the FFI ($r_s = 0.60$ [95% CI 0.47, 0.77], $P < 0.001$), and the FIS impairment/footwear subscale ($r_s = 0.43$ [95% CI 0.09, 0.56], $P = 0.001$). A weaker positive correlation than predicted was observed for the FIS activity limitation/participation restriction subscale ($r_s = 0.19$ [95% CI −0.01, 0.49], $P = 0.156$), and the FFI ($r_s = 0.71$ [95% CI 0.62, 0.79], $P < 0.01$). Eighty per cent of associations for longitudinal validity were in line with a priori hypotheses.

Reliability. Mean ± SD RADAI-F5 scores for baseline and 1 week were 4.8 ± 2.58 and 4.91 ± 2.74, respectively. The mean ± SD difference between baseline and 1 week for the RADAI-F5 was 0.11 ± 1.37. The ICC for 1-week reproducibility was 0.87 (95% CI 0.80, 0.91; $P \leq 0.001$), indicating very good reproducibility.

Absolute measurement error. The SEm value calculated for the RADAI-F5 from baseline and 1-week data was 0.97. This value can be interpreted as follows: if a patient scores 3 on the RADAI-F5, we can be 68% confident that their true score lies between 2.03 and 3.97, and 95% confident that their true score lies between 1.1 and 4.9. The limits of agreement were −2.57 and 2.80. From the Bland-Altman plot (Figure 2), we can conclude that 97.6% of the differences between the 2 time points were within the 95% limits. Exploration of the plot suggests that there may be a minor funnel effect, with spread increasing slightly with increasing mean concentration (higher foot disease activity). The 95% smallest detectable change value was estimated as 2.69, representing 26.9% of the RADAI-F5 scale maximum range, meaning that we can be 95% confident that a change score of 2.69 or more is a true change.

Responsiveness. The RADAI-F5 exhibited high responsiveness to change over 6 months, as evidenced by highly significant Wilcoxon's signed rank tests ($P < 0.001$) with a very large effect size (0.91), Cohen's $d = 0.64$ (medium effect size), and a standardized response mean of 0.97 (very large effect size). The MID value obtained from the distribution method ($0.5 \times SD_{change}$) was 1.16, and the subsequent Guyatt Index value calculated was 0.70 (medium effect size). These values can be interpreted as a consistent pattern of medium-to-high responsiveness for the RADAI-F5.

Interpretability. For remission according to the mRADAI-5, the RADAI-F5 median and third quartile were 0.73 and 1.0 (n = 11). Therefore, the remission state was defined as a RADAI-F5 score ranging from 0 to 1.0. The same procedure applied to define the disease categories for mild, moderate, and high disease activity, resulting in the following ranges: >1 to 3.6 for mild disease activity (n = 15), >3.6 to 5.7 for moderate disease activity (n = 42), and >5.7 to 10 for high disease activity (n = 65) (Table 3). Agreement between the RADAI-F5 and mRADAI-5 categories was good, as expressed by 72.5% exact agreement and Cohen's quadratic weighted $\kappa = 0.71$ (95% CI 0.56, 0.85). For the newly derived RADAI-F5 disease categories, agreement between baseline and 1 week was good, as expressed by 70.0% exact agreement and Cohen's quadratic weighted $\kappa = 0.81$ (95% CI 0.75, 0.88). Characteristics of disease and foot-related disability status within newly developed RADAI-F5 disease categories are shown in Table 3.
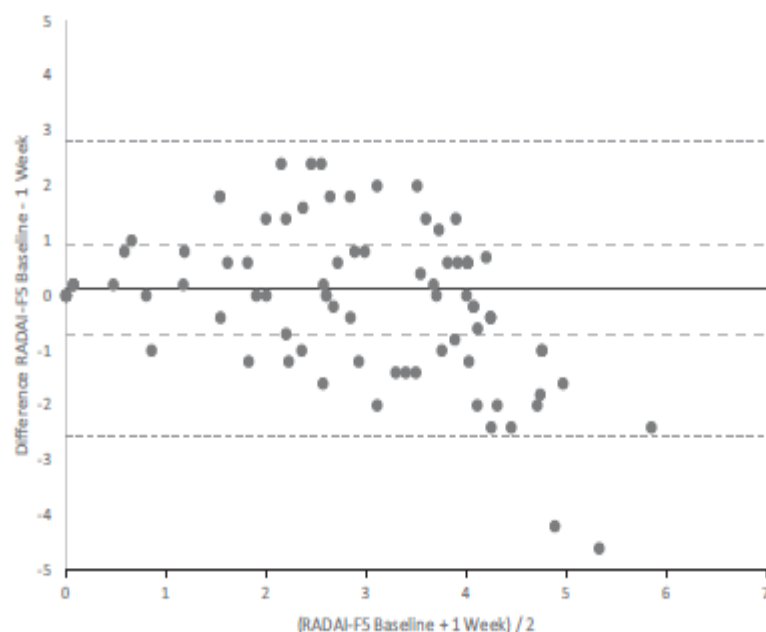
Figure 2. Bland-Altman plot for the Rheumatoid Arthritis Foot Disease Activity Index–5 (RADAI-F5) summary score, with data points illustrating average scores from 2 time points separated by 1 week (n = 84) against the difference between the corresponding baseline and 1-week scores, bias (solid line represents the average SD for baseline to 1-week scores for all participants), bias upper and lower 95% confidence interval limits (inner broken lines), and upper and lower limits of agreement (outer broken lines).

Content validity and practical burden. Participants largely considered the RADAI-F5 to be relevant for measuring foot disease activity in RA, with 53% and 29% indicating that it was relevant and extremely relevant, respectively (Figure 3A). Participants largely considered the RADAI-F5 to be easy to read and understand, with 45.8% and 40% indicating that it was easy and very easy to read/understand, respectively (Figure 3B). The median time to complete the questionnaire was 5 minutes (IQR 2–15). Overall the RADAI-F5 appears to have good content validity and low completion burden.

Floor/ceiling effects. A total of 6 participants (4.33%) achieved the lowest possible RADAI-F5 score (0), and 0 participants achieved the highest possible score (10). Based on the 15% threshold levels, the RADAI-F5 does not exhibit a ceiling or floor effect.

DISCUSSION

We have developed and validated a 5-item patient-reported outcome measure, named the Rheumatoid Arthritis Foot Disease

Table 3. Participant characteristics according to RADAI-F5 foot disease activity categories*

Characteristic	Remission (0–1; n = 11)	Mild (<1–3.6; n = 15)	Moderate (>3.6–5.7; n = 42)	High (>5.7–10; n = 65)
Female, %	75	62.1	89.2	33.3
Age, years	63 (47–74)	59 (53–69)	54.5 (49–59)	55 (50–61)
Disease duration, months	144 (48–246)	10 (3–19)	7 (4–14)	11 (3–22)
DAS remission, no. (%)	3 (2.9)	10 (9.5)	6 (5.7)	3 (2.9)
DAS low disease, no. (%)	0 (0)	2 (1.9)	1 (1.0)	6 (5.7)
DAS moderate disease, no. (%)	0 (0)	10 (9.5)	14 (13.3)	26 (24.8)
DAS high disease, no. (%)	0 (0)	1 (1.0)	8 (7.6)	15 (14.3)
DAS28-ESR	1.76 (0.8–1.8)	2.91 (2.3–4.4)	4.13 (3.0–5.1)	4.33 (3.6–5.3)
mRADAI-5	0.6 (0.2–2.9)	3.2 (2.3–5.2)	5.2 (3.8–6.4)	7.2 (6.0–7.9)
FFI	4.8 (0–10)	17.9 (9.6–43.7)	35.8 (29.4–47.9)	56.9 (48.3–69.2)
FIS IF	0 (0–3.25)	8 (6–11.75)	12 (11–15)	15 (13–17)
FIS AP	1.5 (0–8.25)	10 (4–15)	14 (10–22)	19 (16–24)

* Values are the median (interquartile range) unless indicated otherwise. DAS = Disease Activity Score; DAS28-ESR = 28-joint count DAS using the erythrocyte sedimentation rate; FFI = Foot Function Index; FIS AP = Foot Impact Scale activity/participation subscale; FIS IF = FIS impairment/footwear subscale; mRADAI-5 = modified Rheumatoid Arthritis Disease Activity Index; RADAI-F5 = Rheumatoid Arthritis Foot Disease Activity Index-5.
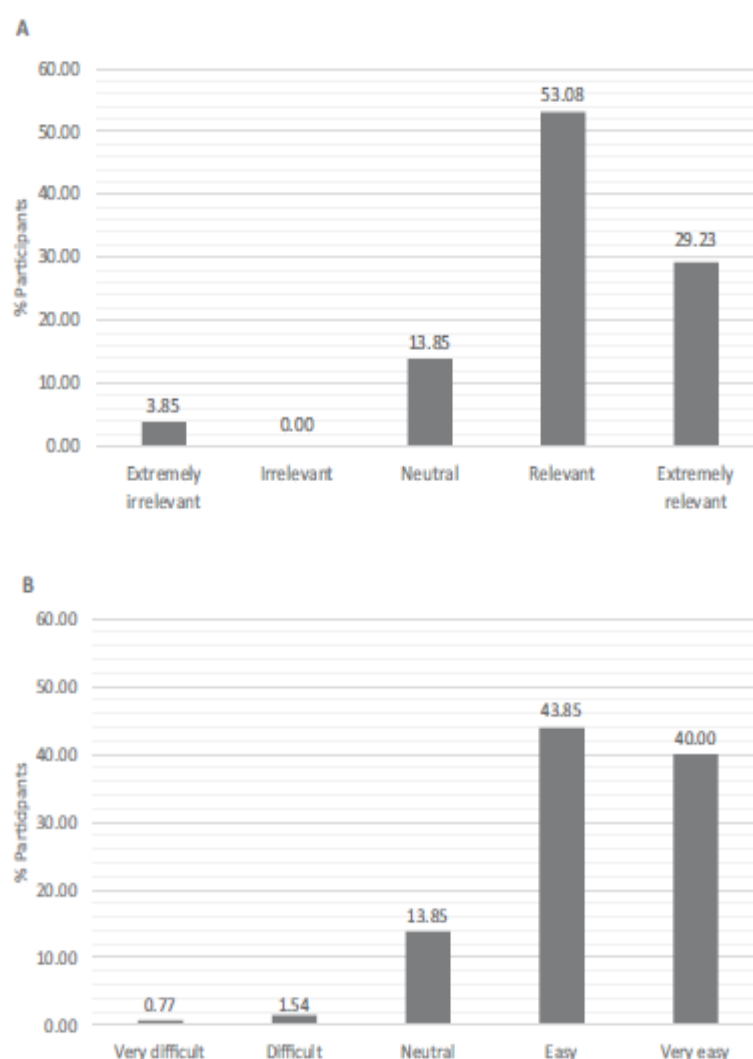
Figure 3. Bar charts of participant responses (n = 130) to Rheumatoid Arthritis Foot Disease Activity Index–5 relevance (**A**) and readability/understanding (**B**) Likert scales.

Activity Index (RADAI-F5) to allow for the monitoring of inflammatory foot disease activity in people with established and early RA. The psychometric properties meet the recommended standards set by the International Society for Quality of Life Research (39) and the Consensus Based Standards for the Selection of Health Measurement Instruments (40), demonstrating good construct validity, reliability, content validity, internal consistency, responsiveness, and interpretability. The new patient-reported outcome measure is designed to be quick and simple for patients to complete and clinicians to score and interpret, so that it can be used alongside composite disease activity indices in clinical practice. We anticipate that future use of the RADAI-F5 as an adjunct to composite disease activity indices will improve local disease monitoring and may facilitate better medical management of foot disease activity. The RADAI-F5 may also be used alongside existing disease-specific foot disability patient-reported outcome measures such as the FIS in rehabilitation settings to distinguish between inflammatory and mechanical/functional foot impairments, which may help to inform new and extended paradigms of foot care in early RA (41). Moreover, the RADAI-F5 could possibly negate the need for composite disease activity scores to be recorded for RA foot research purposes (often collected to account for confounding).

A key finding of this study is that evidence of convergent validity was observed between the RADAI-F5 and the mRADAI-5, and divergent validity between the RADAI-F5 and the DAS28-ESR. This finding was anticipated a priori and is theoretically consistent with existing evidence demonstrating that composite disease activity indices that omit foot joints do not adequately capture foot synovitis (11). Indeed, the majority of our a priori

specified hypotheses were confirmed for strength of associations between disease activity/foot disability measures with the RADAI-F5. The correlation between RADAI-F5 and mRADAI-5 was slightly stronger than anticipated, but perhaps unsurprising given the similarities of these instruments. Another explanation is that relative to the DAS28-ESR, the mRADAI-5 has the ability to capture foot disease activity because it includes questions that cover all joints as a whole (16). Importantly, RADAI-F5 and mRADAI-5 scores were not perfectly correlated, and 72.5% agreement was observed between respective disease activity categories for each instrument, suggesting they capture local and global disease, respectively.

The RADAI-F5 demonstrated very good reliability characteristics in terms of 1-week reproducibility of summary scores and agreement between baseline and 1-week disease categories. However, the 95% smallest detectable change (2.69) derived from the SEm (0.97) was larger than anticipated and exceeded the preliminary MID value (1.16) that was obtained via the distribution method. This means that if an individual patient has a change score as large as the preliminary MID, we cannot be 95% confident that this change is not due to measurement error (33). This finding may be explained by the presence of outliers rather than systematically large change scores (Figure 3, Supplementary Figures 1–5, and Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24259/abstract.

Inspection of outliers suggested a tendency for larger change scores in those patients with shorter disease durations. Moreover, the RADAI-F5 summary change scores appeared to be predominantly driven by larger change scores for individual items 4 (general foot health) and 5 (morning stiffness in the feet), which may be more unstable over shorter periods of time. This possibility suggests that the instrument stability period of 1 week adopted here may be too long to evaluate the instrument in those whose disease may be unstable. Moreover, changes in therapy such as administration of intramuscular steroids could possibly have affected 1-week scores. Anchor-based derivations of RADAI-F5 MID are now planned because these are recommended and should be assigned the most weight when estimating the MID (38,42). We recommend that population-specific RADAI-F5 MID values be derived for future longitudinal studies seeking to measure changes in foot disease over time.

A strength of the RADAI-F5 is that it appears to demonstrate a consistent pattern of good responsiveness and theoretical consistency for longitudinal measurement, as has been reported for other global disease activity patient-reported outcome measures (16,43). We evaluated responsiveness using data from a pragmatic trial comparing customized versus prefabricated foot orthoses plus routine medical care in early RA (25). While the responsiveness results over a 6-month period are promising, medical care was not standardized, and so drugs and dosages varied between participants. Nevertheless, theoretically consistent associations

for change scores between the RADAI-F5 and alternative instruments were observed, suggesting that it could be used longitudinally to measure changes in foot disease activity in early RA.

Preliminary foot disease category thresholds are proposed here to enhance applicability in routine clinical care in line with conventional categories adopted in other global disease activity patient-reported outcome measures and composite indices (24). While there is a relatively broad spectrum of RADAI-F5 scores in the study sample, we observed a negatively skewed distribution, indicative of predominant moderate-to-high foot disease activity within the sample. As a result, there were proportionally fewer participants allocated to remission and mild categories than the moderate and high categories. We also acknowledge that in the absence of a gold standard outcome measure for quantifying foot disease activity, the mRADAI-5 (a global index of disease activity) was the best available reference score for establishing foot disease activity categories. While threshold cut-offs appear to have good face validity, further evaluation using alternative approaches such as receiver operating characteristic curves may be appropriate. Our future work will seek to confirm preliminary foot disease activity category thresholds reported here with greater focus on those with more established disease who are in remission or low global disease activity states. We will also seek to determine whether treatment regimens would frequently be changed due to detection of persistent moderate foot disease in patients who are in low disease activity or remission states according to DAS28-ESR.

We have confirmed that the RADAI-F5 is valid, reliable, responsive, acceptable to patients, and potentially feasible for use in clinical practice in terms of ease of completion, quick scoring, and interpretability. The RADAI-F5 is freely available for use from www.gcu.ac.uk/centreforliving/radai-f5 and is recommended for use by rheumatologists and/or rheumatology nurse specialists alongside composite global disease activity indices, and by Allied Health Professionals such as podiatrists and physiotherapists involved in delivering nonmedical foot care in RA.

AUTHOR CONTRIBUTIONS

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Appendix B: The RADAI-F5 tool

| Rheumatoid Arthritis Foot Disease Activity Index (RADAI-F5) |

THINKING ONLY OF YOUR FEET

1. How active was your arthritis IN YOUR FEET over the last 6 months?

Completely inactive   0 1 2 3 4 5 6 7 8 9 10   Extremely active

2. How active is your FOOT arthritis today with respect to joint tenderness and swelling?

Completely inactive   0 1 2 3 4 5 6 7 8 9 10   Extremely active

3. How severe is your arthritis pain IN YOUR FEET today?

No pain   0 1 2 3 4 5 6 7 8 9 10   Unbearable pain

4. How would you describe your general FOOT health today?

Very good   0 1 2 3 4 5 6 7 8 9 10   Very bad

5.   Did you experience foot joint stiffness on awakening yesterday morning? If yes, how long was this stiffness IN YOUR FEET?

No stiffness	0	1	2	3	4	5	6	7	8	9	10	Stiffness the whole da

No stiffness	0	1	2	3	4	5	6	7	8	9	10	Stiffness the whole da

Appendix C- Findings from stakeholder discussions

The stakeholder sessions included both early and established cases of RA, with participants who had previous experience with NHS rheumatology or podiatry clinics. Participants were contacted through Versus Arthritis gatekeepers. Rheumatologists and AHPs with varying levels of experience were also included in the sessions. Healthcare groups such as the MSK Lanarkshire podiatry group, North West clinical effectiveness group, NHS Lanarkshire Rheumatology group, and the Scottish Society of Rheumatology patient representative group were also included. These groups consisted of RA patients, rheumatologists, podiatrists, and physiotherapists. All participants were provided with a summary of the research project and individual discussions were conducted with RA patients, rheumatologists, and AHPs. Group discussions were used when presenting the RADAI-F5 to research or healthcare groups.

RA patients were identified through established connections with Versus Arthritis, recognised as key "gatekeepers" for engaging patients in arthritis-related research. Concurrently, healthcare groups and professional were approached using contacts who had previously participated in stakeholder sessions at Glasgow Caledonian University. To ensure timely and effective engagement, interactions with National Health Service (NHS) trusts and healthcare groups were thoughtfully scheduled at their monthly meetings, with planning undertaken 3 to 6 weeks in advance. Clear and comprehensive communication channels were employed, including emails, phone calls, and face-to-face discussions tailored to individual and group preferences. During these interactions, the research project's purpose and the integral role of stakeholders were elucidated. Any inquiries or reservations raised by potential participants were diligently addressed to foster informed decision-making and conversation. Robust documentation practices by disseminating the discussion findings ensured transparency and accountability throughout the study process.

The PPI engaged nine individuals diagnosed with RA, four rheumatologists and two physiotherapists. Furthermore, the stakeholder representatives in the MSK and rheumatology network groups included rheumatologists, podiatrists, physiotherapists, rheumatology nurses and orthotists with varying level of clinical experience. The stakeholder engagement process commenced in August 2019 until July 2023 to ensure ongoing input from key stakeholders and to inform subsequent thesis studies. These sessions provided crucial insights into the needs, preferences, and priorities of those directly affected by the health condition, ensuring alignment between the research studies and key stakeholders interests. These findings are summarised in Table 36.

TABLE 36: SUMMARY OF FINDINGS FROM STAKEHOLDER DISCUSSIONS

Event	Date	Participant Characteristics	Methods of Data Collection	Feedback
NHS Musculoskeletal Greater Glasgow and Clyde group	Thursday 15th August 2019	Podiatrists	Group discussions at Glasgow Caledonian University	Positive feedback and receptive to the RADAI-F5 tool: "It is so simple, I am surprised no one has done this before," "An app with the RADAI-F5 would be a good idea," "How will you implement this?"
Sessions with rheumatologists	30th October 2020 - 20th November 2022	Rheumatologists based in NHS Scotland, Years of experience: 3-32 years	Individual interviews on Microsoft Teams	Feedback includes concerns about foot disease being overlooked, time constraints, and the need for objective measures like ultrasound for validation and predictive validity work. Some suggest using the RADAI-F5 as a screening tool and for triaging purposes in clinical practice.
Individuals with rheumatoid arthritis	20th October 2020 - 21st February 2022	Individuals with a rheumatologist diagnosis of RA, Disease duration: 8 months - 17 years, Based around the United Kingdom	Individual interviews on Microsoft Teams	Feedback highlights the importance of addressing foot concerns, early intervention in feet, and the usefulness of RADAI-F5 in clinic. Some patients express discomfort in discussing foot issues with their healthcare providers and inquire about comparisons with blood tests.
Feedback from 2 physiotherapists	4th November	Physiotherapists working in the NHS,	Individual interviews	Feedback suggests the RADAI-F5

	2020 and 23rd November	Years of clinical experience: 7 years and 11 years	on Microsoft Teams	could serve as a screening tool and aid in quantifying foot disease. Consideration for pre and post-foot injection use is mentioned, as well as the need for AUDIT purposes and the RADAI-F5 demonstrates quick and easy usability in clinical practice.
MSK Lanarkshire podiatry group presentation	5th November 2020	5 Podiatrists, Years of clinical experience: N/A	Group discussions on Microsoft Teams	Positive feedback on the RADAI-F5, emphasising its ease and feasibility in clinical practice. Validation work against MSUS is discussed, and a future feasibility study is recommended for implementation.
North West Clinical Effectiveness Group Rheumatology Podiatry	2nd December 2020	10 Podiatrists across the UK with interest in rheumatology, Years of clinical experience: N/A	Group discussions on Microsoft Teams	Feedback acknowledges the need for a tool to assess foot disease in RA patients, with considerations for implementation and utility in clinical practice. The potential for mobile application implementation and usefulness for monitoring treatment effects are discussed. The importance of minimally importance difference is highlighted to help demonstrate how various treatments such as steroid injections could

				improve foot disease activity.
NHS Lanarkshire Rheumatology group	2nd March 2021	1 physiotherapists, 2 podiatrists, 4 rheumatologists, 2 rheumatology nurses, 1 orthotists	Group discussions on Microsoft Teams	Positive feedback on the RADAI-F5's quick and easy use, with some healthcare providers already employing it in clinical practice. Concerns about its association with other objective measures and suggestions for comparing it to ultrasound imaging and thermography are raised. Importance of predictive validity work is highlighted.
SSR patient representative with RA	10th March 2021	Disease duration: 8 years	Individual interviews on Microsoft Teams	Feedback from the patient representative emphasises the importance of including feet in RA assessments and early referral to podiatry. Positive remarks on the questionnaire's layout and effectiveness in raising awareness about foot disease.
PDGR group	8th December 2022	5 specialist rheumatology podiatrists	Group discussion on Microsoft Teams	Positive feedback on the RADAI-F5's significance for foot care in RA, with impressive results from validation work against MSUS. Suggestions for future use in clinical notes or electronic health records are mentioned,

				All members show enthusiasm to incorporate it into their clinical practice.
KE event at Versus Arthritis Glasgow	19th July 2023	7 individuals with RA	Focus group discussions	Impact of RA-related foot problems on daily activities emphasised by all representatives. Lack of foot assessments in routine practice highlighted by participants, with low interest from rheumatologists regarding feet. Positive views on the simplicity of the RADAI-F5. Concerns raised about implementation and whether tool results would be acted upon. Positive discussions on developing a RADAI-F5 mobile app.

Appendix D redacted due to third party copyright

Appendix E- Participant Information Sheet (Qualitative study)

You are invited to take part in a research study. Dr Gordon Hendry, Professor Martijn Steultjens and Dr Diane Dickson at Glasgow Caledonian are supervising the study. The study is being carried out by Anika Hoque and will form part of a PhD educational award.

Before you decide whether or not to take part, it is important that you understand what the research study will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please ask if you are not clear about anything or if you would like more information.

Why is this study important?

The feet are often the first location of joint involvement with rheumatoid arthritis (RA). If left untreated, foot symptoms can worsen and have a harmful impact on patients' QoL. Currently, RA treatment is mainly based on assessments that do not include the joints of the foot and ankle. This can result in patients' foot problems being overlooked.

Questionnaires that collect information directly from patients about how they feel or function, are one way of identifying and measuring foot arthritis. The Rheumatoid Arthritis Foot Disease Activity Index (RADAI-F5) is a questionnaire that collects data that can help determine how active your foot arthritis is and help clinicians decide when your feet should be examined and treated. This could help decide when to refer patients to foot health services (i.e., podiatrists, orthotists or physiotherapists). We want to explore your views on the RADAI-F5 questionnaire.

Who can participate in the study?

You can take part in the study if you have a diagnosis of rheumatoid arthritis (RA) and are 18 or over.

What will I have to do if I take part?

If you decide to take in the study, you will be given this information sheet to keep and be asked to sign a consent form. You will receive a copy of the signed consent form. The original consent form will be stored securely.

You will be invited to participate in a confidential telephone or an interview session using a video app of your choice (i.e.: Zoom, Microsoft teams etc.). The interview will last up to 60 minutes.

This will be arranged for a time and date that is suitable for you. Before the interview, the RADAI-F5 questionnaire will be sent via post for you to complete. During the interview, you will be asked about your daily experience of arthritis and the impact of foot arthritis. You will also be asked questions about the RADAI-F5 questionnaire. The interview will be recorded to, and you may be asked to check the written record of the interview for accuracy at a later date.

Do I have to take part?

You are completely free to decide not to take part. If you choose to participate in the study but then change your mind, you can withdraw at any time without giving a reason. This will not affect your standard of care. We will destroy your identifiable information, but we may use the non-identifiable data collected up until the point of your withdrawal unless you request otherwise.

What are the possible risks with taking part?

We do not expect any risks. However, all studies involve some level of risk. There is a very small risk that you may feel uncomfortable answering some of the questions. However, you can miss questions and/or take breaks when required. The main disadvantage is that you will be asked to give up your own time to complete the interview, but we will arrange a suitable time and date with you.

What are the possible benefits of taking part?

We can't promise the study will help you personally. However, this study will help our understanding of how foot symptoms affects RA patients. The study will also help determine if the RADAI-F5 questionnaire would benefit RA patients. This may improve the ability of doctors to measure and monitor foot problems in people with RA in the future.

What will happen to the information given during the study?

The principal investigator, Anika Hoque, will collect personal data including your name, age, sex, other health conditions and rheumatoid arthritis disease duration. Your information, such as name and address, will be stored securely and will be accessible only to the principal investigator. With your consent, Anika will record the audio and/or video of the interview session. Anika may include quotations from the interview as well. These will be anonymised so you cannot be recognised by it. Notes and recordings will be confidential and anonymised and stored within an encrypted folder, accessible only to the principal researcher.

Data will only be accessed by the researcher and the research team until it is no longer required. After this, the data will be destroyed confidentially. The study complies with the Data Protection Act (2018) and the General Data Protection Regulation (GDPR). The data controller is Glasgow Caledonian University. Information is being processed on the basis of Article 6(1)(e) of the General Data Protection Regulation. Questions and concerns relating to data protection, should be made to the University's Data Protection Officer (DPO). The DPO can be contacted by e-mail: dataprotection@gcu.ac.uk. If you are unhappy with the university's response, you have the right to complain with the Information Commissioner's Office (ICO). The ICO can be contacted by e-mail: casework@ico.org.uk.

If you would like us to stop using your personal data, you can contact the Data Protection Officer at dataprotection@gcu.ac.uk or 01413318392 and ask for your data to be erased. However, it will only be possible to erase data that has not been anonymised and/or published. You can find further information about your rights at https://www.gcu.ac.uk/dataprotection/rights/

Who is organising and funding the study?

This study is being organised by Anika Hoque, a PhD student at Glasgow Caledonian University. The study is being funded by Glasgow Caledonian University.

What if there is a problem?

If you have any concerns the study, you should speak to the principal investigator, Anika Hoque. You may also seek independent advice from a local contact Dr Lisa Newcombe, by e-mail:

What will happen to the results of the study?

The study findings will be presented at conferences, published in a professional journal, and form part of a PhD thesis. The study results will be available to healthcare professionals, researchers, and the public. If you would like a copy of the report, you can request this from Anika Hoque.

Expenses and payments

As no travel is required, no costs are expected. No payments are being offered for participation.

Who has reviewed the study?

An ethics committee reviews all studies involving human participants at Glasgow Caledonian University. The ethics committee's role is to protect the safety, rights, well-being, and dignity of

study participants. This study was reviewed by the School of Health and Life Sciences departmental committee and given ethical approval on 10/02/2021 under the following approval code: HLS/PSWAHS/20/096

What happens next?

If you are interested in participating and would like to know more about the study, please contact Anika Hoque

Thank you for taking the time to read this information sheet.

Appendix F – Interview topic guide

SEMI STRUCTURED INTERVIEW SCHEDULE FOR PATIENTS AND PATIENT-ADVOCATES

General experience of arthritis and foot disease

1. "Can you tell me a bit about how your arthritis affects you?"
2. "Could you tell me about any changes to your feet since developing RA??"
   a) "Can you explain how your foot problems affects you and your day to day life?"
   b) How have your feet and any problems affected your quality of life? Prompts (your daily activity? Activity levels?

Patient perception of foot disease:

1. **"**Does your doctor discuss your DAS score with you and do you know what it means?"
   a) "Can you give me an example of a time that your doctor or rheumatologist has discussed your DAS-score with you?"
   b) "How often does your rheumatologist or doctor discuss your DAS score with you?"

Foot care assessment and access:

1) "How do you decide when it is time to seek help for your foot problems?"

2) "How comfortable are you in discussing your foot problems with your healthcare team?"
   a) "Why are you comfortable/ not comfortable in discussing your foot problems?"
   b) "Do you always get to talk about your feet when you need to? If not, why? If so, what happens next?"

3) "Has anyone examined your feet since developing RA?"
   a) "Who examines your feet?"
   b) "How regularly does someone examine your feet?"
   c) "Do you feel that your foot problems are being examined appropriately?"

4) "If your feet are bad and the doctor knows, what do they do for you?"

5) "Have you had any experience of seeing a podiatrist, physiotherapist or orthotist for treatment for your feet?"
   a) "Why did you get treatment?"
   b) "Have those treatments been beneficial? How have the treatments been beneficial?"

6) "Has your medication changed because your feet have been bad?"

RADAI-F5 tool: We have given you the RADAI-F5 questionnaire to complete in your own time. We think this tool might help to flag up the feet if they need attention. We have a number of questions in relation to the questionnaire to understand how it may impact you.

1) "What did you like about the tool? What did you not like?"
   a) Are there any questions in the tool that are unclear or confusing?
2) "What are your thoughts on completing the questionnaire in the waiting area before seeing a doctor or rheumatologist?"
   a) How would you feel about your questionnaire being handed to the doctor/ rheumatologist to be discussed during your appointment?
3) "Would you want to know your score and what it means?"
   a) "would you write it down somewhere?"
   b) "would you consider using it to monitor your feet?"
   c) "How would you feel about your RADAI-F5 scores being used by other members of your healthcare team?"
4) Due to Covid-19, many appointments have been moved to telephone or video consultations. "How do you think this tool would help in a telephone/video consultation during the Covid-19 pandemic?"

Diagram:

Scenario: You may have found yourself in a situation during a clinic appointment where you had difficulties in removing footwear due to painful hands, a bad back or poor mobility. If you cannot remove your footwear, it can sometimes be difficult to explain where you are experiencing symptoms using just words. Using diagrams of the feet may make it easier for your clinician to get a clearer picture of where you are experiencing pain. Keeping this in mind:

1) "How would you feel about indicating which joints are tender or swollen on a diagram of the feet?"

App:

1) "How would you feel about using an app on your smartphone/ laptop/ tablet to self-monitor your RADAI score?"
   a) "Are there any reasons why you would not want to use an app on a smartphone/ laptop/ tablet?" (privacy, intrusion, difficulty with using hands etc.)?

Closing question:

1) "Is there anything else that you feel is important that we haven't discussed?"

SEMI STRUCTURED INTERVIEW SCHEDULE FOR CLINICIANS AND ALLIED HEALTH PROFESSIONALS

Foot disease in RA and foot assessment:

1) What is your understanding of foot disease activity in rheumatoid arthritis?
2) How do you believe that foot disease is represented by current measures of disease activity?"
3) How does it make you feel that feet are not included in the DAS-28?

4) "How frequently do patients discuss their foot health needs with you?
    a) "Do you believe patients have sufficient opportunity to discuss their foot health needs during appointments? Why?"
5) "What are your reasons for choosing whether to examine feet?"
    a) "How comfortable are you in assessing feet? Do you feel clinically competent in assessing feet?"
    b) "How frequently do you examine feet of RA patients?"
    c) "How much of your decision to not assess the feet are driven by the DAS-28?"
    d) "Is this driven by what the patients are reporting?"

PROMs:

1) "For which reasons do you currently use RA-specific Patient reported outcome measures (PROMS) in routine clinics?" –
   Prompts: screening, monitoring, shared decision making etc.

    a) "How do you use these?"
    b) "How frequently do you use PROMs?"
    c) "What influences your choice on when to use PROMs?"- RA. internal comparative- monitor disease activity- confounders. (inadequate to measure)
2) "How do you use the data gained from the PROMs to inform care or guide management of patients?"
    a) "Are there any barriers to this?"
    b) "Where/How do you record any patient-reported outcomes?" (*Trakcare, Portal*)

RADAI-F5 Tool:

1) "Would this tool be useful in your practice?"
    a) "If yes/no, Why?"
    b) "How would you use the tool in your practice?" (assessment of feet, referring, screening etc.)
2) "What are the advantages of implementing the RADAI-F5 in your routine clinical practice?".

3) "What are the barriers of implementing the RADAI-F5 in your routine clinical practice?"

4) "Do you think the tool is clinically feasible?"

5) "How do you think the RADAI-F5 could be used to inform or guide subsequent further assessment or management including referrals?"

6) Patient-reported outcomes have become increasingly important during the covid-19 pandemic where there is an increase in telephone and video consultations. With this in mind:
"How may the RADAI-F5 be incorporated into telephone/video appointments?"

Diagram:

Due to Covid-19, many appointments have been moved to telephone or video consultations. It can sometimes be difficult for patients to explain where they are experiencing symptoms using just words. Keeping this in mind:

1. "How would you feel about the inclusion of a diagram to highlight which joints or areas of the foot were tender/swollen?"

    a) "How would this diagrammatic information aid your practice?"
    b) In your experience, how accurate do you think patients are at locating pain?
    c) How do you believe patients can differentiate between RA and secondary comorbidity pain?

App:

1) "How would you feel about patients using an app via a smartphone/laptop/table to self-monitor their RADAI score?"

    a) "Are there any reasons why you would not want participants to use an app on a smartphone/tablet/laptop?"

Closing question:

1) "Is there anything else that you feel is important that we haven't mentioned or discussed?"

Appendix G- Outline of IPA Stages (Smith et al., 2009)

Step 1: *Listening and reading*

The interviews were listened to and the transcripts were reviewed numerous times. The goal of this initial stage was for the researcher to get actively engaged in the data and to guarantee that the participant is the centre of analysis (Smith et al., 2009). The researcher documented some of her initial thoughts of the data, as well as any noteworthy recollections of the interview experience itself. these thoughts were bracketed until a later review. An example of a part of an interview transcript from GG01 is shown below.

GG01: Well, you had it well set out and there certainly not too many questions, it was nice and short *(laughs)*. No, because that's the other thing, cause if you give too many questions (*emphasis on word "too")* people get lost in amongst them all and maybe not able to be completed in the 10-minute appointment. This is nice and short.

Interviewer (AH): I know you previously said how you find it difficult to fill in the scales, how did you find filling in the RADAI-F5?

GG01: Yeah, it was nice and easy. I mean the good thing about these forms is that gives you an indication of where you are and where you want to go. You get a starting point and a finishing point, like a start the process of finishing the process, which I like and it can encourage speaking about your foot problem to my man at the Western.

Interviewer (AH): Yeah, and how relevant do you find this questionnaire for you and why?

GG01: I think it's quite good to make you more aware of your feet, because I think it's like all these things you're inclined to. You don't ignore it, you learn to live with it (*laughs)*. When you sent the form, I started to look back knowing that my medication hasn't been right. I started to look back at my feet and I am aware that when my arthritis isn't right, my feet are wrong (*emphasis on word wrong)*. They're not good and I have to be careful when I'm walking, where I am walking, what I am wearing on my feet and that sort.

Interviewer (AH): So, can I clarify…by the previous comment, did you mean that the RADAI-F5 really helped you understand more about your disease?

GG01: Yes, it has (*nods)*.

Interviewer (AH): Great. Thank you for the clarification. What are your thoughts on completing the questionnaire in the waiting area prior to seeing a rheumatologist?

GG01: I think that (the RADAI-F5) would be a good idea because it would give them a rough guide just by looking at it where they thought you were. They are probably needing these tools when they have such a short (*emphasis on word)* gap in time to give them an instant understanding of where you are. I think that would be a great idea.

Step 2: *Initial note-taking*

The data was read and listened to multiple times, both concurrently and independently, allowing the researcher to notice any notable pauses, changes in tone, speed, or word emphasis. Each transcript was examined for descriptive, linguistic, and conceptual comments and creating shorter nodes using Nvivo 12 software.

a. Descriptive comments

The descriptive remarks were the first of three types of first notes collected. These were remarks that summarised the content of what the participant stated, focused on the explicit meaning, and used terms, phrases, or explanations expressed by the interviewee in general. In GG01's transcript, for example, a descriptive comment was:

> They are probably needing these tools when they have such a short (*emphasis on word)* gap in time to give them an instant understanding of where you are. I think that would be a great idea.

b. Linguistic Comments

Note-taking then focused on linguistic comment. Attention was given to aspects such as language choice, along with repetition, pauses, laughter, tone, and emphasis on words. For example, in GG01's interview, a linguistic comment identified was:

> No, because that's the other thing, cause if you give too many questions, people get lost in amongst them all (*emphasis on word "too many questions")* -emphasising the importance of having a short, succinct tool.

c. Conceptual Comments

Third, conceptual remarks were the central objective of note-taking. These comments examined the facts on a more inquisitive and conceptual level. The implicit connotations of what the

> "The RADAI-F5 would give them a rough guide just by looking at it where they thought you were"- It could be used to monitor foot disease status over time.

individuals said were examined analytically. In GG01's transcript, for example, a conceptual comment was:

Step 3: *Identifying emergent themes*

The transcripts were then examined for emergent themes in the next step of analysis. This was accomplished by decreasing the volume of data from the transcription and the preliminary notes in Nvivo 12. In terms of mapping the connections, patterns, and interrelationships between the exploratory comments contained in the initial notes, each theme was linked and referenced to the relevant lines in the transcription to ensure that the essence of the text was reflected in the themes and that the complexity was preserved. The emerging themes were meant to represent the researcher's perceptions of the participants' statements. Some of these themes were taken verbatim from the initial notes and some were paraphrased.

The researcher then used the hermeneutic circle to uncover emergent themes. The hermeneutic circle is concerned with the dynamic, non-linear relationship between the part and the whole; hence, in order to understand the concept as a whole, you must first understand the smaller components that comprise the notion (Gyollai, 2020). This was an iterative analytical procedure in which the researcher went back and forth between several different ways of thinking about the data. The researcher paid attention to what was communicated in the specific statements while keeping the phenomenology or overall tone of the interview in mind. In effect, the initial whole of the interview became a series of pieces as the analysis was carried out; however, these then came together in a different 'whole' at the conclusion of the analysis. The following is an example of an emergent theme based on passages from GG01's transcript.

Emergent Theme	Sample of quotes
Clinical facilitators of the RADAI-F5	"I mean the good thing about these forms is that gives you an indication of where you are and where you want to go." "You get a starting point and a finishing point, like a start the process of finishing the process."

| | "I think that (the RADAI-F5) would be a good idea because it would give them a rough guide just by looking at it where they thought you were" |

Step 4: *Development of subordinate themes*

The emergent themes were then classified into subordinate themes and mapped according to how the researcher thought the themes fit together during the next step of analysis. The emergent topics were transferred into a Microsoft Word document and sorted into related themes to ease this.

Step 5: *Repeat the process for each transcript*

Steps 1-4 were then repeated for the remaining interview transcripts. Each transcript was examined independently, as proposed by Smith et al. (2009), to respect the uniqueness of each case and to adhere to the idiographic approach of IPA, and to allow for the emergence of new themes. The researcher was obliged to bracket concepts that emerged from the investigation of earlier examples as much as possible.

Step 6: *Look for patterns across cases to develop emergent themes*

The researcher then looked for patterns and relationships among the cases as well as the entire group. Subordinate topics from individual transcripts were integrated and grouped into clusters of connected concepts, which eventually evolved into emerging themes.

Appendix H- Investigator triangulation agreement

Initial themes	Themes extracted from each investigator
Foot disease is common	- Foot disease significant - Not trivial, affects mobility - Arthritis damages feet - Affects footwear and family - Social life impacted
Foot problems are damaging	- Feet overlooked in training - Ill health retirement common - Fatigue and deformity - Regret from mismanagement - DAS-28 not reflective - Under-represented foot care
Current measurements where clinicians overlook feet	- DAS-28 overlooks feet - Lengthy PROMs - Used for audit not care - Lack of trust in PROMs - Feet overlooked in exams - Lack of referrals to podiatry
RADAI-F5 facilitators	- Short, quick, and simple PROM - Promotes communication - Guides management - Patient education - Useful in virtual consultations

RADAI-F5 barriers	- Question similarity concerns
	- Lack of electronic systems
	- Administrative burden
	- Lack of clinician time
	- Validity concerns
	- Electronic database integration issues

Agreement between team	- Feet are a priority
	- Need for a clinically feasible foot PROM
	- RADAI-F5 facilitators
	- RADAI-F5 barriers

Appendix I redacted due to third party copyright

Appendix J- Ethical approval for studies in Chapter 5 and 6

NHS
Health Research Authority

North East - Newcastle & North Tyneside 2 Research Ethics Committee

NHS BT Blood Donor Centre

Holland Drive

Newcastle upon Tyne

Tyne and Wear

NE2 4NQ

Dear Miss Hoque

Study title:	**Evaluation of associations between clinical and imaging measures of foot disease in rheumatoid arthritis (RA).**
REC reference:	**21/NE/0130**
Protocol number:	**HLS/PSWAHS/20/242**
IRAS project ID:	**296058**

Thank you for responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved on behalf of the PR subcommittee.

With the Committee's best wishes for the success of this project.

Yours sincerely

Signature redacted

Appendix K- Patient information sheet for FOOTRADIUS study

Participant Information Sheet

Study title: An evaluation of associations between ultrasound and the Rheumatoid Arthritis Disease Activity Index-F5.

You have been invited to take part in a research study. The study is supervised by Chief Investigator Dr Gordon Hendry and academic supervisors Professor Martijn Steultjens and Dr Diane Dickson at Glasgow Caledonian University (GCU). The study is being carried out by the principle investigator Anika Hoque and will form part of her PhD educational award.

Before you decide whether or not to take part, it is important that you understand what the research study will involve. Feel free to talk to others about the study if you wish. Please contact the principal investigator – Anika Hoque - if you are not clear about anything or if you would like more information.

What is the purpose of this study?

The feet are often the first location of joint involvement with rheumatoid arthritis (RA). If left untreated, foot symptoms can worsen and negatively impact a patient's quality of life. Currently, RA treatment is mainly based on assessments that do not include the foot and ankle joints. This can result in patients' foot problems being under-recognised and under-treated.

Questionnaires that collect information directly from patients about how they feel or function are one way of identifying and measuring foot arthritis. The Rheumatoid Arthritis Foot Disease Activity Index (RADAI-F5) is a questionnaire that collects data that can help determine how active your foot arthritis is and help clinicians decide when your feet should be examined and treated. This could help decide when to refer patients to foot health services such as podiatry and potentially inform outcome-driven care This study aims to further validate this RADAI-F5 tool with the use of measures including a clinical examination of the foot and ankle, ultrasound imaging

of the internal foot structures and thermography imaging, which uses an infrared camera to detect heat patterns and blood flow in the foot and ankle. We hope the results of this study will help inform how we manage the rheumatoid foot in the future.

Why have I been invited?

We are recruiting participants with a clinician diagnosis of rheumatoid arthritis from rheumatology clinics across NHS Greater Glasgow, and Clyde and NHS Lanarkshire. Patients must be above the age of eighteen and be able to provide informed consent. Your participation in the study will not affect any medical care you may receive.

What will I have to do?

If you decide that you do not want to participate in the study, please complete and return the opt-out form and return with the stamp addressed envelope. If you are interested in taking part in the study, the researcher will contact you via telephone once you have had time to read all of the study information and allow you to ask any questions. If you decide you would like to participate, the researcher will book your study assessment at GCU lab at a date and time convenient for you. You will only have to attend for a one-off study assessment. If you decide to participate in the study, you will be asked to sign a consent form. You will receive a copy of the signed consent form. The original consent form will be stored securely.

To limit bias and make certain that the thermographic readings are accurate, you will have to avoid the following before attending the examination;

- Avoid alcoholic beverages, smoking and caffeine 4 hours before   the examination.
- Avoid using ointments or lotions on the foot and ankle 4 hours before the examination.
- Avoid exercise 4 hours prior to the examination.
- Avoid physical therapy, Electrical Muscle Stimulation (EMS), Transcutaneous electrical nerve stimulation (TENS), ultrasound treatment, acupuncture, chiropractic, physical stimulation, hot or cold pack use for the foot and ankle 24 hours before the examination.
- Avoid shaving of the foot and ankle region. If shaving is required, this should be done the evening before or at least 4 hours prior to examination.
- Avoid showering for 4 hours before the examination.
- Avoid sunbathing without protection 5 days prior to the examination.

At the study 1 assessment, you will be asked to remove footwear and hosiery on arrival to allow your feet to adapt to the room temperature and environment. During this time, you will be asked to complete 3 short questionnaires, which should take a total of 20 minutes to complete.

- Two questionnaires will ask about your RA disease activity.
- One questionnaire will ask you about how your RA affects your daily physical function.

The principal researcher will then take a quick thermographic image of both feet. An independent investigator will then conduct a clinical examination of your foot joints and tendons. This will be followed by an ultrasound examination of your foot joints and tendons. The researcher will then measure your walking speed over a distance of 10 metres. If you any discomfort during the physical tests or ultrasound examination, you can take a break or stop the assessment. The time taken to complete the study assessment should take around 1.5 to 2 hours.

A subgroup of participants who have started on a new biologic therapy will be asked to complete the RADAI-F5 again at 3 months along with a global rating scale (GRC) (Study 2). The GRC scale will be on a 5-point scale from much worse, -2; worse, -1; same, 0; better, +1 and much better, +2 to quantify your improvement or deterioration of foot pain over the 3 months. Stamp addressed envelopes will be provided for the return of the RADAI-F5 and GRC questionnaire to Anika Hoque.

What are the possible advantages, disadvantages and risks of taking part?

There are no direct advantages to you from taking part in this study. However, your participation may improve our knowledge of the RADAI-F5 tools clinical application. This could help us to monitor and manage RA foot disease more effectively in the future.

The main disadvantage to you is that you will be asked to give up your own time to complete the study assessment. We estimate your study visit will take no longer than 120 minutes. There is a minor risk that you may feel some discomfort during or after completing the physical and performance-based examinations of your foot and ankle. However, we will give you sufficient rest times between assessments, and you may ask for breaks or stop the assessment at any time. You will also receive an ultrasound scan of your feet as part of this study. If any unexpected or suspicious medical findings are uncovered through the ultrasound scan, your GP will be informed.

There is a potential increased risk of Covid-19 exposure when attending the lab. However, measures will be put in place in an attempt to mitigate the risk of infection. **If you have been in contact with an individual who has Covid-19 or if you have Covid-19 symptoms yourself, such as a persistent cough, fever, shortness of breath or a loss of taste or smell, please contact the principal investigator, Anika Hoque. Then, we can re-arrange the study assessment for a later date.** Face coverings will be compulsory for all research staff and participants unless exempt for medical reasons. We have also introduced enhanced cleaning measures, personal protective equipment (PPE), 2-metre social distancing and a good ventilation system to ensure that you are safe during your study assessment at GCU. There are only three assessments where 2-metre distancing will not be possible, and there are no alternative measurements we can collect. Nonetheless, both the researcher and participant will be wearing appropriate PPE, and all PPE will be decontaminated after every use as per the manufacturer's instructions. You will also be entering the building through a rear entrance from the GCU car park to reduce contact with the rest of the public.

What if I decide I don't want to participate in the study?

You are entirely free to decide not to participate. If you choose to take part in the study but then change your mind, you can withdraw at any time without giving a reason. We will destroy your personal information, but we may use the non-identifiable data collected until the point of your withdrawal**.**

Will my taking part in the study be kept confidential?

Yes. Any information collected about you during the study will be kept strictly confidential. On entering the study, you will be given a unique study ID number. From there on, all data collected will bear this number, so you cannot be recognised from it. Your information, such as name and address, will be stored securely and accessible only to the principal investigator Anika Hoque. Data will only be accessed by the researcher and the research team until it is no longer required. All personal data will then be destroyed confidentially 6 months after the study has ended. The study complies with the Data Protection Act (2018) and the General Data Protection Regulation (GDPR).

If you would like us to stop using your personal data, you can contact the Data Protection Officer at dataprotection@gcu.ac.uk or 01413318392 and ask for your data to be erased. However, it will only be possible to erase data that has not been anonymised and/or published. You can find further information about your rights at https://www.gcu.ac.uk/dataprotection/rights/.

Who is organising and funding the research?

This research is being organised by Anika Hoque, a PhD research student at GCU. This research is being conducted as part of her PhD studies and is funded by GCU.

What should you expect after the study is completed?

The last contact from the study team will be at the GCU study assessment lab (for study 1) or 3 months after commenting on new biologic therapy for the subgroup of participants (study 2). Following this, you should not expect to be contacted by the study team. The data collected during this study will be published in academic and medical journals, presented at conferences and written up as part of a PhD thesis. All information will be anonymised, and individual participants will not be identified. If you are interested in receiving a copy of the final summary report, please contact Anika Hoque, and it will be sent to you.

Who has reviewed the study?

The study has been reviewed and the methodology approved by the **Newcastle & North Tyneside 2 Research Ethics Committee (HLS/PSWAHS/20/2/42).** The study has also been approved by the GCU Psychology, Social Work and Allied Health Sciences Ethics committee (**HLS/PSWAHS/20/096).**

Expenses and payments?

Travel expenses to GCU will be reimbursed. No payments are being offered for participation.

What if there is a problem?

If you have a concern about any aspect of the study, you should first speak to the principal investigator:

Anika Hoque
Glasgow Caledonian University, Cowcaddens Road, Glasgow, G4 0BA

You may also wish to contact the Director of Studies:

Dr Gordon Hendry
Room A101d, Govan Mbeki Building, Glasgow Caledonian University, Cowcaddens Road, Glasgow G4 0BA

If you would like to speak to an independent person about taking part in this research study, please contact:

Dr Lisa Newcombe

Room A366, Govan Mbeki Building, Glasgow Caledonian University, Cowcaddens Road, Glasgow Caledonian University, G4 0BA

If you remain unhappy and wish to complain formally, you can do this through Glasgow Caledonian University.

Thank you for taking the time to read this study information sheet

Appendix L- The Modified RADAI (Leeb et al, 2008)

RADAI-5

How active was your arthritis the last six months?

completely inactive | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | extremely active

How active is your arthritis today with respect to joint tenderness and swelling?

completely inactive | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | extremely active

How severe is your arthritis pain today?

no pain | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | unbearable pain

How would you describe your general health today?

excellent | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | extremely bad

Did you experience joint (hand) stiffness on awaking yesterday morning? If yes, how long was this stiffness?

no stiffness | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | stiffness the whole day

Appendix M: MID results including outlier participant

Table 1: Descriptive statistics of baseline, follow-up and change scores of the RADAI-F5 by response categorise of the global rating of change scale based off n=15

Instrument	Baseline scores mean[±SD]	Follow-up scores mean[±SD]	Change scores mean [±SD]
RADAI-F5			
Much worse (n=1)	7.2 [±0]	10 [±0]	-2.8 [±0]
Slightly worse (n=4)	4.5 [±2.46]	4.4 [±2.29]	0.1 [±0.61]
No change (n=5)	3.54 [±3.05]	3.93 [±2.75]	-0.39 [±3.61]
Slightly better (n=3)	3.13 [±1.54]	2.09 [±1.48]	1.05 [±0.23]
Much better (n=2)	5.2 [±0.6]	4.2 [±1.2]	1 [±0.6]

Table 2: Anchor based calculations for MID for the RADAI-F5 n=15

Outcome	0 to -1	+1 to +2	MID values
RADAI-F5	-0.67	1.03	0.36

Appendix N redacted due to third party copyright

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