Monitoring of Charcot neuroarthropathy.

A mixed methods, feasibility study

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Abstract

Background: Charcot neuroarthropathy (CN) is a serious complication of diabetes neuropathy which affects the lower limb. The best method to monitor disease progression and, diagnose remission is unknown. Magnetic resonance imaging (MRI) may be useful for monitoring disease, but this has not been evaluated. Furthermore, there is a lack of understanding about people's experiences of living with CN and receiving treatment.

Aim: To investigate the feasibility of using serial MRI to monitor and diagnose remission in CN and to understand people's experiences of living with CN.

Methods: A mixed methods approach was used: 1) a systematic review to assess the effectiveness of techniques for monitoring response to treatment in acute CN; 2) a multicentre, randomised, prospective, two arm, open feasibility study of using serial MRI to monitor CN; 3) a qualitative study to understand people's experiences of CN.

Results:
The systematic review showed multiple techniques to monitor response to treatment, but uncertainty remains about their effectiveness.

Five sites participated in the feasibility study. Two-thirds of eligible participants agreed to take part. Forty-three participants were recruited. The main reason for ineligibility was a previous episode of CN. Thirteen participants were withdrawn post-randomisation due to an alternative diagnosis. Nineteen participates achieved remission, six did not. This study found that the intervention, serial MRI was achievable, safe, and acceptable.

The qualitative study showed that receiving treatment for CN has physical, socio-economic, and psychological consequences, for the individual and their family which extend beyond the burden of wearing an offloading device.

Conclusion: The rates of recruitment, retention, data, and MRI completeness show that a definitive study to evaluate the effectiveness of MRI in disease monitoring in CN is justified and feasible. Healthcare professionals should use a more holistic and person-centred approach to supporting individuals with CN

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Declaration

No part of this thesis has been submitted for any other degree or qualification at this or any other University.

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Publications and statement of authorship

Publications arising from this thesis

Chapter	Citation
Chapter 4	Gooday C, Gray K, Game F, Woodburn J, Poland F, Hardeman W. (2020) 'Systematic review of techniques to monitor remission of acute Charcot-neuroarthropathy in people with diabetes'. *Diabetes Metabolism Research and Reviews*. 36:e3328 This publication can be found at: https://www.onlinelibrary.wiley.com/doi/epdf/10.1002/dmrr.3328
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Chapter 6	Has been submitted for publication and is currently under review Gooday C, Game F, Woodburn J, Poland F, Sims E, Dhatariya K, Shepstone L, Barton G, Hardeman W. (2022) 'A randomised feasibility study of serial magnetic resonance imaging to reduce treatment times in Charcot neuroarthropathy in people with diabetes (CADOM)'.
Chapter 7	Gooday C, Hardeman W, Game F, Woodburn J, Poland F. (2022) 'A qualitative study to understand people's experiences of living with Charcot neuroarthropathy'. *Diabetic Medicine. (*00), e14787 This publication can be found at: https://onlinelibrary.wiley.com/doi/abs/10.1111/dme.14784

Statement of Authorship

Chapter one: Written by Catherine Gooday

Chapter two: Written by Catherine Gooday

Chapter three: Written by Catherine Gooday

Chapter four: Catherine Gooday was the lead author of the following published paper:

> Gooday, C., Gray, K., Game, F., Woodburn, J., Poland, F. and Hardeman, W. (2020) 'Systematic review of techniques to monitor remission of acute Charcot neuroarthropathy in people with diabetes', *Diabetes/Metabolism Research and Reviews*, 36, p. e3328 (25 pages).

CG and FG developed the initial idea for the research. CG, KG, FG, JW, FP and WH made substantial contributions to the conception and design of the review. CG and KG screened the papers. CG extracted data from all the included papers. KG validated data extraction. CG drafted the manuscript. All authors critically reviewed and revised the manuscript for important intellectual content. All authors read, amended, and approved the final manuscript.

Chapter five: Catherine Gooday was the lead author of the following published paper:

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CG and FG developed the initial idea for the research. WH, FP, FG, JW, ES and KD all made substantial contributions to the conception and design of the study. CG drafted the manuscript. All authors critically reviewed and revised the manuscript for important intellectual content. LS provided statistical support. All authors read, amended, and approved the final manuscript.

Chapter six: Catherine Gooday was the lead author of the following paper which has been submitted for publication and is currently under review:

> Gooday C, Game F, Woodburn J, Poland F, Sims E, Dhatariya K, Shepstone L, Barton G, Hardeman W. (2022) 'A randomised feasibility study of serial magnetic resonance imaging to reduce treatment times in Charcot neuroarthropathy in people with diabetes (CADOM)'.

CG and FG developed the initial idea for the study. FG, WH, FP, JW, ES and KD made substantial contributions to the conception and design of the study. CG led the study, data analysis and interpretation. CG drafted the manuscript. All authors critically reviewed and revised the manuscript for important intellectual content. ES provided clinical trial operations and quality assurance expertise, LS provided statistical expertise, and GB provided health economics expertise. All authors read, amended, and approved the final manuscript.

Chapter seven: Written by Catherine Gooday. From this chapter the following paper has been published.

> Gooday, C., Hardeman, W., Game, F., Woodburn, J. and Poland, F. (2022) 'A qualitative study to understand people's experiences of living with Charcot neuroarthropathy', *Diabetic Medicine*, 00, p. e14784 (9 pages).

CG and FG developed the initial idea for the study. CG, WH and FP designed the study. CG conducted the interviews. CG and FP completed the analysis. CG drafted the manuscript. All authors contributed to the manuscript for important intellectual content. All authors read, amended, and approved the final manuscript.

Chapter eight: Written by Catherine Gooday

Abbreviations

ABPI Ankle Brachial Pressure Index

BMI Body Mass Index

CI Confidence interval

CN Charcot neuroarthropathy

CROW Charcot restraining orthotic walker

eGRF Estimated Glomerular Filtration Rate

EQ- 5D-5L European Quality of Life-5 Dimensions

DM Diabetes mellitus

GCP Good Clinical Practice

HADS Hospital Anxiety and Depression Scale

HbA1c Glycated haemoglobin

HRA Health Research Authority

HRQoL Health-Related Quality of Life

HZ Hazard Ratio

ICF Informed Consent Form

IDDM Insulin dependent diabetes mellitus

ITT Intention-to-treat

MRI Magnetic Resonance Imaging

NHS National Health Service

NICE National Institute for Health & Care Excellence

NIDDM Non-insulin dependent diabetes mellitus

NIHR National Institute for Health Research

PPI Patient and public involvement

PPIRes Patient and Public Involvement in Research

PROMs Patient reported outcome measures

PIS Participant Information Sheet

QALY Quality Adjusted Life Year

R&D Research and Development

REC Research Ethics Committee

RCT Randomised Controlled Trial

SAP Statistical Analysis Plan

SD Standard deviation

SF-12 The 12-Item Short Form Survey

SF-36 The Short Form Health Survey

T1DM Type 1 diabetes mellitus

T2DM Type 2 diabetes mellitus

TCI Total contact insole

TCC Total contact cast

UK United Kingdom

USA United States America

VAS Visual Analogue Scale

1 Thesis introduction

This chapter will provide a brief overview of the thesis and its aim and objectives, an overview of the chapters, and reasons for conducting my PhD study.

1.1 Thesis overview

The number of people with diabetes is rising rapidly (IDF, 2019). Long-term poorly controlled diabetes can cause multiple complications. People with diabetes are at risk of developing life-changing and life-threatening complications with diabetes being a leading cause of blindness (Amoaku *et al.*, 2020) , kidney failure requiring renal dialysis (Saran *et al.*, 2020) and non-traumatic amputation (Bernatchez, Mayo and Kayssi, 2021). People with diabetes are twice as likely to develop a stroke and heart attack compared to people who do not have diabetes (Haffner *et al.*, 1998).

Diabetes can cause nerve disease which usually starts in the smallest, finest nerves furthest away from the brain which are the sensation nerves in the feet. Nerve disease progresses very slowly: people do not realise that they are losing sensation in their feet. Eventually the foot can become numb (Dyck et al., 1993; Adler et al., 1997). This means that if the patient has any trauma, then they may not notice it and continue to walk with an injured foot (Brand and Yancey, 1997). As with other injuries the foot will become hot, red, and swollen, the bones then may start to rub together and result in inflammation within the bone. This condition is called Charcot neuroarthropathy (CN) it is a devastating complication of diabetes (Jordan, 1936). If the inflammation continues it can cause fractures and dislocations within the foot. If left untreated this can lead to foot deformity and complications such as ulcerations (Armstrong *et al.*, 1997; Fabrin, Larsen and Holstein, 2007; Leung, Ho and Wong, 2009; Pakarinen *et al.*, 2009; O'Loughlin *et al.*, 2016; Nilsen, Molund and Hvaal, 2018; Rahman *et al.*, 2020) . CN is still poorly understood by health care professionals (Donegan, Sumpio and Blume, 2013).

A diagnosis of CN has been shown to reduce people's quality of life (Pinzur and Evans, 2003; Willrich *et al.*, 2005; Sochocki *et al.*, 2008; Raspovic and Wukich, 2014). People who have been diagnosed with CN are at increased risk of lower limb amputation and die on average 14 years earlier than the general population (Van Baal *et al.*, 2010).

Treatment involves wearing an offloading device, usually a non-removable below knee cast or walker boot (Frykberg and Mendeszoon, 2000; National Institute for Health and Care Excellence, 2015). This aims to stop the inflammatory process, relieve pain, and maintain foot architecture.

Evidence is lacking about the optimal duration of treatment; recommendations range from six months to more than a year. Studies from the UK show a median time to remission, when the CN is assessed as healed of between 9-12 months (Game *et al.*, 2012; Stark *et al.*, 2016). However, international studies report considerably shorter time to remission, 3-5 months in the US (Pinzur, Lio and Posner, 2006; de Souza, 2008), 3-12 months and 3-6 months, in Brazil and Germany respectively (Chantelau, Kimmerle and Poll, 2007; Moura-Neto *et al.*, 2012).

A systematic review on the outcomes of CN have shown healthcare professionals and researchers use monitoring techniques with unknown diagnostic precision to detect remission (Gooday *et al.*, 2020a). There is evidence from small observational studies that repeated assessment with magnetic resonance imaging (serial MRI) may improve decision making about remission and help healthcare professionals decide when to stop treatment, which may decrease treatment times (Schlossbauer *et al.*, 2008; Zampa *et al.*, 2011; Chantelau and Grützner, 2014). This needs to be investigated through a study.

In addition to uncertainty about monitoring CN, evidence is lacking about the impact of CN and wearing an off-loading device for this length of time can have on people's physical, and psychological, health (Tzeravini *et al.*, 2018). An in-depth understanding of the physical and psychological experiences of people with diabetes and CN, could inform interventions to improve experiences of people receiving treatment for CN and so reduce personal, health, social care and societal costs.

1.2 Aims and objectives

The aim of this doctorate is to investigate the feasibility of using serial MRI to monitor and diagnose remission in CN and to understand people's experiences of living with CN.

The research has three objectives:

1. Identify the current evidence base for the use of monitoring techniques to identify disease remission in CN.
2. Examine the feasibility of using serial MRI without contrast in monitoring CN to reduce length of time the foot is immobilised.
3. Explore the expressed thoughts, emotions, and views of people receiving treatment for CN and how this may affect the individual, their families, and their relationships.

1.3 Thesis structure

This thesis includes eight chapters. The research is primarily reported using the third person. In some places the first person is used to highlight that this is a personal research journey and emphasise my own thoughts, emotions, and views about the research.

The thesis reports three original research studies which have been published or are under review as four articles in peer reviewed journals. These publications are outlined in the "publication and statement of authorship" section (page 15). Three chapters are largely a replication of the publications: systematic review (chapter 4), protocol for the feasibility study (chapter 5), and results of the feasibility study (chapter 6). Chapter 7 reports the qualitative study, which has been adapted and published. In additional the thesis includes an introduction (this chapter), background (chapter 2), methodological overview (chapter 3), discussion and conclusion (chapter 8), and appendices. The chapters are introduced below.

Chapter one: this chapter reports the structure of the thesis. It provides an overview of the research and my motivation for conducting PhD studies.

Chapter two: this chapter describes the pathology, diagnosis, management, morbidity, and mortality of CN. It places the research in the context of what is already known about CN, and the evidence gaps.

Chapter three: this chapter provides the justification for the methodological approaches.

Chapter four: this chapter reports the systematic review of techniques to monitor resolution of acute CN in people with diabetes.

Chapter five: this chapter reports the protocol of a feasibility study of serial magnetic resonance imaging to reduce treatment times in CN in people with diabetes.

Chapter six: this chapter reports the results of a feasibility study of serial magnetic resonance imaging to reduce treatment times in CN in people with diabetes.

Chapter seven: this chapter reports a convergent qualitative study to explore the participants' lived experience of CN.

Chapter eight: this chapter discusses the contribution of the research to the evidence base, and reports the strengths and limitations, and implications for clinical practice, policy, and future research.

1.4 Motivation for the PhD research

I qualified in 1996 as a podiatrist, and subsequently completed my Post Graduate Diploma. I realised early on that I wanted to focus on the management of the diabetic foot. I have been Principal Podiatrist within the Elsie Bertram Diabetes Centre, at the Norfolk and Norwich University Hospitals NHS Foundation Trust since 2002. I have worked alongside my colleagues in the multidisciplinary team to turn the service into a centre of clinical and research excellence.

Alongside my clinical role I was a member of the group that developed the National Institute for Health and Care Excellence (NICE) (2015) guidelines – the prevention and management of diabetic foot disease. I am also an expert adviser for the NICE Centre for Guidelines. I have also worked nationally to improve the outcomes of people with diabetic foot disease through, the National Diabetes Audit Advisory Board and the National Diabetes Foot Audit steering group.

These roles have shown me that the evidence base for the management of diabetic foot disease is limited and where available of poor quality. This is particularly true for CN where the guidance available to support clinical decision making is primarily based on level three and four evidence, case studies and expert opinion. This has driven my desire to work towards developing a clinical academic career, to benefit people living with diabetes and foot complications, healthcare professionals and to influence the future of diabetic foot management.

2 Background

2.1 Introduction

This chapter will first provide a brief overview of diabetes. It will then introduce Charcot neuroarthropathy (CN), and what is currently known about its, pathogenesis, incidence, prevalence, diagnosis, treatment, monitoring, and complications. It will examine and evaluate the evidence base for the techniques used to monitor CN, and the challenges faced by healthcare professionals in diagnosing remission. Secondly, it will examine and evaluate what is known about the experiences of people with CN in terms of people's social, physical, and psychological wellbeing. Finally, it will report the aims and objectives of this research.

2.2 Diabetes

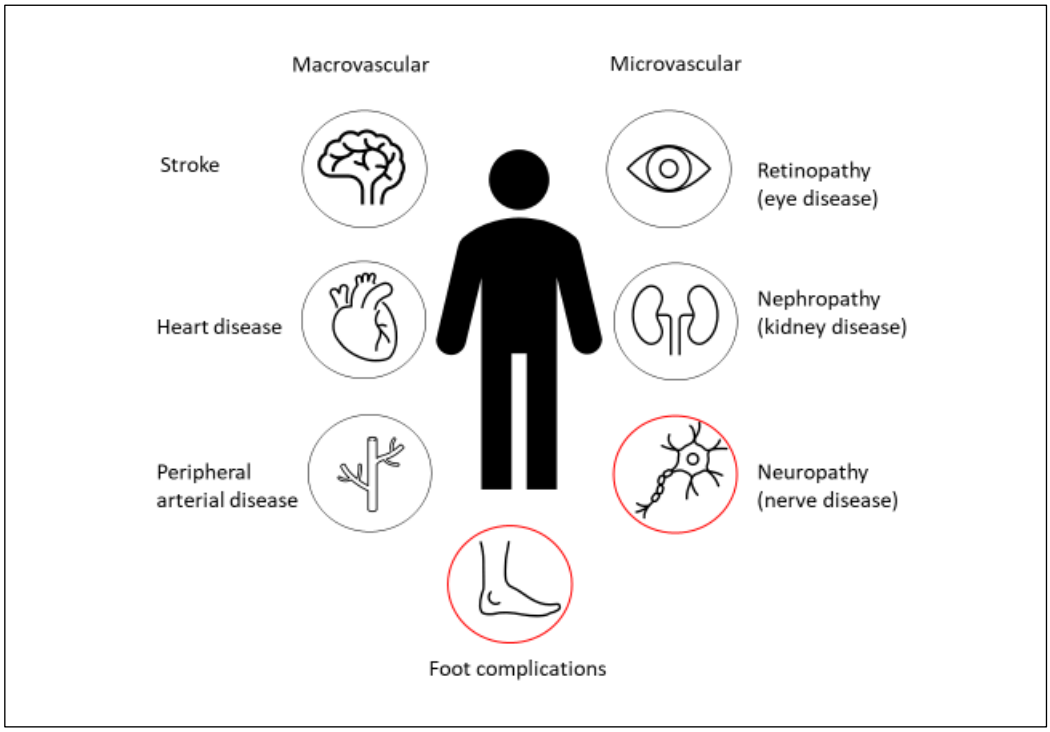
Diabetes mellitus is a chronic metabolic disorder which is characterised by high glucose (blood sugar) known as hyperglycaemia. There are two main types of diabetes. Type 1 diabetes is an autoimmune disease which destroys the insulin producing cells in the pancreas (Alberti and Zimmet, 1998). Type 2 diabetes develops when insulin cannot work effectively or not enough insulin is being produced (Cersosimo *et al.*, 2018).

People with type 1 diabetes require insulin treatment (Donner and Sarkar, 2019) whereas people with type 2 diabetes can manage their diabetes with behaviour choices, oral glucose lowering medication, insulin treatment or a combination of these. Regardless of the cause or type of diabetes, effective self-management relies on behavioural, adaptions and interventions.

Worldwide the incidence of diabetes is rising. In 2019 the estimated number of people with diabetes (type 1, type 2 and undiagnosed diabetes) worldwide was 463 million people, which equates to 1 in 11 adults living with diabetes (IDF, 2019). The number of people with diabetes in the UK has risen from 1.4 million in 1996 to 3.9 million in 2019, 90% of whom have type 2 diabetes. Diabetes costs at least $760 billion USA dollars (£565 billion UK pounds) in health expenditure in 2019 – 10% of total healthcare spending on adults (IDF, 2019).

The principal aim of diabetes treatment is to keep blood glucose levels as near normal as possible to prevent the long-term complications of diabetes (Figure 2-1).

Figure 2-1 The long-term complications of diabetes

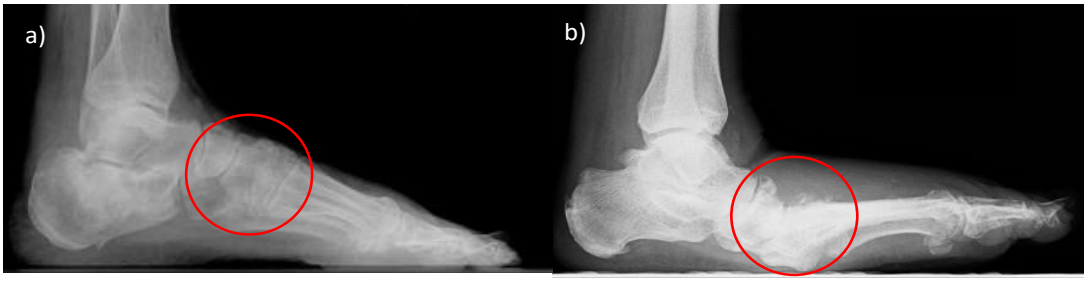


The focus of this thesis will be Charcot neuroarthropathy (CN), a complication of diabetes related nerve damage that most commonly affects the foot and ankle.

2.3 The epidemiology of Charcot neuroarthropathy

CN is a relatively rare but serious complication that can affect people with peripheral neuropathy (nerve damage) and is most commonly diagnosed in people with diabetes in countries where diabetes is the most common cause of peripheral neuropathy. It is a progressive condition that affects the bones, joints, and soft tissues. CN is divided into two phases. Firstly, the active phase when there is uncontrolled inflammation and bones become osteopenic (weak) which can lead to fractures, joint dislocation, and deformity (Figure 2-2). Then the second phase, chronic CN this is when the inflammation resolves, the foot is stable and in remission. The person is then living with the complications of CN, i.e., foot deformity, and ulceration. This research will focus on the active phase of CN. It will examine and evaluate opportunities to improve the monitoring of active CN and diagnoses of remission, and better understand people's experiences of receiving treatment for CN.

Figure 2-2 Plain X-rays to illustrate the progression of deformity in CN leading to fractures, dislocation, and deformity



a) X-ray of normal foot structure b) X-ray with dislocation and deformity caused by CN.

Diabetic neuropathy is the leading cause of CN (Sanders, 2004). Other causes include infection, drugs (Dhatariya *et al.*, 2009), autoimmune diseases, and trauma or tumours that damage the spinal cord (Table 2-1). CN most frequently affects the foot and ankle (Dardari, 2020), but can also affect the knee (Lu *et al.*, 2021), hip (Berg, 1997), spine, (Phillips, Williams and Peters, 1995) and the wrist (Lambert and Close, 2005; Wilmot, Jadoon and Olczak, 2008). The underlying pathological process is the same regardless of the cause or site of the CN. This thesis will focus on CN of the foot and ankle. Although CN is a relative rare complication of diabetes it is known to cause significant morbidity and contribute to high levels of mortality, and this will be discussed later on in the background.

Table 2-1 Causes of Charcot neuroarthropathy

Metabolic	**Autoimmune**	**Congenital**	**Infective**	**Drugs**	**Other**
Diabetes	Pernicious anaemia	Spina bifida	Leprosy	Steroids	Trauma
	Multiple sclerosis	Charcot-Marie-Tooth disease (Hereditary motor and sensory neuropathy (HMSN)	Poliomyelitis	Alcohol	Tumours
	Rheumatoid arthritis	Insensitivity to pain	Neurosyphilis/tabes dorsalis		Amyloidosis
					Syringomyelia

2.3.1 History of Charcot neuroarthropathy

Mitchell (1831) was the first to describe 'arthritis' linked to nerve damage, but the original description of CN was attributed to French neurologist Jean-Martin Charcot. He described it as a complication of tabes dorsalis, a rare neurologic form of tertiary syphilis (Charcot, 1868). Jordan (1936) was the first to describe the condition in people with diabetes.

CN is known by several different terms which are all used interchangeably in the literature: neuroarthropathy, arthropathy, neuropathic osteoarthropathy, and neuro-osteoarthropathy. These terms indicate a disease of joints that is associated with damage or disruption to the peripheral nervous system. As inflammation is a key feature of this disease and often the first clinical sign, the term 'neuropathic inflammatory sarco-osteoarthropathy' has been proposed as an alternative for CN (Jeffcoate, 2015). Given the importance of neuropathy in the development of CN I will now give an overview of how this effects the lower limb.

2.3.2 The effect of peripheral neuropathy on the lower limb

In diabetes, high blood glucose levels can damage nerves (known as neuropathy) by interfering with their ability to send signals. The exact pathogenesis is not fully understood and is likely to be multifactorial (Brownlee, 2001). In diabetes, neuropathy most frequently affects the nerves in the leg and foot, known as peripheral neuropathy. Neuropathy can lead to CN. Three types of neuropathies can affect the legs and feet: sensory peripheral neuropathy, autonomic neuropathy, and motor neuropathy. These are explained below.

Firstly, sensory peripheral neuropathy usually begins in the toes and can spread up the leg. It leads to reduced ability to feel pain or temperature and numbness. Up to 36% of people with diabetes for longer than 10 years have diabetes sensory peripheral neuropathy (Young et al., 1993); they have partially or completely lost the ability to detect pain (Dyck et al., 1993; Adler et al., 1997). In sensory peripheral neuropathy wounds and injuries can go unnoticed. People continue to walk on an injured foot, and in some instances, this can lead to CN.

The second type of neuropathy is autonomic neuropathy. In the lower limbs the autonomic nervous system has two main functions. The first function is to control peripheral capillary blood flow. In healthy people the size of blood vessels can be influenced by the autonomic nervous system acting on smooth muscles. A normal response is for blood vessels to vasodilate (widen) in response to warm weather and injury, and vasoconstrict (narrow) in cold weather or when

experiencing anxiety. In the presence of autonomic neuropathy this ability to rapidly change the calibre of blood vessels is lost, and the blood flow around the foot changes (Vinik, Casellini and Nevoret, 2018). Charcot himself concluded that this autonomic neuropathy led to osteopenia, seen in CN (Charcot, 1868). Secondly, the autonomic nervous system regulates moisture in the skin. Autonomic neuropathy leads to reduced sweating which leads to dry skin that is prone to cracks ulceration and infection (Dhatariya, 2014).

Motor neuropathy is the third type of neuropathy. Motor nerves are responsible for maintaining normal posture and balance. Motor neuropathy can lead to instability, and subsequent changes in walking style and increased risk of falls (Fernando *et al.*, 2013; Timar *et al.*, 2016). In healthy people, normal foot shape is maintained by the balance between the flexor and extensor muscles. In the presence of motor neuropathy, the flexor muscles of the foot become weaker (Cheuy *et al.*, 2013). The extensor muscles are less affected and therefore become more powerful than the flexor muscles (Dhatariya, 2014). This leads to the development of a high arched foot shape with retracted toes, prominent metatarsal heads this is known as a cavoid foot (Robertson *et al.*, 2002). There is also displacement of the fatty pad on the sole of the foot which normally protects the metatarsal heads. This means the metatarsal heads are subjected to increased pressure which can lead to tissue breakdown and ulceration (Veves *et al.*, 1992; Caselli *et al.*, 2002). This increased pressure can also lead to microfractures or micro-dislocations, and instigate a cycle of inflammation which is seen in CN (Jeffcoate, 2014).

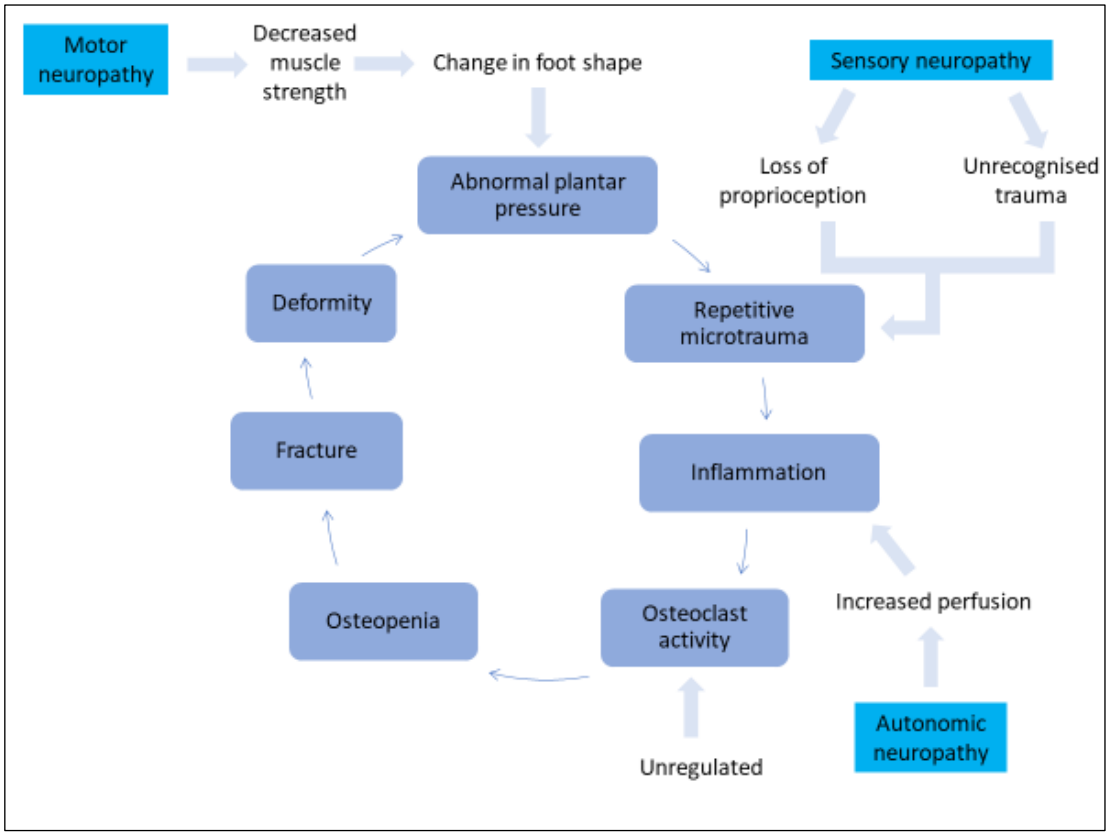
To summarise diabetic peripheral neuropathy can affect the lower limb in a variety of ways. Neuropathy can make people more suspectable to both intrinsic and extrinsic injury, which can go unnoticed and lead to diabetic foot complications such as CN. In the next section, I will discuss the role of neuropathy in the pathogenesis of CN.

2.3.3 Hypothesis for the pathogenesis of Charcot neuroarthropathy

The pathogenesis of CN has been explained by two main theories: neurotrophic/neurovascular theories and neurotraumatic theories. The neurotrophic/neurovascular theory was proposed by Charcot. He hypothesised that increased blood flow to the foot, now known to be associated with autonomic neuropathy, leads to bone resorption and bone weakness (osteopenia). The second theory the neurotraumatic theory, focuses on an insensate joint or bone being subjected to continued, repetitive pressure and trauma. This causes progressive damage to the affected bones and joints which leads to fractures and deformity.

However, it is increasingly unlikely that either of these theoretical pathogenic pathways in isolation cause CN: it is generally unilateral, self-limiting and only develops in a small proportion of people who have neuropathy (Jeffcoate, Game and Cavanagh, 2005). A different mechanism which involves both theories, and is initiated by trauma either from an injury, loss of proprioception or increased plantar pressure, which causes repetitive microtrauma to the foot has been suggested (Jeffcoate, Game and Cavanagh, 2005). This continual loading causes inflammation, and disrupts the relationship between bone formation and resorption, so that the bones become osteopenic (less dense). The person often does not recognise any problems due to loss of usual sensation (Pinzur, 1999; Game *et al.*, 2012). Fractures occur and continued walking on these broken bones leads to foot deformity (Figure 2-3) and causes further abnormal pressure to the foot (Kaynak *et al.*, 2013).

Figure 2-3 Pathogenesis of Charcot neuroarthropathy



adapted from Kaynak et al., (2013)

The true pathogenesis of CN is not fully understood, and it is likely that the causes are multifactorial, with perhaps currently unknown mechanisms and factors contributing to the development of CN. It is not known how to prevent the development of CN, other than

maintaining good diabetes control to reduce the risk of the development of neuropathy. However, this does not eliminate the risk.

2.3.4 Incidence and prevalence of Charcot neuroarthropathy

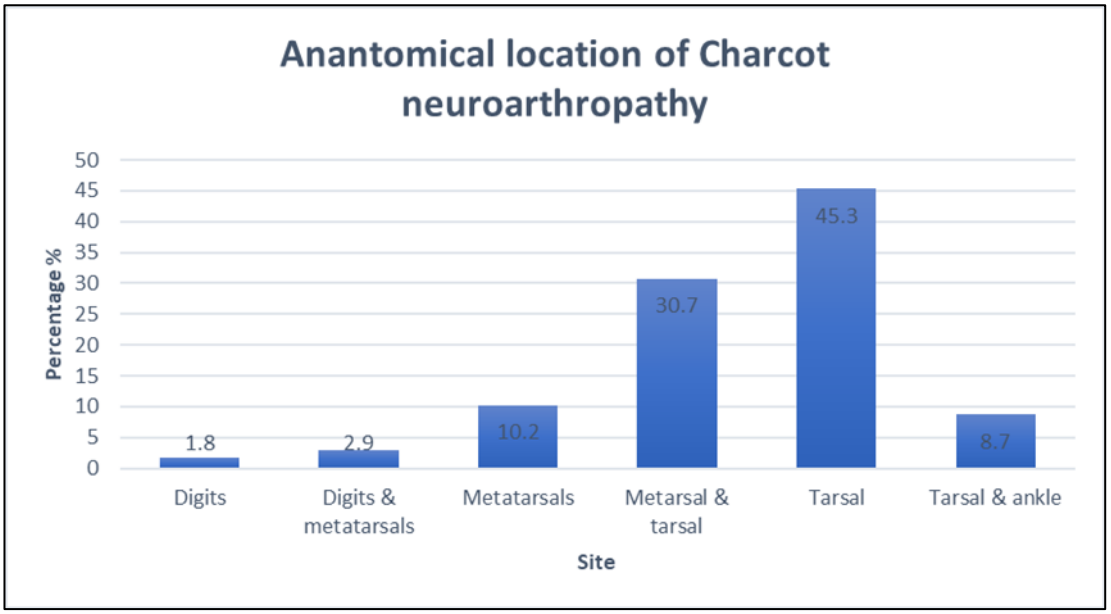
Population-based studies have estimated a life time cumulative incidence for CN of 0.1% to 7.5% in people living with diabetes (Frykberg and Belczyk, 2008). This rises to 13% in people who attend diabetic foot specialist clinics (Armstrong *et al.*, 1997). In 2018 a regional survey of 205,033 people with diabetes in the East Midlands, UK, reported a point prevalence of 0.04% (Metcalf *et al.*, 2018). The largest epidemiological study to date comes from Denmark with 309,557 people with diabetes identified from hospital codes over a 23-year period (1995-2018). This study reported an incidence rate of 7.4 per 10,000 person-years, and a prevalence of 0.56% (Svendsen *et al.*, 2021). These two studies are the only large epidemiological studies on CN, so its true incidence and prevalence is still largely unknown. More recent studies report an increase in the numbers of people with CN, but this could be a result of increased awareness, rather than an actual increase. Further studies are needed to confirm this.

CN typically presents during the fifth or sixth decade of life (Petrova, Foster and Edmonds, 2004), in people who have been diagnosed with diabetes for longer than ten years. It is most frequently unilateral. The reported incidence of concurrent bilateral involvement varies considerably from 9-30% of cases (Clouse *et al.*, 1974; Armstrong *et al.*, 1997; Brodsky, 1999a). From a biomechanical perspective, off-loading and immobilisation of one foot will increase pressure on the contra-lateral foot and thus increase the likelihood of bilateral CN (Hartsell, Brand and Saltzman, 2002; Crews and Wrobel, 2008).

Peripheral neuropathy is the only prerequisite for the development of CN. Small cohort studies with 50-115 participants have reported that: standing for long periods, poorly controlled diabetes (Fabrin, Larsen and Holstein, 2000; Stuck *et al.*, 2008), neuropathy and other microvascular complications of diabetes, i.e., retinopathy and nephropathy, being male, being taller, being overweight, and history of concurrent diabetic foot complications are all associated with an increased risk of CN.

CN commonly starts in a single joint in the foot or ankle and can progress to involve multiple joints. An audit from the UK demonstrated that the metatarsals and tarsal joints, located in the midfoot, were most frequently affected (Figure 2-4) (Game *et al.*, 2012).

Figure 2-4 Anatomical location of Charcot neuroarthropathy



Game et al., (2012)

To summarise this section, despite CN first being described over 150 years ago, it remains a poorly understood and frequently overlooked complication of diabetes (Donegan, Sumpio and Blume, 2013). We know that it is a condition of diabetes neuropathy affecting joints, and more recently the role of soft tissue inflammation has been recognised. However there remains uncertainty around the pathogenesis of CN, and the true incidence and prevalence are not known.

2.3.5 Classification of Charcot neuroarthropathy

In healthcare, classification systems are important as they can provide more detailed information on the stage of a disease, and guide treatment. They can also be used to compare outcomes, in research and public health reporting. There is no universal agreed classification system for CN. Existing systems can be divided into systems that describe the progression of the destructive pathological process and those which describe the anatomical location of the affected bones or joints.

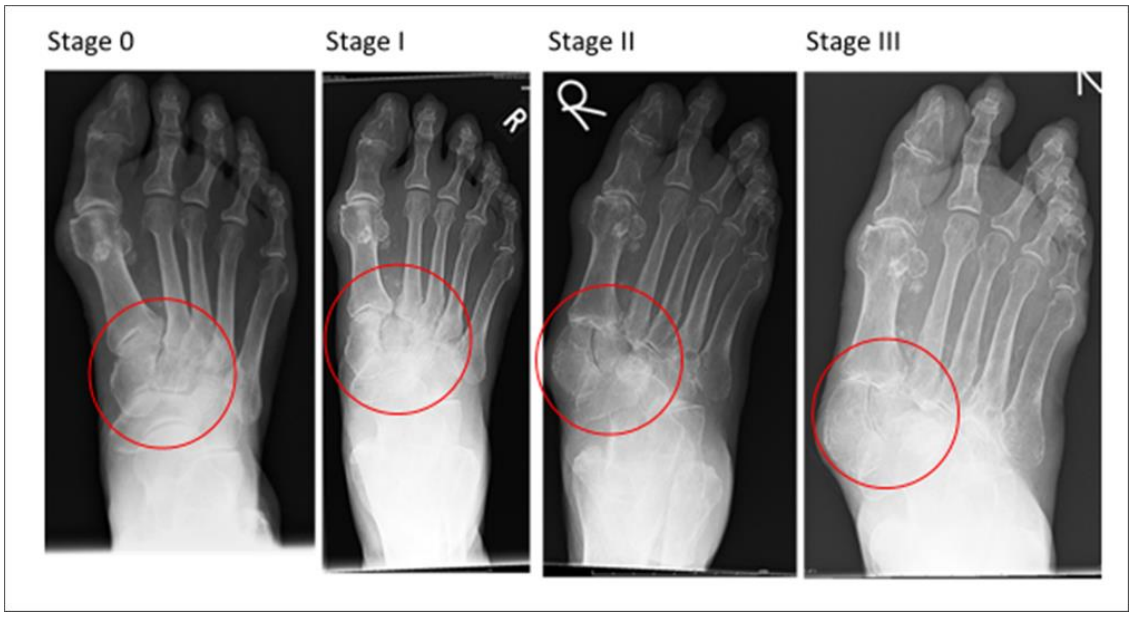
The first classification system was devised by Eichenholtz and grades the progression of CN using plain X-rays based on the destructive pathological process (Eichenholtz, 1966). He identified three stages: development, coalescence, and reconstruction. This system was adapted by Shibata, Tada and Hashizume (1990) to include a stage 0, the prodromal stage this reflects the early stages of CN when plain X-rays are normal and the diagnosis is based on clinical observations (Table 2-2 and Figure 2-5).

Table 2-2 Modified Eichenholtz classification system

	Stage	Radiographic finding	Clinical finding
Stage 0	Prodromal	Normal radiographs	Swelling, erythema, warmth
Stage I	Developmental	Osteopenia, osseous fragmentation, joint subluxation, or dislocation	Swelling, erythema, warmth, ligamentous laxity
Stage II	Coalescence	Absorption of debris, sclerosis, fusion of larger fragments	Decreased warmth, decreased swelling, decreased erythema
Stage III	Reconstruction	Consolidation of deformity, fibrous ankylosis, rounding and smoothing of bone fragments	Absence of warmth, absence of swelling, absence of erythema, fixed foot/ ankle deformity

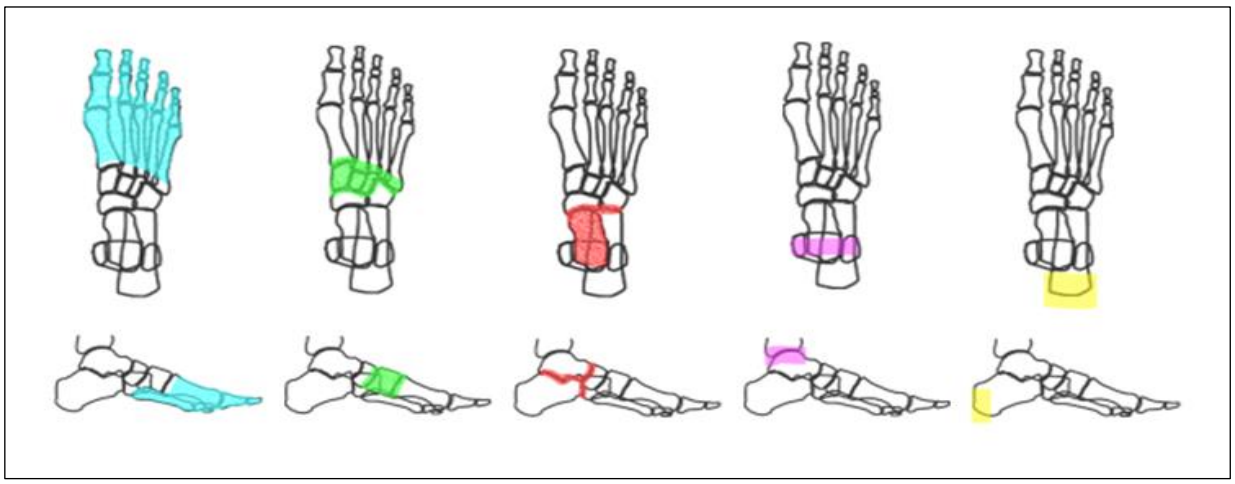
Wukich and Sung (2009)

Figure 2-5 Plain X-rays demonstrating the different stages of the Eichenholtz classification system



The second type of classification systems is based on the anatomical location of the bones and joints affected by CN. The two most common systems are firstly the Sanders and Frykberg (1991) and secondly the Brodsky (1999a), which was later modified by Trepman, Nihal and Pinzur (2005) (Figure 2-6 and Table 2-3). Other classification systems exist for CN, but the ones described here are the most widely used in research and clinical practice.

Figure 2-6 Pictorial representation of the anatomical classification systems described by Sanders and Frykberg and Brodsky



Sanders and Frykberg (1991); Brodsky (1999a); Trepman, Nihal and Pinzur (2005)

Table 2-3 Sanders and Frykberg and Brodsky classification systems

Brodsky	Sanders and Frykberg	Colour	Site
1	II		Lisfranc, tarsometatarsal joints
2	III		Hindfoot
3A	IV		Ankle
3B	V		Posterior calcaneum
4	Not reported		Combined
5	I		Forefoot

Sanders and Frykberg (1991); Brodsky (1999a) ; Trepman, Nihal and Pinzur (2005)

2.4 Diagnosis and monitoring of Charcot neuroarthropathy

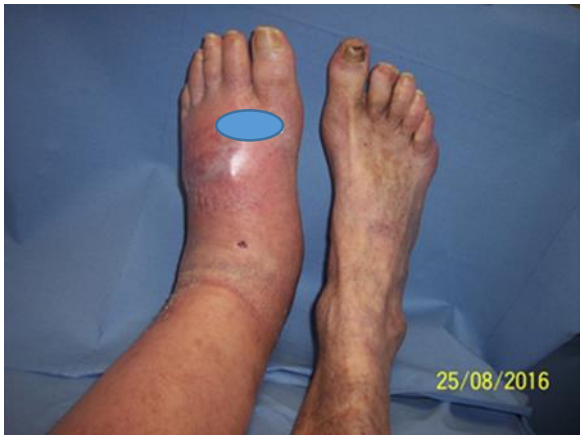
The diagnosis of CN is primarily based on clinical findings, supported by radiological investigations. There is no universally agreed method or series of investigations to diagnose CN in the early stages.

2.4.1 History and clinical examination to diagnose Charcot neuroarthropathy

An in-depth patient history and assessment, with a high index of suspicion, in a person with diabetes, neuropathy and an unexplained inflammation in their foot are key to making an accurate diagnosis. The classic presentation of acute CN is a unilateral red, hot, swollen, foot with

or without pain (Figure 2-7). These are often the first symptoms of early CN, before changes to bones and joints are evident. At diagnosis, up to 76% of people with CN report pain (Armstrong *et al.*, 1997). However, the level of reported pain often does not correspond with the extent of inflammation and, where present, the level of bone destruction evident on clinical and radiological examination (Rogers *et al.*, 2011).

Figure 2-7 Clinical presentation of Charcot neuroarthropathy of the left foot



CN is often misdiagnosed as other more common conditions with similar presentations which can include soft tissue injury, infection, cellulitis, arthritis, gout, and deep vein thrombosis. People initially attend a range of non-specialist settings, GP surgeries, urgent or emergency care centres, physiotherapy, rheumatology, or orthopaedic clinics. CN is rare and is not always diagnosed by non-specialists due to a lack of knowledge about it.

The causes of CN are multifactorial but is often precipitated by minor trauma in the foot, inflammation secondary to foot ulceration, infection, or surgery. Between 22—36% of people with CN report an episode of trauma, such as a trip or fall, prior to noticing a problem (Armstrong *et al.*, 1997; Game *et al.*, 2012). A further 12% reported undergoing surgery (orthopaedic, vascular or endovascular) on the foot or leg within the last six months (Game *et al.*, 2012). However, the presence of neuropathy may mean that people with diabetes do not recall any trauma and hence do not report it.

After an in-depth patient history, the next step is an assessment of the neurovascular status of the feet. A validated instrument such as a neurotheisometer determines a person's ability to detect vibration or a monofilament can be used to check for protective pain sensation. Peripheral circulation is normally intact, with palpable foot pulses unless masked by the presence of oedema. In theory it is not possible to develop CN in the presence of severe peripheral arterial

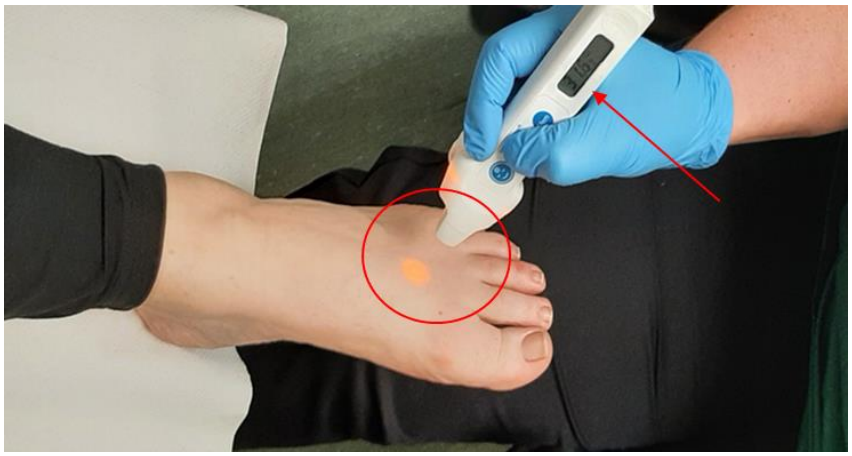
disease as there is insufficient blood supply to mount the necessary inflammatory response (Jeffcoate, 2014).

Following the neurovascular assessment, the next step is to assess the degree of inflammation in the feet, usually with infrared thermography. The same technique for infrared thermography is used both to diagnose and monitor for remission in CN. Therefore, in the next section I will describe the method of using infrared thermography to diagnose and monitor CN.

2.4.2 The use of Infrared thermography to diagnose and monitor Charcot neuroarthropathy

In healthy individuals there is a symmetry in skin temperature. However, in the presence of inflammation this symmetry is lost and asymmetrical foot temperature measurements can indicate an abnormality (Hernandez-Contreras *et al.*, 2016). CN is a disease process within the soft tissue, bones and joints characterised by inflammation. Increased skin surface heat is a proxy measure of the degree of inflammation measured over the site of inflammation. The temperature difference between the affected and unaffected foot is used to help diagnose and monitor the progression of disease activity. Skin temperature measurements at standardised sites are measured using a handheld infrared thermometry device (Figure 2-8).

Figure 2-8 Photography of the assessment of foot temperature using infrared thermography



The red circle shows where the temperature is being measured, and the red arrow shows the reading

The advantages of infrared skin temperature measurements are that they can be completed quickly and are non-invasive (Lahiri *et al.*, 2012). To diagnose and monitor CN the corresponding sites of the affected and unaffected foot are compared. A temperature difference of greater than 2°C between the affected and unaffected foot is indicative of inflammation. It is important to

remember that a temperature difference does not confirm the diagnosis of CN as many other conditions can present with a temperature difference between the affected and unaffected foot.

The most detailed protocol for measuring the temperature difference between feet using infrared thermography requires a 15 minute acclimatisation period, controlled ambient room temperature, and readings collected from nine different anatomical sites on each foot (Armstrong and Lavery, 1997). This protocol is not always feasible in a busy clinical environment, with time constraints and an inability to control room temperatures. These factors may have prevented the widespread adoption of this protocol, and many healthcare professionals have simplified this protocol. Whilst most diabetic foot clinics use infrared thermography as a guide to assessing residual disease activity, there is inconsistency in the methods used (Gooday *et al.*, 2020a). There is a lack of consensus on the period of acclimatisation after removing shoes and socks before the temperature readings are taken and which sites on the foot to use to take the temperature measurements.

A recent cohort study with 32 people with CN, assessed the intra and inter-rater reliability of using infrared thermography to assess CN (Dallimore *et al.*, 2020). They reported good intra and inter rater reliability of the test. However, this study did not address the uncertainties around the sensitivity and specificity of using infrared thermography to monitor CN.

Following diagnosis of CN people are followed up at intervals of between 2-4 weeks until the foot is assessed as in remission. At these follow-up appointments the temperature difference between the affected and unaffected foot is reassessed. The diagnosis of remission will be considered in more detail later on in the thesis.

Comparison of the skin temperature between the affected and unaffected foot assumes that the any inflammatory process is limited to just one foot. The presence of bilateral foot disease, or the absence of a contra-lateral limb will invalidate the use of skin temperature measurement. Thus, there is a need to find alternative approach to monitoring CN that overcomes these issues.

Alongside clinical examination and infrared thermography, the use of laboratory and radiological investigations can be helpful to arrive at an accurate diagnosis, and these are described in detail in the next section.

2.4.3 *The use of laboratory and radiological investigations to diagnose and monitor Charcot neuroarthropathy*

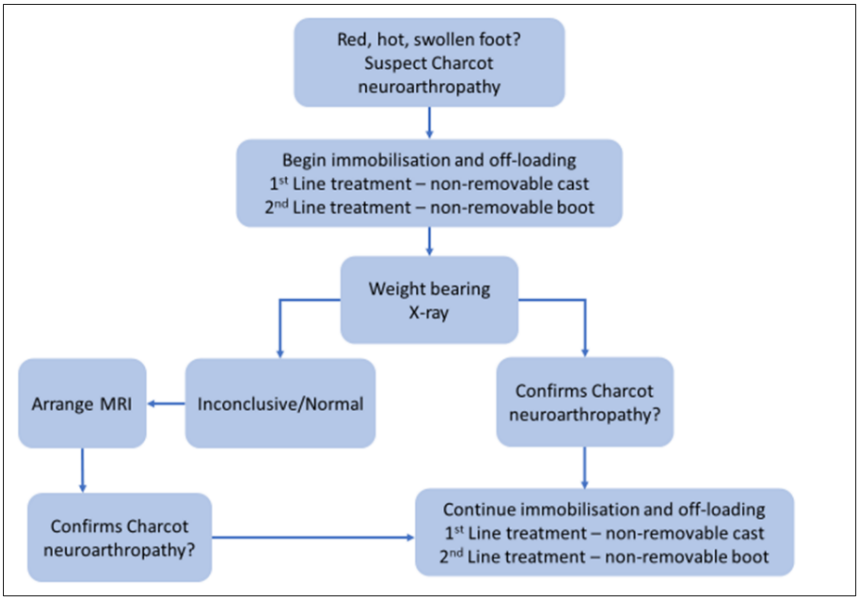
In CN, chemical and haematological markers in the blood are usually normal or only marginally outside normal reference ranges unless there is concurrent infection (Petrova and Edmonds, 2020).

The following section will focus on the use of radiological investigation and specifically plain X-rays and MRIs for diagnosing and monitoring CN. This is because although there are other radiological imaging techniques which could be used such as three phase bone scanning, computer tomography, Positron emission tomography scan and Single-photon emission computed tomography scan the value of these newer imaging technologies in CN has yet to be established (Jeffcoate, 2014).

2.4.3.1 The use of plain X-rays to diagnose and monitor Charcot neuroarthropathy

Current guidelines for healthcare professionals who deliver treatment to people with CN recommend baseline plain X-rays as the initial radiological investigation to diagnose CN (Figure 2-9) (National Institute for Health and Care Excellence, 2015). Plain X-rays are a relatively inexpensive, simple investigation which are readily available in most hospitals. They provide a two-dimensional picture of bones but do not show soft tissues. The main disadvantage of plain X-ray is that it uses ionising radiation which can be harmful to the individual and the environment.

Figure 2-9 Algorithm for the assessment and management of Charcot neuroarthropathy



Based on reccommendations from the National Insititute for Health and Care Excellence, 2015 Diabetic Foot Problems: prevention and management

However, there are some problems with using plain X-ray to diagnose CN. Firstly at Eichenholtz stage 0 there may be no changes evident on plain X-ray, (Shibata, Tada and Hashizume, 1990). This means that plain X-rays will be normal, and a diagnosis of CN could be missed.

There is no evidence on the sensitivity and specificity of plain X-rays in identifying bone abnormalities in CN. However, evidence from other studies assessing the utility of plain X-rays to identify foot and ankle injuries report poor sensitivity. A cohort study of 54 people with sports injuries reported that MRI scans showed osteochondral fractures that were frequently missed on plain X-ray, (Yammine and Fathi, 2011). Another cohort study in 388 people with sports injuries compared Computer Tomography to plain X-ray to diagnose foot and ankle trauma. They reported a sensitivity of between 25-33% for mid foot fractures on plain X-rays (Haapamaki, Kiuru and Koskinen, 2004). A case study review of two misdiagnosis traumatic cuneiform fractures, report how the overlapping structure of the bones in the mid-foot make identifying abnormalities on plain X-ray more difficult (Olson, Mendicino and Rockett, 2000). This means that at Eichenholtz stage 0 and I, using plain X-rays to diagnose CN may mean that foot and ankle fractures and abnormalities associated with CN may be missed.

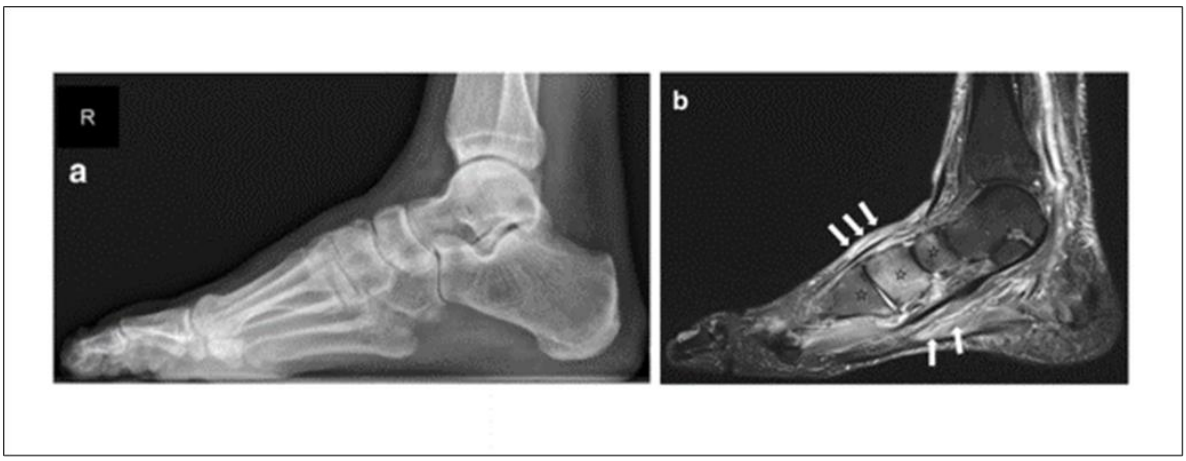
Finally, plain X-rays show deformity, therefore they are a measure of outcome rather than disease process. They can be used to evaluate whether off-loading and immobilisation has been effective in preventing the progression of foot deformity, not whether the CN is in remission.

Given the potential problems with plain X-rays, if the results of the plain X-ray are inconclusive and there is still a high index of clinical suspicion, then guidelines recommend that healthcare professionals should consider using MRI to diagnose CN (Figure 2-9) (National Institute for Health and Care Excellence, 2015).

2.4.3.2 The use of MRIs to diagnose and monitor Charcot neuroarthropathy

Unlike plain X-rays, MRI can show changes associated with CN even at Eichenholtz stage – 0 when plain X-rays are normal. Bone oedema, and soft tissues structures, can be seen very clearly on MRI (Figure 2-10 Imaging in early Charcot neuroarthropathy. The ability to be able to see soft tissue structures is particularly important given the more recent hypothesis that CN is a condition of soft tissue as well as bone (Jeffcoate, 2015).

Figure 2-10 Imaging in early Charcot neuroarthropathy



a= plain X-ray no abnormalities Rosskopf et al., (2019)
b=MRI with arrows showing classic bone marrow and soft tissue oedema not evident on plain X-ray

A cohort study with 20 people and 26 episodes of CN retrospectively compared the plain X-rays and MRIs of people with CN (Chantelau and Poll, 2012). This study found that MRI demonstrated bone stress injuries, micro trabecular fractures, oedema of the soft tissue and joint effusion when plain X-rays failed to show any abnormalities. All these features are consistent with an early diagnosis of CN when plain X-rays fail to show an abnormality. In another cohort study the medical notes and imaging of 59 people with 71 episodes of CN were reviewed; when plain X-ray was used as the initial diagnostic imaging technique, 18% (13/71) cases were missed, which led to delayed referral and treatment (Chantelau and Richter, 2013). From these studies the authors concluded that MRI is superior to plain X-rays in the diagnosis of CN.

The use of MRI as a superior diagnostic tool in the diagnosis of CN is now well-established (National Institute for Health and Care Excellence, 2015). Chantelau and Grützner, (2014) have suggested that the findings on MRI should be adopted as the standard criterion for establishing disease activity and remission. This is because it has the greatest potential to monitor the effect of treatment since the findings more directly reflect the degree of soft tissue and bone inflammation. There are three observational studies on MRI and disease monitoring in CN. A cohort study with 40 participants demonstrated that mean healing time was significantly related to the baseline contrast medium uptake during MRI scanning (Zampa *et al.*, 2011). Another cohort study compared the images of 13 people with CN, they reported a significant correlation of intensity of bone marrow oedema in MRI and clinical measures of soft tissue oedema and pain (Schlossbauer *et al.*, 2008). In a third cohort study three radiologists assessed 45 MRI scans, they reported that semi-quantitative scoring for bone marrow oedema and fracture on MRI might be useful in monitoring treatment of CN (Meacock *et al.*, 2017).

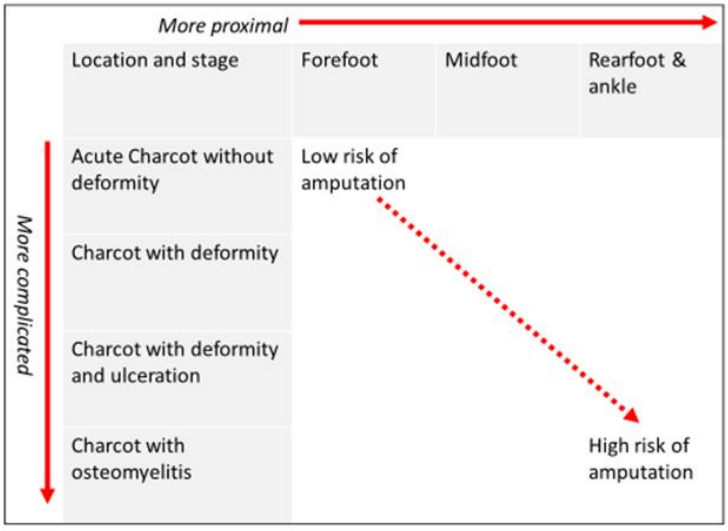
The advantage of MRI scanning is that people are not exposed to radiation as with plain X-rays. Having an MRI involves lying flat and still in a noisy enclosed space. This can make MRI unsuitable for people with claustrophobia, or for those who cannot lie flat. MRI is contraindicated in people with some pacemakers, and some metals implants such as those who have had joint replacement surgery. MRI with contrast is contraindicated for people with kidney disease.

In summary the sensitivity and specificity of using infrared thermography, and plain X-ray to diagnose and monitor CN is poor. This means it is challenging for healthcare professionals to make decisions about when to stop or prolong treatment. Access to MRI is becoming more readily available. This offers an opportunity to examine the potential benefits of expanding the use of MRI from purely diagnostic to include monitoring for remission in CN. However, the use of MRI in monitoring CN has not been formally evaluated. High quality evidence to support the superiority of MRI to current monitoring techniques for diagnosing remission in CN is needed before recommending a change in practice.

2.5 Treatment of Charcot neuroarthropathy

CN treatment aims to stop the inflammatory process, relieve pain, and maintain foot architecture (Frykberg and Mendeszoon, 2000). The success of treatment depends on many factors including the stage of CN at presentation, the location of the bones and joints involved the degree of deformity at presentation, and presence of concurrent ulceration and infection (Figure 2-11).

Figure 2-11 Roger's classification system



Rogers and Bevilacqua (2008)

People with suspected or confirmed CN should be referred without delay to specialist multidisciplinary foot teams (National Institute for Health and Care Excellence, 2015). The

response to treatment is monitored with regular reviews to identify remission. Remission means that there are no longer clinical signs of inflammation, and radiological imaging show no further progression of foot deformity with signs of bone healing (Milne *et al.*, 2013). In the next section I will provide a brief overview of the different treatment approaches for CN: conservation, pharmacological and surgical.

2.5.1 Conservative treatment of Charcot neuroarthropathy

Non-surgical management of CN is to off-load and immobilised the foot by wearing a non-removable device, either a cast or boot (Figure 2-12) (National Institute for Health and Care Excellence, 2015). A non-removable device immobilises the foot and minimises the potential for any further damage (McGill *et al.*, 2000).

Figure 2-12 Examples of the different types of off-loading devices

Edmonds and Watkins (1984) were the first to show the association between commencing treatment as early as possible after the onset of symptoms and preventing the progression of deformity. This association between early treatment and improved outcomes has been confirmed in more recent studies (Chantelau and Richter, 2013; Ruotolo *et al.*, 2013). Off-loading continues to be the main treatment for CN four decades since these original observations.

Cast or boots share the load and redistribute the pressure away from the affected bone/s or joint/s. Non-removable devices are recommended as studies have shown that people's adherence to wearing removable devices is low (Armstrong *et al.*, 2003), which could contribute to the longer healing times. A UK study showed that median time to healing was 9 months among people who received initial treatment with a non-removable off-loading device, compared to 12 months for those who did not (Game *et al.*, 2012).

Alongside wearing the cast or boot, it is common practice among specialist healthcare professionals to advise people with CN to rest their foot and minimise weight bearing, as this further off-loads the foot. However, there is no high-quality evidence that this reduces time to resolution or reduces deformity. Resting the foot, and the resulting restrictions on people's lives for prolonged periods of time can be extremely challenging.

2.5.2 Pharmacological treatment of Charcot neuroarthropathy

Pharmacological treatment refers to the use of drugs to treat a condition. The pathophysiology of CN is associated with increased bone resorption, leading to osteopenia (Jeffcoate, Game and Cavanagh, 2005). Therefore, the use of pharmacological therapies to treat CN has focused on the re-establishment of the balance between bone formation and destruction. The poor quality of the evidence and inconsistency in the results, have led to UK guidelines and international consensus documents not recommending the use of pharmacological therapies to treat CN unless being evaluated in a clinical trial (Rogers *et al.*, 2011; National Institute for Health and Care Excellence, 2015).

2.5.3 Surgical treatment of Charcot neuroarthropathy

Surgery is generally only considered when conservative treatment has failed to prevent the progression of foot deformity which could lead to ulceration and amputation. Surgical intervention aims to correct any deformity and achieve a stable flat foot (Wukich and Sung, 2009).

In summary the main treatment for CN is conservative, with the use of a non-removable cast or boot. There appears to be variation in the reported treatment times for CN, and the reason for this is not entirely clear. Currently there is no evidence to support the use of pharmacological therapies to treat CN, and surgery is primarily reserved for when conservative treatment has failed.

2.6 Diagnosing remission in Charcot neuroarthropathy

As the disease process of CN progresses, signs of inflammation usually resolve, however the decision for healthcare professions to discontinue or prolong immobilisation is challenging. The presence of neuropathy means that subjective symptoms are often absent, and the signs of inflammation can be subtle, and this can make it difficult to assess when the foot has gone into remission.

Current management guidelines recommend that immobilisation should be continued until the temperature difference between the feet is less than 2°C, with no further radiological changes on imaging (National Institute for Health and Care Excellence, 2015). However, this recommendation is only based on evidence level IV, i.e., derived from case series. The potential problems associated with using infrared thermography and plain X-rays to diagnose CN discussed earlier in the background are also applicable to using these techniques to diagnose remission.

Jeffcoate, (2014) has suggested that the cut off temperature difference of less than 2°C may be set too high, as there is still a noticeable difference between the foot temperatures. This could indicate ongoing inflammation and could mean that the foot is not in remission. However, in a study with 28 participants temperature differences were shown as an objective marker of remission. Remission was defined as a temperature difference of >2°C, and relapse as a new incidence of a temperature difference of >2°C. However, the sensitivity and specificity was not reported (Moura-Neto *et al.*, 2012).

There is no consensus on the definition of remission, the evidence to support current guidelines is poor and there are subtle differences in the ways clinical teams and researchers define remission. An over or underestimation of the degree of inflammation could mean that treatment is continued for longer than necessary or discontinued prematurely increasing the burden on people with CN and healthcare providers. Studies from the UK show a median time to remission of between 9-12 months (Bates, Petrova and Edmonds, 2006; Game *et al.*, 2012; Stark *et al.*, 2016). Studies from the USA show considerably shorter immobilisation times between 3-5 months (Armstrong *et al.*, 1997; Sinacore, 1998; Pinzur, Lio and Posner, 2006; de Souza, 2008). Studies conducted in Brazil, Germany, Denmark and Australia show remission times of 3-12 months, 3-6 months 8.3, and 4.3 months respectively (Kimmerle and Chantelau, 2007; Moura-Neto *et al.*, 2012; Jansen *et al.*, 2018; Griffiths and Kaminski, 2021). Such prolonged periods of immobilisation cause social limitations and reduced people's quality of life (Pinzur and Evans, 2003).

The sensitivity and specificity of the current monitoring techniques to diagnose remission is low or unknown which may contribute to the apparent variation in time to remission. However, other clinical factors may account for this variation which need to be considered. Firstly, time to remission is quicker if immobilisation and off-loading is started early at Eichenholtz Stage 0 compared to Stage I (Lavery, Armstrong and Walker, 2012). The second factor is the anatomical location of the CN. Hind foot CN takes a longer time to go into remission than midfoot and forefoot disease (Lavery, Armstrong and Walker, 2012). Finally as described earlier the use of different types of off-loading devices, can affect time to remission. (Game *et al.*, 2012). The question remains whether MRI is superior to current care in diagnosing remission in CN.

2.7 Relapse of Charcot neuroarthropathy

As with the diagnosis and monitoring for remission identifying a potential relapse of CN can be challenging. Infrared thermography is the main technique used to monitor for signs of relapse. There is variation in the reported relapse rates. An observational study from Denmark with 173 people with CN reported a total recurrence rates of 29% of which 80% were in the same foot, the time to recurrence ranged from 1-103 months (Jansen *et al.*, 2018).

Observational studies from the UK on between 46-50 people with CN report longer treatment times with high rates of relapse ranging between 33-35% (Bates, Petrova and Edmonds, 2006; Stark *et al.*, 2016). Observational studies from the USA found shorter treatment times were associated with lower incidence of relapse (Armstrong *et al.*, 1997; Sinacore, 1998). In the studies from the USA the follow-up period was between 1-35months, shorter than those reported by the Danish team.

It is challenging to compare the reported incidence of relapse from different case series due to lack of agreement about what constitutes a relapse. Variation exists between the time relapse to differentiate between a relapse or 'new' case, or whether the anatomical site for the relapse needs to be the same, adjacent to, or in the same foot. Armstrong *et al., (*1997) described a potential but short-lived relapse of the CN following transfer from the offloading cast into footwear, with the offloading cast being reapplied for a period of 2.9 ±1.2 weeks before temperatures stabilised again. This may be a short-lived transient period of raised temperatures when people transfer from casts or boots into footwear, which could be part of the normal healing trajectory.

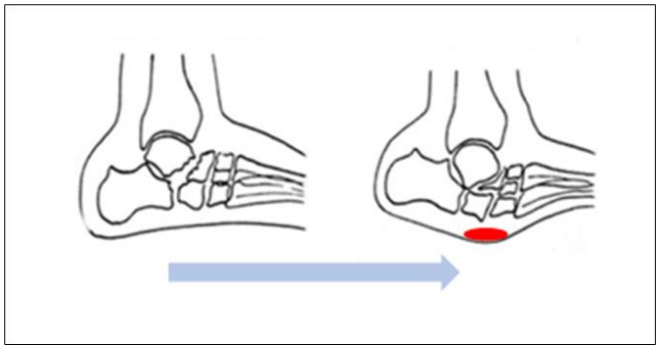
In summary, these sections have highlighted the challenges and evidence gaps associated with the current approaches to monitoring CN and diagnosing remission and relapse. There is a need to agree on the terminology used to describe the different stages of CN. Alongside this a more sensitive and specific monitoring technique for CN could reduce the variation in treatment times and the total number and variation in the level of relapses reported. This could reduce the burden of this disease on people with CN and healthcare providers.

2.8 Complications of Charcot neuroarthropathy

Foot deformity and secondary ulceration are the most commonly reported complications of CN. Ulcers are extremely difficult to heal, and osteomyelitis (bone infection) increases the risk of amputation. The most recognised deformity associated with CN and ulceration is the classic

"rocker-bottom" deformity (Figure 2-13). The arch of the foot collapses, it changes from a concave to a convex structure and the foot shape is likened to the bottom of a boat.

Figure 2-13 Pictorial representation of the progression of deformity leading to ulceration



Rosskopf et al., (2019)

Any of the bones and/or joints in the foot can be affected, and then lead to deformity and ulceration. Early treatment with immobilisation and off-loading is known to prevent or limit the development of deformity, subsequent ulceration and improve quality of life (Chantelau, 2005; Pakarinen et al., 2009).

People with CN have an increased risk of major amputation, with rates as high as 28% if ulceration is present on the initial evaluation (Saltzman *et al.*, 2005). The Rogers and Bevilacqua, (2008) classification system predicts that people with rearfoot and ankle CN complicated by osteomyelitis are most likely to undergo amputation (Figure 2-11). Major lower limb amputation rates are higher in people who do not receive off-loading 23% compared to those who did receive off-loading 17% (O'Loughlin *et al.*, 2016). Amputation can have a major impact on the individual, their families and society. In many cases, people who have undergone an amputation can no longer work and this has financial consequences for the individual and their families (Fejfarová *et al.*, 2014).

A diagnosis of CN increases mortality; average life expectancy is reduced by 14.4 years compared to the general UK population. A study from Nottingham found no difference between mortality rates in people with CN, compared to those with neuropathic foot ulceration, and concluded that the neuropathy itself is associated with increased mortality (Gazis *et al.*, 2004). CN does not happen in isolation, people may also have other microvascular complications of disease, i.e., retinopathy and nephropathy which are independent risk factors of cardiovascular events.

For people with CN, wearing a non-removable off-loading device for many months can be challenging. Furthermore, they may experience short and long-term risks of relapse of the CN, ulceration, amputation, and premature death. In the next section of this chapter, I will discuss the effect of all these factors on people's physical, social, and psychological well-being.

2.9 The physical, social, and psychological consequences of Charcot neuroarthropathy

Living with a long-term condition such as diabetes can affect people's lives. These changes can affect the individual, their families, and their relationships and for everyone involved can be difficult to accept and adapt to. Living with diabetes has a negative effect on people's experiences their emotional wellbeing and quality of life (Redekop *et al.*, 2002; Goldney *et al.*, 2004). Diabetes related complications, such as CN can perhaps make these problems worse.

2.9.1 The effects of Charcot neuroarthropathy on depression

To my knowledge, only one study has been conducted exploring the effect of CN on people's emotional wellbeing. The link between depression and the development of CN has not been fully investigated. There is more evidence on the experiences of people with diabetic foot ulceration, than CN. This is primarily because foot ulceration is more common. Whether the experiences of people with CN and ulceration are the same is not known.

There is some evidence from one small study which reported that people with diabetes and CN experience more serious levels of depression and anxiety compared to people with diabetes without CN (Chapman, Shuttleworth and Huber, 2014). The study found that females with CN reported more anxiety and depression than males and people out of work reported more severe anxiety than people working (Chapman, Shuttleworth and Huber, 2014). This study was carried out at one point in time, and the mean duration of CN was reported as five years (SD±3.4) this means that the study group comprised of a mixture of people at different stages of the CN process appearing to be biased towards people who were living with chronic rather than acute CN. This study has shown the effect of chronic CN on individuals; however, we do not know whether people with acute CN will have similar or different experiences.

Despite the important role depression appears to play in the development and management of diabetes foot complications studies have shown that it is not always recognised by the healthcare professionals. In people enrolled in a study to investigate the presence of depression in people attending outpatient podiatry clinics for the treatment of foot ulcers 28.3% had depression which

had not been recognised prior to the study (Pearson, Nash and Ireland, 2014). A qualitative study with semi-structured interviews with 19 physicians treating people with Type 2 diabetes identified three themes. Although physicians' were aware of people's social and emotional difficulties they felt intervening was challenging with few options to help, and they lacked the necessary expertise to support people (Beverly *et al.*, 2011). This highlights the need to increase awareness on the importance for screening for depression in people attending specialist foot clinics and the need for further investment in psychological services who can then support people.

There is a need to develop strategies that firstly support healthcare professionals to identify people with depression and secondly supports people to effectively self-manage their depression. This may have an overall positive effect in terms of reducing the number and severity of diabetes related complications, including CN. The current evidence on CN and depression comes from one study with a small sample size, with people whose CN was in remission. We need a deeper understanding of how receiving treatment for CN effects people psychological wellbeing. This will help policy makers and healthcare professionals consider the possibilities to redesign services and treatments which may improve people's experiences of CN.

2.9.2 The effect of Charcot neuroarthropathy on health-related quality of life

Health-related quality of life specifically focuses on the effect of illness, the symptoms of the disease, its treatment, and any side effects, has on a person's experiences, physical and social functioning, and emotional well-being (WHOQOL Group, 1995). The World Health Organisation goes on to say that addressing and improving health-related quality of life is one of the most important strategies in improving health and wellbeing outcomes.

It is recognised that diabetic foot disease has an adverse effect on health-related quality of life. There have been two systematic reviews on health-related quality of life in people with diabetic foot ulceration with some overlap in the studies included in each review. The meta-analysis showed that health-related quality of life measured using the SF-36 was lower in four of the eight subscales: 1) physical functioning, 2) role physical, 3) general health and 4) vitality (Khunkaew, Fernandez and Sim, 2019). These reviews reported that a reduction in health-related quality of life was associated with the duration of the ulcer, unemployment, presence of cardiovascular complications, pain, infection, pharmacological treatment for diabetes, poorly controlled diabetes and body mass index (Kossioris and Karousi, 2015; Khunkaew, Fernandez and Sim, 2019). However, these reviews did not include people with CN.

The evidence on the effect of CN on people's health-related quality of life is smaller. There have been four cross sectional studies which investigated the effect of CN on quality of life (Pinzur and Evans, 2003; Willrich *et al.*, 2005; Sochocki *et al.*, 2008; Raspovic and Wukich, 2014). These studies used standardised patient reported outcome measures, most frequently the SF-36 questionnaire (Ware and Sherbourn, 1992). These studies found that CN had a negative effect on people health-related quality of life (Pinzur and Evans, 2003; Sochocki *et al.*, 2008). People with CN had a lower health-related quality of life than people with diabetes without foot problems (Raspovic and Wukich, 2014). One study found that CN had a similar effect on health-related quality of life to lower limb amputation (Willrich *et al.*, 2005).

Another study investigated the change in health-related quality of life over three months in 89 people with CN at different stages of the disease (Dhawan *et al.*, 2005). 64% of the participants completed both the questionnaires. The researchers reported that the Eichenholtz stage and scores for health-related quality of life measured using their non-validated patient reported outcome measures were stable over the three months. Treatment included a mixture of different off-loading devices and surgery. The heterogeneity of the population, and treatments means it is difficult to understand the potential longitudinal impact of CN on health-related quality of life.

Data shows that improved wellbeing and health-related quality of life can help prevent the onset and progression of diabetes related complications. Therefore, it is important to identify and intervene early to support people, which may help slow the development of diabetes related complications. Current published research on the health-related quality of life of people with CN have used a cross sectional design. To date no longitudinal studies have explored how health-related quality of life changes from diagnosis and during the 9-12months of treatment. A systematic review into measures of health-related quality of life in diabetes related foot disease concluded that that more in-depth research is needed into the lived experiences of people with CN (Hogg *et al.*, 2012).

In all these studies variations in the participants baseline characteristics, and treatments limit the applicability of these studies. Research into the health-related quality of life in people with CN has focused on people whose CN is in remission. People who have just received a diagnosis of CN or those still receiving ongoing treatment with an off-loading cast or boot may have different experiences to those whose foot is in remission, and this needs to be investigate in a future study.

2.10 Lived experience of Charcot neuroarthropathy

Qualitative research allows for a more in-depth understanding of a person's lived experience. It allows people to talk about what is meaningful to them in managing their everyday lives and the researcher explore the reasons which inform people's expressed thoughts and feelings.

In healthcare effective shared decision making relies on people being able to understand, and appraise the information provided. In CN there is a need for healthcare professionals to work with people to balance the need to rest and offload the foot against the substantial physical limitations and emotional stresses of wearing an off-loading device for many months. To date there have been no published qualitative studies which have explored the experiences of people living with CN. Most work has focused on exploring people's experience of the prevention and management of ulceration, rather than CN. It is not known whether the experiences of people with CN are similar to people with foot ulceration.

A recent qualitative meta-synthesis of 42 papers on the perceptions and experiences of diabetic foot ulceration and care in people with diabetes has shown that living with foot ulceration has significant consequences for people's physical, social and psychological well-being (Coffey, Mahon and Gallagher, 2019). Only one of the 812 participants included in the 42 studies in this systematic review, however, were recorded as having CN.

Health and social care professionals provide advice to people on how to self-manage their diabetes and foot complications. In some instances, there is a discordance between healthcare advice and people's decisions. This can be for two reasons, firstly people trying to minimise the effect of receiving treatment (Beattie, Campbell and Vedhara, 2014). Secondly that people's ideas and beliefs differ to that of healthcare professionals on how to prevent and treat foot complications, (Gale *et al.*, 2008). A study used semi-structured interviews (n=8) to evaluate the perception of social support for people with a diabetic foot ulcer, reported three broad themes which need to be considered to improve knowledge and understand why people develop foot ulcers and what kind of support people feel they need: 1) psychological well-being, 2) people centre approaches, and 3) inclusion and equality in healthcare and society (Palaya, Pearson and Nash, 2018). To develop effective strategies and interventions to improve the experience of foot complication it is important for healthcare professionals to identify and understand the reason behind people's beliefs and behaviours. Understanding the wider social circumstances of people with diabetic foot complications, including CN is also important for ensuring truly shared decision making and to ensure the support given to people can be more effective (Delea *et al.*, 2015). If people feel more in control of their own health and CN, then this could have a positive effect of

people's physical and emotional well-being. It may also reduce the financial burden on health and social care providers. People will need fewer healthcare appointments, they will be more independent, and it reduce the number of workdays lost due to foot complications.

2.11 Summary

The background has demonstrated the variability in the approaches to the management that have been reported for CN. These variations have arisen because of a lack of robust evidence to guide healthcare professionals to diagnose, monitor and treat CN. Current guidance is primarily based on low quality evidence: level 3 evidence, case control studies and level 4 evidence, expert opinion rather than high quality meta-analysis, systematic reviews, and randomised controlled trials, level 1 evidence. It is not known whether this lack of evidence and variability in the approaches to management has led to the reported variations in time to healing and frequency of CN related complications.

Given this lack of evidence to support the treatment and management of CN national and international health and care organisations and experts have identified CN as a research priority. In 2009 the US National Institute of Diabetes, Digestive and Kidney Diseases and the Office of Rare Diseases of the National Institutes of Health highlighted the need for a co-ordinated international approach to research into the pathophysiology, and management of CN (Boulton *et al.*, 2009). While acknowledging the complexities of developing a randomised controlled trial, a review paper from the Lancet in 2015 emphasised the need for further research into CN including diagnosis, management, outcomes and the impact on people's health-related quality of life (Jeffcoate, 2015). The NICE guidelines, Diabetic foot problem: prevention and management, have also included research into CN as one of its top five research priorities for the diabetic foot (National Institute for Health and Care Excellence, 2015).

Despite these recommendations a search of the four main clinical trial registries, EU Clinical Trials Registry, UK Clinical Trials Gateway, ISRCTN registry and ClinicalTrials.gov only identified 17 trials on CN over the last 15 years, with 10/17 (66.7%) being randomised controlled trials (Table 2-4). Of these randomised controlled trials 9/10 (90 %) have investigated the use of pharmacological therapies to improve healing in CN. The final randomised controlled trial measured the effectiveness of insoles to off-load ulceration overlying foot deformity in CN. Despite the fact that the call for future research into CN was originally made over 10 years ago, this search has shown that there are still gaps in the evidence base for the management of this condition.

In addition to the research recommendations identified from clinical practice and policy, Diabetes UK have worked with the James Lind Alliance to co-produce the Top-10 research priorities for people with type 1 and type 2 diabetes (Gadsby *et al.*, 2012; Finer *et al.*, 2018; James Lind Allliance, 2021a). The resulting priorities were the primary prevention of diabetes, secondary prevention of complications, medical management of diabetes and the role of psychosocial support.

In 2021 the Vascular Society for Great Britain and Ireland collaborated with the James Lind Alliance to produce a number of top-10 research priorities for vascular conditions. This included developing a specific list of priorities for research into the diabetic foot. CN was not identified as one of the top-10 research priorities for the diabetic foot (James Lind Allliance, 2021b). This may be because CN is not a vascular condition or because the lifetime incidence of CN is lower than diabetic foot ulceration: 0.4-1.3% (Armstrong *et al.*, 1997) compared to 15-20% (Singh, Armstrong and Lipsky, 2005). Therefore, it may not have been identified by patients and carers as a research priority. Finally, CN is a frequently overlooked complication of diabetes (Donegan, Sumpio and Blume, 2013). Although CN was not identified as a research priority, this chapter has shown the many evidence gaps that exist, in the assessment and management of CN.

There is a lack of evidence to support the use of monitoring techniques in CN. Healthcare professionals rely on methods and devices which may not accurately reflect disease progression, which makes it more difficult to diagnose remission accurately and confidently. Without gaining an understanding of people's experiences of living with CN, we do not know how current treatments meet their needs. It also means their experiences, thoughts and opinions are not being considered when developing new treatment strategies and pathways, which is likely to reduce the effectiveness of any new approaches to the management of CN.

Table 2-4 List of the registered, completed, and ongoing trials on Charcot neuroarthropathy (2006-2021)

	Registered	Trial Registration Numbers	Study Title	Study Type	Location
1	Clinical Trials.gov	NCT03289338	Zoledronic Acid or Methylprednisolone for Active Charcot's Neuroarthropathy of Foot in Patients with Diabetes Mellitus	RCT	India
2	Clinical Trials.gov	NCT02316483	Genetic Contribution to the Pathophysiology of the Charcot Foot in Qatari Patients with Diabetes	Cohort	Qatar
3	Clinical Trials.gov	NCT02435329	Microcirculation and Bone Metabolism in Patients with Type 2 Diabetes Mellitus and Charcot Foot - A Pilot Study	Cross sectional	UK
4	Clinical Trials.gov	NCT02386579	Characterization of Local and Systemic Bone Markers in Diabetes Patients with Charcot Osteoarthropathy	Before-after study	Germany
5	Clinical Trials.gov	NCT02335931	Characterization of the Charcot Foot	Case control	Denmark
6	Clinical Trials.gov	NCT02023411	Efficacy of Teriparatide in Diabetic Inactive Charcot Neuroarthropathy of Foot	RCT	India
7	Clinical Trials.gov	NCT00194298	FDG-PET Imaging in Complicated Diabetic Foot	Cohort	USA
8	Clinical Trials.gov	NCT04668755	Effect of CROW 3d Printed Sole on Charcot Foot Ulcer	RCT	Egypt
9	Clinical Trials.gov	NCT03174366	Investigating the Use of Prolia (Denosumab) in the Treatment of Acute Charcot Neuroarthropathy	Case control	USA
10	EU Clinical Trials Registry	2009-016873-13	A novel therapy using recombinant human PTH 1-84 to stimulate bone repair and enhance fracture healing in the acute Charcot foot: a double-blind placebo-controlled phase IV trial	RCT	UK

Table 2-4 List of the registered completed and ongoing trials on Charcot neuroarthropathy (2006-2021) (continued)

	Registered	Trial Registration Numbers	Study Title	Study Type	Location
11	EU Clinical Trials Registry	2006-000900-17	A randomised double-blind placebo-controlled trial of the oral bisphosphonate, Alendronate, plus intravenous Pamidronate, in active diabetic Charcot neuroarthropathy (CN).	RCT	UK
12	EU Clinical Trials Registry	2018-003724-36	The DENOCHARCOT trial Efficacy of treatment with DENOsumab of an acute CHARCOT foot in patients with diabetes. A multicentre, double-blind, randomized, placebo-controlled trial.	RCT	Denmark
14	EU Clinical Trials Registry	2016-003594-17	Effects of a single denosumab injection on reduction of total contact cast treatment and consolidation of bone fractures caused by acute Charcot foot in patients with diabetes mellitus (CHARCOT study)	RCT	Netherlands
15	ISRCTN registry	ISRCTN86625608	Oral bisphosphonate, alendronate, for the treatment of acute Charcot neuroarthropathy in diabetic patients	RCT	UK
16	ISRCTN registry	ISRCTN91576704	Intranasal calcitonin in the treatment of acute Charcot neuro-osteoarthropathy: a randomized controlled trial	RCT	Czech Republic
17	ISRCTN registry	ISRCTN79270457	The effectiveness of Pamidronate in the management of Charcot arthropathy in people with diabetes: a comparative study	RCT	UK

2.12 Aims and objectives

The overarching aim of this doctoral research is to investigate the feasibility of using serial MRI to monitor and diagnose remission in CN and to understand people's experiences of living with CN. This thesis has three separate, but interlinked objectives developed from reviewing the literature. These objectives were to:

1. Identify the current evidence base for the use of monitoring techniques to diagnose disease remission in CN.
2. Examine the feasibility of using serial MRI without contrast in monitoring CN to reduce the length of time the foot is immobilised.
3. Explore the expressed thoughts, emotions, and views of people receiving treatment for and living with CN and how this may affect the individual, their families, and their relationships.

3 Methods

3.1 Introduction

This chapter justifies the methodological approach to this research. It details the rationale for selecting a mixed methods research design. It also provides justification for the different quantitative and qualitative methods used to address each research objective.

3.2 Rationale for overall methodological approach

The process of developing and evaluating an intervention can be divided into four phases: development, feasibility, evaluation, and implementation. The most recent Medical Research Council framework argues that interventions should be developed based on the best available evidence, evaluated to address uncertainties about designing the intervention (feasibility), the effectiveness of the new intervention assessed in a definitive evaluation, and the final phase, implementation considers ways to increase the impact and uptake of the research recommendations into policy and practice (Skivington *et al.*, 2021). The aim of this thesis is to investigate the feasibility of using serial MRI to monitor and diagnose remission in CN and to understand people's experiences of living with CN . This research was developed based on the Medical Research Council Framework guidance published in 2008 (Craig *et al.*, 2008). It will address the first two phases of the Medical Research Council framework, development, and feasibility through three objectives:

1. Identify the current evidence base for the use of monitoring techniques to diagnose disease remission in CN.
2. Examine the feasibility of using serial MRI without contrast in monitoring CN to reduce the length of time the foot is immobilised.
3. Explore the expressed thoughts, emotions, and views of people receiving treatment for and living with CN and how this may affect the individual, their families, and their relationships.

If the study findings warrant a full-scale trial, I expect to complete the final two phases of the Medical Research Council framework through a post-doctoral research project. Firstly, I would conduct a definitive evaluation on the use of serial MRI to diagnose remission in CN. Secondly, I would then examine and evaluate implementation strategies to promote the uptake of serial MRI for monitoring and diagnosing remission in CN into policy and practice.

In the next section I will provide the rationale for the methodological approaches I chose to address the three study objectives and the overall aim of the thesis.

3.3 Developing the design for this research

Addressing each of the three research objectives required different types of data and data analysis. For the first objective, I needed descriptive and numerical data to examine and evaluate the evidence base for monitoring CN, by searching for and extracting data from relevant journals. For the second objective, I collected numerical data on the recruitment and retention rates of participants, and the feasibility and acceptability of the intervention serial MRI. Finally, for the third objective, I collected descriptive data on people's thoughts, views, and emotions on living with and receiving treatment for CN.

Research on CN has been dominated by the biomedical model of health research, with a focus on the biological factors of the disease, its assessment, diagnosis, and management. In contrast to the biomedical model the biopsychosocial model of health research investigates the interconnection between biological, psychological, and social factors that can cause or be a consequence of ill health (Engel, 1977, 1997).

The biopsychosocial model provides the opportunity to understand people's decisions and judgements in the context of health (Ranby, 2019). The starting point for this research was to seek to provide understanding and evidence to help reduce the burden of CN by supporting improvements in disease monitoring and to better understand people's experiences of living with and receiving treatment for CN. Therefore, a biopsychosocial model, and a mixed methods approach to data collection was the most appropriate design.

Mixed methods research uses quantitative and qualitative methods, to provide a more detailed understanding of a research question. Mixed methods research has the potential to balance the strengths and weaknesses of using a single quantitative or qualitative research design. It can be beneficial when evaluating healthcare interventions and understanding people's experiences of living with chronic illness (Tariq and Woodman, 2010). This approach can provide a more comprehensive understanding of the research question. Mixed methods research can increase the strength of the findings and the recommendations for patients, healthcare professionals, policy makers, and future research, compared to using only one methodological approach (Teddlie and Tashakkori, 2008; Creswell and Plano Clark, 2011). Mixed methods research can be used to answer questions around the effectiveness of interventions in a real-world setting (Godwin *et al.*, 2003). Different mixed methods designs can be used to answer a research question: multiphase, transformative, embedded, exploratory, explanatory, and convergent (Creswell and Plano Clark, 2011). Each of these different study designs has a different purpose and synthesises the data in different ways (Table 3-1).

Table 3-1 Different mixed methods designs and their data mixing strategies

	Purpose	Mixing strategies
Multiphase	Need to implement multiphases such as for program development and evaluation	Mixing within a program objective framework
Transformative	Need to conduct research that identifies and challenges social injustice	Mixing within a theoretical framework
Embedded	To explore or provide understanding before an experimental trial	Embedding one strand within a design based on the other type
Exploratory	Need to test or measure quantitative findings	Connecting the two strands
Explanatory	Need to explain quantitative results	Connecting the two strands
Convergent	Need a more complete understanding of a topic	Merging the two strands

The convergent mixed method research design is most suitable for validating the results of one piece of research with another. My research sought to evaluate the feasibility of conducting a definitive trial on the effectiveness of serial MRI to diagnose disease remission in CN and understand people's experiences of living with CN. Therefore, the aims and objectives of this research are consistent with the convergent mixed methods design with concurrent design of the quantitative and qualitative studies and data collection. The quantitative and qualitative studies both collect different types of data around the same concepts: quality of life and wellbeing of people living with CN (Creswell and Plano Clark, 2011). The data from each study will be analysed separately. In the discussion I will appraise the results of the two studies and examine how they may contribute to a deeper understanding of people's experiences of living with CN and how they may strengthen the recommendations for policy and practice (Creswell and Plano Clark, 2011). This synthesis of the findings will be used to overcome some of the limitations of individual approaches to data collection. It will provide a more comprehensive and valid understanding of the findings and implications for the research (Farmer *et al.*, 2006). In this study results of the patient reported outcomes from the feasibility study will provide numerical data on the effect of CN on people's quality of life and emotional wellbeing. The findings from the qualitative study will then provide some explanations for the reasons for and the effects of these potential changes on quality of life and wellbeing.

3.3.1 Rationale for methodological approach for the systematic review

Objective one: identify the current evidence base for the use of monitoring techniques to diagnose disease remission in CN.

Following the Medical Research Council guidance on developing and evaluating complex interventions, in the first stage of my research I aim to identify, evaluate, and synthesise the evidence base for the current monitoring techniques used to identify disease remission in CN (Skivington *et al.*, 2021).

Several designs can be used to synthesise quantitative evidence: a scoping review, realist review, systematic review, and meta-analysis, conducted as part of a systematic review. A scoping review identifies research gaps and opportunities for evidence synthesis rather than searching for the effect of an intervention and does not attempt to synthesis the evidence (Peterson *et al.*, 2017). A realist review is designed to answer questions around how an intervention works, for which people and in which settings and is often considered when evaluating interventions (Pawson *et al.*, 2005). A systematic review describes, compares, evaluates, and synthesises the evidence, this can be on the effect of an intervention, the accuracy of a diagnostic or monitoring test or investigation, association between variables, or the feasibility and acceptability of behavioural change therapies (Page *et al.*, 2021).

Robustly-conducted systematic reviews are widely seen as the highest quality of research evidence for quantitative research (Paul and Leibovici, 2014). Systematic reviews collate and synthesise knowledge to answer uncertainties around best practice for the diagnosis, assessment, and management of a particular health issue. They are often the first step in developing guidelines. They can be used to answer questions that cannot be answered by individual studies, appraise the quality of research and make recommendations to improve the quality of future research, and evaluate theories (Page *et al.*, 2021). The objective of this study is: firstly, to search the evidence base to identify the current techniques used by healthcare professionals to monitor for remission in CN, secondly examine and evaluate the evidence based for each technique by assessing the sensitivity, specificity, safety, cost effectiveness, patient acceptability and finally identify whether the current approaches to monitoring contribute to the apparent variations in the reported outcomes for CN. Therefore, a systematic review was judged to be the appropriate methodological approach to examine and evaluate the effectiveness of monitoring investigations for CN, identify evidence gaps and make recommendations about future research. This systematic review will provide a comprehensive, critical appraisal and synthesis of all the available evidence on monitoring for disease remission in CN. The results of the systematic review will inform the design and protocol for the next phase in the Medical Research Councils framework for developing and evaluating complex interventions, the feasibility phase.

The protocol for this systematic review was registered on PROSPERO PROPSERO (CRD42018093340) and can be found at: www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018093340 . Publishing the protocol on PROSPERO prior to completing the review ensures that the review methods are transparent and reproducible, and adherence to this prespecified research plan helps to avoid bias. The systematic review was reported according to the PRISMA guidelines (Moher *et al.*, 2009). Chapter 4 describes the methods for, results from, and discussion to evaluate the systematic review.

3.3.2 Rationale for methodological approach to the feasibility study

Objective two: examine the feasibility of using serial MRI without contrast in monitoring CN to reduce the length of time the foot is immobilised.

The background chapter has shown there is some promising evidence to support the use of MRI in disease monitoring in CN. Given the physical, emotional, and financial burden of CN a relatively inexpensive intervention, MRI that reduces treatment times has the potential to be cost effective and is worthy of exploration. Therefore, the second objective of the research programme is to test the feasibility of using serial MRI to monitor for disease remission in CN. Conducting trials is often costly, therefore researchers and funders have an ethical responsibility to ensure that investment in research contributes to improvements in the delivery of health and social care interventions and outcomes for people (NHS Health Research Authority, 2020). Funders and regulators require evidence that the key elements of a proposed definitive trial are practicable and achievable.

Background (chapter 2) has reported that there have been no large-scale trials evaluating the feasibility or effectiveness of using serial MRI to monitor CN. Consequently, there is no evidence which can be used to ascertain if a definitive trial is warranted, and there are specific uncertainties concerning relevant issues for planning such a trial. Firstly, the feasibility of recruitment based on the willingness of patients to be randomised and the likelihood of recruiting healthcare professionals in diabetic foot clinics to the study. Secondly, whether the intervention serial MRI is acceptable to participants. Thirdly, is whether sites would be able to complete all the intervention MRIs within the timeframe. Finally, there is a need to ascertain the patient acceptability and value of a range of different clinical and patient reported outcome

measures, collected at various timepoints over the course of the study, assessed by analysing data completeness levels. Therefore, there is a need to undertake a preliminary feasibility study to, answer these uncertainties and inform the design of any future full-scale trial to evaluate the effectiveness of serial MRI as an intervention to diagnose remission in CN (Skivington *et al.*, 2021).

There are two types of study designs which can be used to inform decisions about whether to proceed to a full-scale trial: feasibility and pilot studies (Lancaster, 2015). A feasibility study is a study which investigates whether a study and the planned intervention can be done (Eldridge *et al.*, 2016a). Feasibility studies produce findings that help determine whether an intervention should undergo definitive efficacy testing (Bowen *et al.*, 2009). They can provide evidence on rates and factors which may influence levels of participant recruitment, retention, and acceptability of the intervention. They can also test the fidelity and feasibility of completing the intervention. A pilot study focuses on the processes within the study and how well all the components of the study work together. Pilot studies are often designed to conduct smaller versions of the main trial and can form the first phase of a definitive trial (Thabane *et al.*, 2010). Pilot studies are subdivided into internal and external studies dependent on whether the data collected during the pilot trial are included in the trial analyses (Arain *et al.*, 2010). However, pilot and feasibility studies are no longer seen as mutually exclusive, with pilot studies often being considered as a subset of feasibility studies (Eldridge *et al.*, 2016a).

Based on these uncertainties, the evidence on the rationale for pilot and feasibility studies and guidance from NIHR (National Institute for Health Research, 2021b) I decided that a feasibility study was the most appropriate study design. The results and levels of data completeness from this study will provide valuable information to predict likely recruitment and retention rates, and about the likely feasibility and acceptability of the intervention serial MRI.

The next step was to consider the design of the feasibility study. There are a variety of different types of designs for feasibility studies and definitive trials. Experimental studies can be divided into randomised controlled trials and non-randomised controlled trials. Randomised controlled trials are considered the most rigorous way of conducting studies to determine whether there is a cause/effect relationship between the intervention and outcome (Sackett *et al.*, 1996).

Randomised controlled trials can be further subdivided into cluster randomised controlled trials and individual randomised controlled trials. The difference between the two designs is that in cluster randomised controlled trials the intervention is assigned to a group of patients or a specific healthcare setting rather than an individual basis. Cluster randomised trials can be used to

test differences in a method or approach to patient care, whereas individual randomised controlled trials tend to evaluate the effect of a specific intervention.

This study aimed to assess the feasibility of conducting a future definitive trial to examine the effectiveness of using serial MRI (intervention) without contrast in monitoring CN to reduce length of time the foot is immobilised. In a definitive trial participants will be randomised to either standard care or the intervention. Therefore, in this feasibility trial I will collect data to ascertain participants willingness to be recruited and randomised. I will use an individual randomisation-controlled design rather than a cluster design as serial MRI is a specific intervention.

The feasibility study will be open label design. This is a pragmatic decision: the MRIs will be reported by radiologists and interpreted by the healthcare professionals working in multidisciplinary specialist diabetic foot clinics to determine when remission has been achieved. As determining when remission has been achieved relies on comparison of the current MRI to the previous images, this could indicate to the radiologist and research team the study arm to which the participant has been randomised to.

In the feasibility study I will collect a wide range of clinical, and patient reported outcomes. The specific rationale for using these outcomes is reported in chapter 5.

3.3.3 Rationale for methodological approach to qualitative research

Objective three: explore the expressed thoughts, emotions, and views of people receiving treatment for and living with CN and how this may affect the individual, their families, and their relationships.

An understanding of people's thoughts, emotions, and views on living with and receiving treatment for CN is important to identify and understand their priorities. A deeper understanding of the impact of CN on individuals will provide insight to healthcare professionals to understand the reasons behind people's motivations and choices and what can be done to better met their needs. To my knowledge no qualitative studies have been conducted exploring the effect of CN on people. Health and social care professionals can use this new information to develop better strategies and interventions that reflect the concerns and priorities of people with CN. Thus, supporting them to self-manage their diabetes and foot complications more actively.

A qualitative approach was the best research method to answer this question as this would allow me to achieve a more meaningful and specific understanding of what may characterise people's

personal experience of living with CN. Qualitative research can provide a depth of understanding that can be difficult to achieve with predefined questionnaires or surveys (Mason, 2002).
A range of qualitative study methods can be used to understand people's views, practises, and experiences about their own health and healthcare: grounded theory, ethnography, and phenomenology. Grounded theory is design to create theoretical models from real world situations. Ethnography explores cultural phenomena, and seeks to learn about people, it is characterised by in-depth observations of groups of individuals. Phenomenology focuses on an individual's lived experiences (Mason, 2002). In this study my underlying question was to explore the expressed thoughts, emotions, views, and practices of people receiving treatment for CN. Ground theory, and ethnography are less suitable approaches for this research as I did not seek to develop a theoretical model or understand group culture. A phenomenology approach would be the most appropriate approach as it will provide participants with the opportunity to self-define their individual experiences of CN and the meanings, they attribute to these. Both interviews and focus groups can be used to collect data for phenomenological research.

Interviews and focus groups would provide the opportunity for participants to discuss and self-define their individual experiences of CN. Interviews and focus groups are a way of exploring people's experiences and the meanings they attribute to them. They can provide a contextual understanding about people's beliefs, experiences, attitudes, and behaviour. This depth of information can be difficult to gain from questionnaires or surveys, where responses are constrained by preconceived multiple choice answers and there is no opportunity to explore the reasons behind individuals' responses. However, not everyone can be confident or comfortable discussing their experiences in group settings. CN is associated with amputation, and increased mortality, discussing experiences of these type of issues could be distressing and emotional for the individual concerned and the other participants in the group. Focus groups can be influenced by the type of people who are willing to participate and the dynamics of the group. In this study I will interview some participants from the feasibility study sites. This means that the participants are likely to know each other. This could lead to conscious or unconscious filtering of the experiences people are willing to share in a focus group setting. In a focus group with several participants, which usually lasts 90 minutes, the time that each individual has to speak is less than in an interview. This may mean that it is not possible to capture the depth of understanding that can be achieved in an interview.

In this study I aimed to collect participant's own opinions, thoughts, feelings, and to identify meanings that they may attribute in different CN-related areas of experience. Given that using focus groups would limit the amount of data I could collect and may cause people to censor

the experiences they were willing to share, I decided that interviews would be the best approach to answer objective three. Interviews are thought to be particularly useful when little is known about a particular topic, which is the case for people's experiences of CN (Adams, 2010).

Interviews allow the participant to determine the direction of the discussion and allow for a richer, more natural conversation to develop (Kvale, 2007). Interviews are helpful in building rapport with the participant, where the participant has the space to think, speak and be heard, thus allowing them to describe what is meaningful or important to them using their own words. Using a semi-structured approach allows the researcher to direct the conversation to the key research topic questions and follow-up any unanticipated and unexpected topics. In this study I will use semi-structured interviews. This will help ensure that I meet the objectives of the study, whilst allowing me to explore the participant's own priorities. It will also allow me to probe for more detailed information about a point, providing richer data and more holistic insight. This semi-structured approach reduces the possibility that the analysis will only reflect the topics identified by the researcher.

Interviews can be conducted face-to-face, on the telephone or through media platforms such as Skype. Face-to-face interviews are more costly to complete than the other options, but they allow the interviewer to observe the participant's non-verbal language, which can give greater insight into the persons thoughts, emotions, views, and practises. In interviews about people's experience of health, participants may share sensitive or upsetting information about their physical, social, and psychological experiences. As I sought to understand people's experiences of CN which may involve participants talking about physical and psychological distress, I decided to use face-to-face interviews. These will firstly encourage participants to speak more frankly about their experiences and secondly allow me to respond in a more sensitive nature and notice and respond to nonverbal signals from the participant.

The data will be analysed using inductive thematic analysis which is compatible with the phenomenological methodology (Braun and Clarke, 2008). Little is known about people's experiences of living with CN, and there are no pre-existing frameworks or theories to guide the analysis. Therefore, I will use an inductive reflexive approach rather than deductive style with structured code books. This will allow me to identify codes which are strongly linked to the data, with the subsequent themes developed from clustering related codes together. The methods and results of the qualitative study are reported in chapter 7.

3.3.4 Synthesis of the results from the feasibility and qualitative studies

In this research I will use a convergent mixed methods design (Table 3-1). The results of the quantitative and qualitative studies will be analysed separately. In the discussion I will appraise the results from the two studies to examine how this programme of research provides a better understanding of the experiences of people living with CN, and secondly what opportunities exist to reduce the burden for healthcare professionals and people with CN.

The quantitative data from the patient reported measures and the patient diary will be compared with the qualitative data from the interviews to consider what extent the findings agree, complement, or contradict each other (Farmer *et al.*, 2006). The findings of the qualitative study will provide a richer picture of the impact of CN adding context to the patient reported outcomes. The qualitative findings will provide insight into the impact of limited mobility on the individual, their families, and relationships and how this influences the individuals' thoughts, views, emotions, and practises. This would not be captured using purely quantitative research methods.

3.3.5 Rationale for patient and public involvement in the research

The importance of co-producing research with patient and public involvement (PPI) to improve the relevance and quality of research is well recognised. PPI representatives can include current and future service users, people with lived experiences of the condition, carers as well as stakeholders from communities and organisations that represent service users. The NIHR proposes three ways in which PPI can contribute to research: involvement, engagement, and participation (National Institute of Health Research, 2021). PPI members can be included in setting research priorities, as co-applicants on grants, members of steering groups, supporting the development of study materials such as patient information sheets, and carrying out the research. In terms of engagement, information about research is shared with the public. Finally, participation in research could include taking part in a trial, completing a questionnaire, or taking part in a focus group. In this study I will include PPI in developing the research idea, the design of the study, study management, and analysis and dissemination of the findings.

3.4 Summary

This chapter has provided justification for the design of each of the three studies and the different methodological approaches to be used to provide data and analyse the findings of this research. This research can realise the first and second phase of the Medical Research Council framework for developing a complex intervention and examining its feasibility (Skivington et al., 2021). The systematic review (chapter 4) will examine and evaluate the current evidence base for monitoring in CN. The feasibility study (chapter 5 and 6) will demonstrate whether a fully powered pragmatic

randomised controlled trial is warranted. The qualitative sub-study (chapter 7) will provide an insight into what may be the experiences of people receiving treatment for CN. The Discussion and Conclusion (chapter 8) will discuss the findings and identify recommendations for policy, practice, and further research.

4 A systematic review of techniques to monitor resolution of acute Charcot neuroarthropathy in people with diabetes

4.1 Introduction

This chapter is a copy of the published article (appendix A) (Gooday, *et al.*, 2020a). It reports the methods, results, and analysis of the systematic review of techniques to monitor resolution of acute CN in people with diabetes. Firstly, it examines the evidence base for the current monitoring techniques used to identify remission in CN. Secondly, it evaluates whether the current approaches used to monitor CN could contribute to the apparent variations seen in CN outcomes. The results of this systematic review have been updated prior to submitting this thesis. There are minor edits to the chapter to ensure consistency within the thesis.

4.2 Background

CN is a complication of peripheral neuropathy associated with diabetes which affects the lower limb. It may be precipitated by minor trauma or other inflammatory insult which the person does not notice due to insensitivity to pain. When, the person does not rest the foot, an exaggerated inflammatory response occurs (Pinzur, 1999). The symptoms include redness, warmth and swelling in the foot and/or leg. It can cause fractures and dislocations within the foot, which may progress to deformity and ulceration.

The treatment aims to stop the inflammatory process, relieve any pain and maintain foot structure (Milne *et al.*, 2013). Treatment for CN is 'off-loading' with the application of a non-removable plaster or fibreglass cast or boot; this rests and immobilises the foot and redistributes the weight and pressure from the foot to the leg (Begg *et al.*, 2016). Off-loading is continued until remission when there are no longer clinical signs of inflammation, and plain X-rays are stable with signs of healing (Milne *et al.*, 2013).

Globally, evidence suggests significant variation in treatment times. In the UK, observational studies report treatment times of 9-12 months before remission is achieved (Bates, Petrova and Edmonds, 2006; Game *et al.*, 2012; Stark *et al.*, 2016) whilst data from the USA (Armstrong *et al.*, 1997; Sinacore, 1998; Pinzur, Lio and Posner, 2006; de Souza, 2008) and other European centres report treatment times of only 4-6 months (Fabrin, Larsen and Holstein, 2000; Chantelau, 2005; Zampa *et al.*, 2011; Christensen *et al.*, 2012; Ruotolo *et al.*, 2013; Renner *et al.*, 2016). Several factors could contribute to this global variation, these include participant characteristics, different

techniques for monitoring, different protocols for the same monitoring techniques, variations in approach to off-loading and study design variability (Game *et al.*, 2012).

The current evidence base for the treatment of CN is poor. It is principally based on small retrospective cohort and observational studies of people attending multidisciplinary foot clinics. Evidence to support the effectiveness of techniques to monitor CN is lacking, and current practice is primarily based on expert opinion (Milne *et al.*, 2013). Skin temperature measured using infrared thermography is used because CN involves inflammation of the soft tissue and bone (Jeffcoate, 2015). Skin temperature is, however, a proxy measure of inflammation measured on the dorsum of the foot over the site of injury, which may not reflect the degree of inflammation within the affected deeper tissues, bones and/or joints. Plain X-rays show damage to the foot skeleton rather than disease activity and are a measure of foot deformity. Despite these limitations, serial temperature measurements and plain X-rays remain the most widely used monitoring technique in CN.

Improvements in monitoring CN could reduce treatment times. Lack of evidence to support healthcare professionals in the choice of the type of monitoring and decision thresholds for remission may account for variability in treatment times. To the best of our knowledge there are no systematic reviews focused on monitoring techniques to identify remission in CN.

4.3 Aim and objectives

This systematic review aims to identify the current evidence base for the use of monitoring techniques to diagnose disease remission in CN. The objectives are:

1. To identify the techniques used in the monitoring of CN.
2. To identify the sensitivity and specificity of different techniques used to monitor CN.
3. To identify the financial implications to healthcare providers and the NHS and the clinical feasibility of the identified techniques.
4. To identify the safety considerations, and participant acceptability of the identified techniques.
5. To identify whether different techniques used for monitoring influence the outcomes of CN.

4.4 Methods

The original systematic review included a search strategy from 1993-June 2018 (Gooday *et al.*, 2020a). In order to update the systematic review prior to submission of this thesis, the searches were repeated using the same databases and same search terms for the period from July 2018 - November 2021.

4.4.1 Inclusion and exclusion criteria

The inclusion criteria for study design were purposefully wide, based on prior knowledge of research studies on CN. We included randomised controlled trials, preference-controlled trials, and observational studies with or without control group(s). We excluded abstracts, systematic reviews and meta-analyses, studies on surgical and pharmacological management of CN, expert opinion, observations of single case studies, and laboratory studies (Table 4-1).

We included studies on off-loading which evaluated or reported monitoring techniques in adults with diabetes with a diagnosis of acute CN managed in any setting, including hospital, primary care, or community. The control condition included other techniques used to monitor CN or the same technique used differently, for example different protocols for infrared thermography monitoring.

Table 4-1 Inclusion and Exclusion Criteria in relation for study design

Inclusion	Exclusion
Randomised Controlled Trials	Expert Opinion
Preference Controlled Trials	Observational reports of single case studies
Observational studies with controls	Laboratory studies
Observational studies without controls	

We completed searches in PubMed, Embase, CINAHL, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov. The searches were restricted to English language, from 1993-June 2018 and adapted for each database. See appendix B for an example of the search strategy. We used search terms for diabetes, Charcot, neuroarthropathy, and osteoarthropathy. We also checked the reference lists of relevant published systematic reviews.

4.4.2 Search strategy

We downloaded all papers identified into EndNote® and removed duplicates. Screening was conducted independently by two reviewers (CG and KG) in all three phases: title, abstract and full-text screening. Reasons for exclusion were recorded during abstract and full text screening. Inter-

rater agreement was calculated by the number of papers on which the two reviewers agreed in terms of inclusion and exclusion, divided by the total number of double screened papers. Discrepancies were resolved by consensus (CG and KG). All records deemed eligible following this consensus process were included for full text assessment and data extraction.

We extracted information on participant and CN related characteristics. We also extracted information on sensitivity and specificity of the techniques, protocol for application of the technique, costs, and feasibility, safety, and participant considerations. Finally, we extracted methods of off-loading and clinical outcomes such as time to healing, and relapse rates.

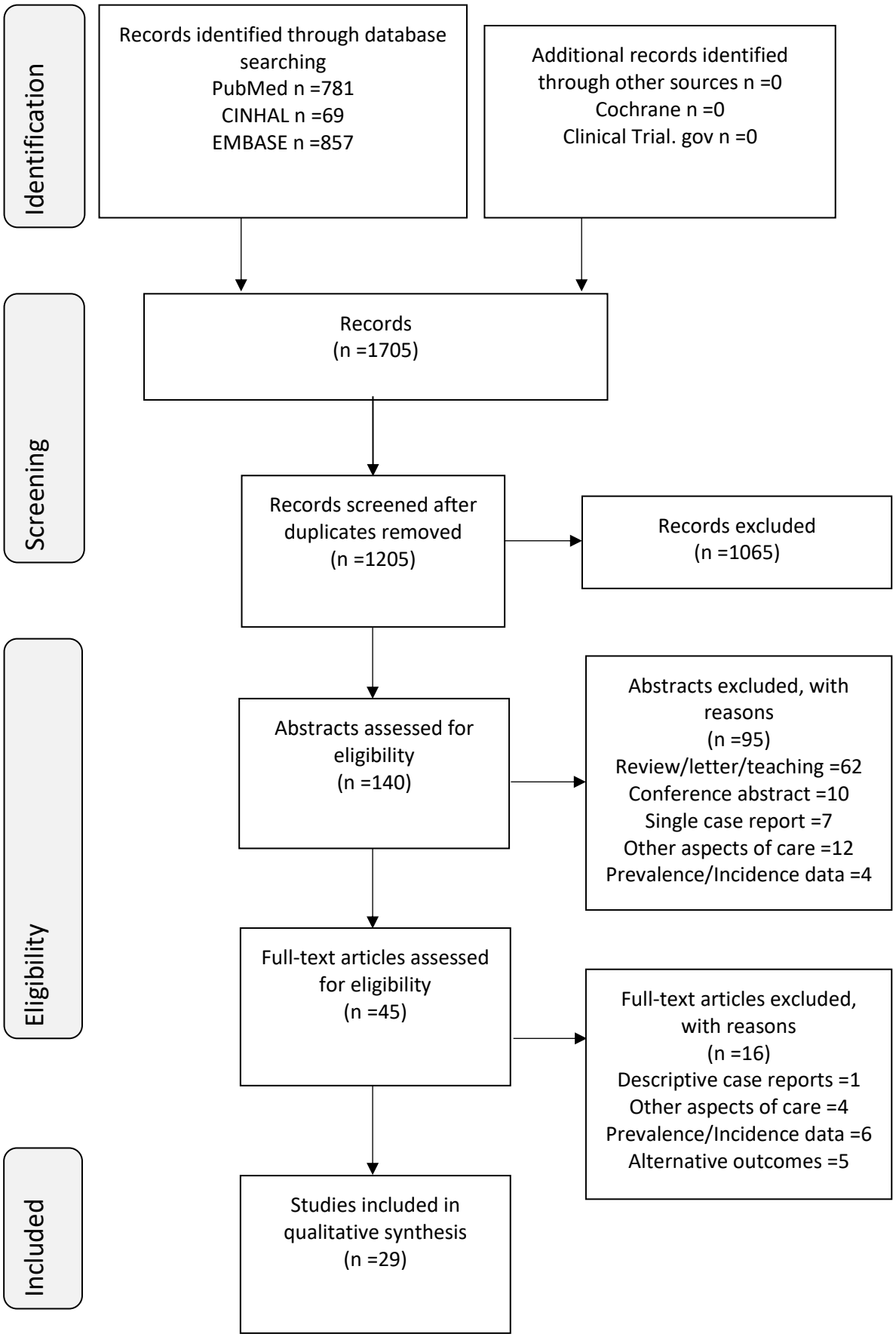
The first author (CG) extracted data from all included papers. The completed data extraction sheets were independently validated by a second reviewer (KG) against the papers. Given the wide range of study designs included, data synthesis was narrative. For the update to the systematic review screening and data extraction was completed by one reviewer (CG).

4.5 Results

4.5.1 Search Results

After removal of duplicates, we identified 1,205 papers (Figure 4-1) and excluded 1,065 during title screening. During abstract screening we excluded 95/140 papers, most exclusions concerned expert reviews, papers describing other aspects of care and conference abstracts.

Figure 4-1 PRISMA flow diagram for systematic review



Inter-rater agreement during title screening was 94.1% (1134/1205), 81.4% (114/140) during abstract screening and 87% (39/45) during full text screening. 45 full text papers were screened; most common exclusion reasons were that studies evaluated other aspects of care, and outcomes or were epidemiological reports.

We included 29 papers (Table 4-2). We used the Scottish Intercollegiate Guidelines Network criteria for assigning level of evidence. Three papers were case control and one a cohort study, i.e., level 2 studies. The remaining 25 were level 3, non-analytic case series. Ten studies were prospective and the remaining 19 retrospective reviews of medical records. All included studies were of low or very low quality.

Table 4-2 List of studies included in the systematic review and their evidence grade

Studies evaluating monitoring	**Evidence Grading**
Armstrong and Lavery (1997)	Level 3
Chantelau *et al.*, (2018)	Level 3
McGill *et al.*, (2000)	Level 3
Moura-Neto *et al.*, (2012)	Level 3
Schlossbauer *et al.*, (2008)	Level 3
Wu *et al.*, (2012)	Level 3
Zampa *et al.*, (2011)	Level 3
Studies evaluating off-loading which describe monitoring	**Evidence Grading**
Armstrong *et al.*, (1997)	Level 3
Chantelau, (2005)	Level 2-
Chantelau and Richter, (2013)	Level 3
Christensen *et al.*, (2012)	Level 3
de Souza, (2008)	Level 3
Dixon *et al.*, (2017)	Level 3
Fabrin, Larsen and Holstein, (2000)	Level 3
Holmes Jr and Hill, (1994)	Level 3
O'Loughlin *et al.*, (2016)	Level 3
Osterhoff, Boni and Berli, (2013)	Level 2-
Pakarinen *et al.*, (2002)	Level 3
Parisi *et al.*, (2013)	Level 3
Pinzur, Lio and Posner, (2006)	Level 3
Renner *et al.*, (2016)	Level 2-
Ruotolo *et al.*, (2013)	Level 3
Saltzman *et al.*, (2005)	Level 3
Sinacore, (1998)	Level 3
Stark *et al.*, (2016)	Level 3
Thewjitcharoen *et al.*, (2018)	Level 3
Verity *et al.*, (2008)	Level 3
Visan *et al.*, (2012)	Level 3
Wukich *et al.*, (2011)	Level 2-

4.5.2 Study and participant characteristics

Eight studies were conducted in the USA, four studies in Germany, and two in Denmark, Switzerland, and Brazil (Table 4-3). In total 1132 participants were included across all studies with 1239 episodes of CN. Mean sample size was 39(±27 range 13-115). The studies collected data for between 4 months-20 years.

The mean age of participants was reported in 20 studies and ranged from 52-62.5 years old. Participants' sex was reported in 26 studies: 56% (614/1095) who experienced an episode of acute CN in these studies were male (range 4-68). 23 studies clearly reported the type of diabetes. 67.7% (598/896) of participants with acute CN had a diagnosis of type 2 diabetes (range 5-84). The mean duration of all types of diabetes ranged from 13.0-24.5 years. Any data reported on severity and anatomical location of the CN are reported in Table 4-3.

We divided the studies into two groups. In the first group the evaluation of monitoring techniques was the study's primary aim, so likely to report data to address the first four objectives on the efficacy and acceptability of the techniques (Armstrong and Lavery, 1997; McGill *et al.*, 2000; Schlossbauer *et al.*, 2008; Zampa *et al.*, 2011; Moura-Neto *et al.*, 2012; Wu *et al.*, 2012; Chantelau *et al.*, 2018). In the second group the study's primary aim was to report outcomes of CN but they may also describe monitoring techniques used, thus providing data to answer our fifth objective on whether monitoring techniques influence outcomes (Holmes and Hill, 1994; Armstrong *et al.*, 1997; Sinacore, 1998; Fabrin, Larsen and Holstein, 2000; Pakarinen *et al.*, 2002; Chantelau, 2005; Saltzman *et al.*, 2005; Pinzur, Lio and Posner, 2006; Verity *et al.*, 2008; de Souza, 2008; Wukich *et al.*, 2011; Visan *et al.*, 2012; Christensen *et al.*, 2012; Parisi *et al.*, 2013; Ruotolo *et al.*, 2013; Chantelau and Richter, 2013; Osterhoff, Böni and Berli, 2013; Thewjitcharoen *et al.*, 2014; Renner *et al.*, 2016; Stark *et al.*, 2016; O'Loughlin *et al.*, 2016; Dixon *et al.*, 2017).

Table 4-3 Study and Participant Characteristics

Studies evaluating monitoring					
Author, year, country, study type	**Inclusion and exclusion criteria**	**Sample size CN classification**	**Participant characteristics**		
			Age yrs.	**Sex**	**Diabetes**
Armstrong & Lavery (1997) USA Retrospective observational study without controls 1993-1994 (3yrs)	*Inclusion* Diagnosis of DM Acute CN *Exclusion* Osteomyelitis Extending to bone Chronic CN Open reduction of fracture	39 participants *Sanders & Frykberg's* I =2.6% II =64.1% III =25.6% IV =7.7% V =0%	mean (SD) = 59 (9.5)	Male n =20 (51%) Female n =19 (49%)	T1DM n =1 (2.6%) T2DM n =38 (97.4%) DM duration mean (SD)= 16.5 (4.9)
Chantelau et al (2018) Germany Retrospective observational study without controls 1994 to 2017 (23yrs)	*Inclusion* Active stage CN based on typical clinical and MRI findings *Exclusion* Cases with skin defects or infections Non-compliant patients' Insufficient clinical documentation	37 participants 45 feet *Modified Eichenholtz* 0 =17 (38%) I =28 (62%) II =0 III =0	median (range) =59 (37-81)	Male n = 21 (57%) Female n= 16 (43%)	T2DM =19 (51%) T1DM =17 (46%) No diabetes =1 (3%)

Table 4-3 Study and Participant Characteristics (continued)

Studies evaluating monitoring					
Author, year, country, study type	**Inclusion and exclusion criteria**	**Sample size CN classification**	**Participant characteristics**		
			Age yrs.	**Sex**	**Diabetes**
McGill et al (2000) **Australia** Prospective observational study with controls Time frame not reported	Inclusion Acute unilateral CN Exclusion Not reported	17 participants 8/17 participants received bone scans every 3 months maxmium12 months	median (IQR) =58.5 (53.5-65.5)	Not reported	T2DM =13 (75%) T1DM =4 (25%) DM duration median (IQR)= 13.5 (7-19.5)
Moura-Neto et al (2012) **Brazil** Prospective observational study without controls 2007-2009 (2yrs)	*Inclusion* Acute CN *Exclusion* Not reported	28 participants Brodsky 1 =71.40% 2 =17.90% 3A =0% 3B =0% 4 =10.7% 5 =0%	Age years mean (SD) =58.8 (11.7)	Male n =14 (50%) Female n =14 (50%)	T2DM n =28 (100%) DM duration mean (SD)= 14.3 (5.1)

Table 4-3 Study and Participant Characteristics (continued)

Studies evaluating monitoring					
Author, year, country, study type	**Inclusion and exclusion criteria**	**Sample size CN classification**	**Participant characteristics**		
			Age yrs.	**Sex**	**Diabetes**
Schlossbauer (2008) Germany Prospective observational study without controls Time frame not reported	*Inclusion* Acute clinical signs of CN *Exclusion* Foot ulcers Previous foot surgery Fractures Apparent deformity	13 participants *Modified Eichenholtz* 0 =13 (100%) I =0 II =0 III =0	Age years mean = 61.2	Male n =20 (51%) Female n=19 (49%)	T1DM n =7 (54%) T2DM n =5 (38%) Idiopathic neuropathy n =1 (8%) DM duration mean =20.5
Wu et al (2012) Taiwan Prospective observational study without controls 2001-2009 (8yrs)	*Inclusion* Acute CN *Exclusion* Undergone no previous evaluation or treatment	15 participants Brodsky 1 =40% 2 =27% 3A =13% 3B =7% 4 =13% 5 =0%	Age years mean (range) = 55.6 (28-76)	Male n =7 (47%) Female n =8 (53%)	T1DM n =4 (27%) T2DM n =11 (73%) DM duration mean (range)=22.2 (13-34)

Table 4-3 Study and Participant Characteristics (continued)

Studies evaluating monitoring					
Author, year, country, study type	**Inclusion and exclusion criteria**	**Sample size CN classification**	**Participant characteristics**		
			Age yrs.	**Sex**	**Diabetes**
Zampa et al (2011) Italy Prospective observational study without controls 2001-no end date reported	*Inclusion* Acute CN *Exclusion* Not reported	40 participants Forefoot =12.5% Mid-foot =80% Hind-foot =7.5%	Age years mean (SD) =58.3 (13)	Male n =22 (55.5%) Female n =18 (45.5%)	T1DM n =17 (42.5%) T2DM n =23 (57.5%) DM duration mean (SD) =19.1 (12.1) HbA1c mean (SD) =8.9 (2)

Table 4-3 Study and Participant Characteristics (continued)

Studies evaluating off-loading which describe monitoring					
Author, year, country, study type	**Inclusion and exclusion criteria**	**Sample size CN classification**	**Participant characteristics**		
			Age yrs.	**Sex**	**Diabetes**
Armstrong et al (1997) USA Retrospective observational study without controls 1991-1994 (3yrs)	*Inclusion* Acute CN *Exclusion* Concomitant osteomyelitis Chronic CN Bilateral CN Open reduction of fracture	55 participants 60 feet *Sanders & Frykberg's* I =3% II =48% III =34% IV =13% V =2%	mean (SD) =58.6 (8.5)	Male n =27 (49%) Female n= 28 (51%)	T1DM n =1 (2%) T1DM duration =12 T2DM n =54 (98%) T2DM duration mean (SD) = 15.9 (5.7)
Chantelau (2005) Germany Case control study 1997-2004 (7yrs)	*Inclusion* Clinical signs of CN. Selected if fractures were undetected on 1st plain X-ray after onset of symptoms or presumed OA changes in only one WB joint *Exclusion* Previous CN on the same foot Active ulceration	24 participants Unable to summarise from paper	early initiation treatment group mean (range) =61 (44-73) late initiation treatment group mean (range) =52 (28-73)	Male n =13 (54.2%) Female n =11 (45.8%)	T1DM n =8 (33%) T2DM n =16 (77%) DM duration median early initiation treatment group (range) =25 (3-53) DM duration median late initiation treatment group (range) =14 (3-32)

Table 4-3 Study and Participant Characteristics (continued)

Studies evaluating off-loading which describe monitoring						
Author, year, country, study type	**Inclusion and exclusion criteria**		**Sample size CN classification**	**Participant characteristics**		
				Age yrs.	**Sex**	**Diabetes**
Chantelau & Richter (2013) Germany Retrospective observational cohort study without controls 2000-2012 (13yrs)	*Inclusion* Cases treated and followed up by the diabetic foot clinic until healing *Exclusion* Cases with coexisting plantar ulceration or possible septic skeletal pathology		59 participants 71 feet Forefoot =18 (25%) Midfoot =48 (68%) Hindfoot =5 (7%) *Modified Eichenholtz* 0 =27 (38%) I =44 (62%) II =0 III =0	T1DM median (range) =55 (48.5-59.5) T2DM median (range) =62 (56-59)	Male n =30 (50.1%) Female n= 29 (49.9%)	T2DM n =35 (59%) T2DM duration median (range) = 10 (5-19) T1DM n =24 (40.1%) T1DM duration median (range) = 32 (25.5-41)
Christensen et al (2012) Denmark	Retrospective observational study without controls 2000-2005 (5yrs)	*Inclusion* Persistent swelling of the foot and an increase skin temperature of more than 2°C with spontaneous onset over a few days or following minimal trauma or sudden overuse of the feet *Exclusion* -Not reported	56 participants Forefoot =15 (26.8%) Midfoot =31 (55%) Heel =3 (5%) Ankle =7 (12.5%)	mean (SD) =58.3 (11.6)	Male n =33 (59%) Female n =23 (41%)	T2DM =32 (57%) T2DM duration mean (SD) =17.1 (7.8) T1DM= 24 (43%) T1DM duration mean (SD) =34.4 (13) DM duration mean (SD) =24.5 (13.6) HbA1c mean (SD) = 8.9 (1.7)

Table 4-3 Study and Participant Characteristics (continued)

Studies evaluating off-loading which describe monitoring					
Author, year, country, study type	**Inclusion and exclusion criteria**	**Sample size CN classification**	**Participant characteristics**		
			Age yrs.	**Sex**	**Diabetes**
De Souza (2008) USA Retrospective observational study without controls 1998-2006 (18yrs)	*Inclusion* CN of the foot and ankle *Exclusion* Irregular attendance Noncompliance Inadequate/lost radiographs Inadequate follow up	27 participants 34 feet *Brodsky* 1 =17 2 =8 3A =7 3B =0 4 =0 5 =0	Not reported	Male n =6 (22%) Female n =21 (78%)	T2DM =17 (65%) T1DM =9 (35%)
Dixon et al (2017) New Zealand Retrospective observational case series study without controls 2000-2014 (15yrs)	*Inclusion* Not reported *Exclusion* Not reported	41 participants	mean (range) =54 (34-73)	Male n =28 (68%) Female n =13 (32%)	T2DM =31 (76%) T1DM =10 (24%) DM duration median (range) =15 (1-47) HbA1c median (range) =70 (36-178)

Table 4-3 Study and Participant Characteristics (continued)

Studies evaluating off-loading which describe monitoring					
Author, year, country, study type	**Inclusion and exclusion criteria**	**Sample size CN classification**	**Participant characteristics**		
			Age yrs.	**Sex**	**Diabetes**
Fabrin et al (2000) Denmark Retrospective observational case series study without controls 1984-1994 (10yrs)	*Inclusion* 107 patients presenting a red, hot swollen foot with spontaneous onset who exhibited radiological evidence of osteoarthropathy. 8 patients with typical CN rocker bottom deformity that had developed over a period of some months in adult life with radiological evidence of CN *Exclusion* Deformities caused by bone fractures related to accidents were not included	115 participants 140 feet	median (range) =54 (27-80)	Male n =59 (51%) Female n =56 (46%)	T2DM =21 (18%) T2DM duration median (range) =8 (0-19) T1DM =94 (82%) T1DM duration median (range) 22 (0-50) HbA1c median (range) =9.4 (5.6-14)
Holmes & Hill (1994) USA Retrospective observational case series study without controls 1985-1990 (4yrs 6m)	*Inclusion* Fracture/dislocations of the foot and ankle *Exclusion* Not reported	18 participants 20 fracture/dislocations Forefoot =2 (10%) Mid-foot =7 (35%) (including base 2nd metatarsal) Hind-foot =5 (25%) Ankle =6 (30%)	mean (range) =55 (38-78)	Male n =11 (61%) Female n =7 (39%)	T1DM =1 (6%) T2DM =17 (94%)

Table 4-3 Study and Participant Characteristics (continued)

Studies evaluating off-loading which describe monitoring					
Author, year, country, study type	**Inclusion and exclusion criteria**	**Sample size CN classification**	**Participant characteristics**		
			Age yrs.	**Sex**	**Diabetes**
O'Loughlin et al (2016) Ireland Retrospective observational case series study without controls 2006-2012 (7yrs)	*Inclusion* Not reported *Exclusion* Not reported	40 participants	mean (SD) =58 (10)	Male n =27 (68%) Female n =13 (32%)	T1DM =11 (27%) T2DM =29 (73%) DM duration mean (SD) =15 (9) HbA1c mean (SD) =65 (16)
Osterhoff et al (2013) Switzerland Retrospective case control study 2005-2012 (7yrs 6m)	*Inclusion* Diagnosed with acute CN; stages 0-2. Non-diabetes related CN included in the analysis *Exclusion* Echienholz's stage 3 at diagnosis Follow up <3months after casting Immunosuppressive or osteo-active medication Post arthrodesis of the foot before the onset of CN. Amputation proximal to the Lisfranc joint during treatment	52 participants 57 feet *Sanders & Frykberg's* I =10 (18%) II =30 (53%) III =13 (23%) IV =3 (5%) V =1 (2%)	mean (SD) =59 (11)	Male n=36 (69%) Female n =16 (31%)	Not reported

Table 4-3 Study and Participant Characteristics (continued)

Studies evaluating off-loading which describe monitoring					
Author, year, country, study type	**Inclusion and exclusion criteria**	**Sample size CN classification**	**Participant characteristics**		
			Age yrs.	**Sex**	**Diabetes**
Pakarinen et al (2002) Finland Retrospective observational case series study without controls 1994-2000 (6yrs)	*Inclusion* Not reported *Exclusion* Not reported	32 participants 36 feet *Sanders & Frykberg's* I =5 (%) II =31 (%) III =0 (%) IV =3 (%) V =1 (%) 11% more than 1 area involved *Modified Eichenholtz* I =29 (80.5%) II =2 (5.5%) III =5 (14%)	Not reported	Male n =22 (69%) Female n =10 (31%)	NIDDM =19 (59%) NIDDM duration mean (range) =14 (1-28) IDDM =13 (41%) IDDM duration mean (range) =28 (8-58) HbA1c mean =9.4%

Table 4-3 Study and Participant Characteristics (continued)

Studies evaluating off-loading which describe monitoring					
Author, year, country, study type	**Inclusion and exclusion criteria**	**Sample size CN classification**	**Participant characteristics**		
			Age yrs.	**Sex**	**Diabetes**
Parisi et al (2013) **Brazil** Prospective observational study without controls 2004-2009 (5yrs)	*Inclusion* Patient with type 2 diabetes CN Eichenholtz stages I and II without previous treatment Abnormalities in the neuropathy evaluation Endocrinology follow-up Compliance with the proposed treatment protocol Regular follow-up with the institution's social services. *Exclusion* Presence of plantar foot ulcer at initial evaluation Preceding surgical procedure on affected foot Preceding osteomyelitis Presence of rheumatological and immunological diseases or alcoholism Patients on haemodialysis Contralateral limb amputation Pregnancy Cognitive impairment	22 participants	mean (range) =56 (47-64)	Male n =7 (32%) Female n =15 (68%)	T2DM =22 (100%) DM duration mean (range) =13 (8-25)

Table 4-3 Study and Participant Characteristics (continued)

Studies evaluating off-loading which describe monitoring					
Author, year, country, study type	**Inclusion and exclusion criteria**	**Sample size CN classification**	**Participant characteristics**		
			Age yrs.	**Sex**	**Diabetes**
Pinzur et al (2006) USA Prospective observational study without controls Time frame not reported	*Inclusion* First occurrence of CN as diagnosed by the original Eichenholtz criteria ≥40 years age Diabetes CN localised to the mid-foot Peripheral neuropathy Deformity within defined criteria No more than 1 superficial ulcer ≤3cm Also, radiographic angle criteria *Exclusion* Pacemaker or defibrillator Full thickness foot ulcer or exposed bone History of osteomyelitis in the involved foot Inflammatory arthritis, malignancy, dialysis, oral corticosteroid therapy during the 6months before entry Organ transplant Prior foot surgery for infection Contralateral amputation Pregnancy or lactating	10 participants (1 dropped out before completion of treatment)	mean (range) =58.2 (39-72)	Male n =4 (44%) Female n =5 (56%)	DM duration mean (range) =16.4 (7-30)

Table 4-3 Study and Participant Characteristics (continued)

Studies evaluating off-loading which describe monitoring					
Author, year, country, study type	**Inclusion and exclusion criteria**	**Sample size CN classification**	**Participant characteristics**		
			Age yrs.	**Sex**	**Diabetes**
Renner et al (2016) Switerzland Retrospective case control 2002-2012 (10yrs)	Inclusion T1DM or T2DM Peripheral neuropathy Exclusion Immunosuppressive or osteo-active medication Osteo-destructive bone pathologies Osteomyelitis Idiopathic osteoarthropathy	90 participants 101 feet *Sanders & Frykberg's* I =12 (12%) II =35 (35%) III =13 (13%) IV =6 (6%) V =2 (2%) I & II =6 (6%) II & III =1 (1%) II & IV =24 (24%) III & IV =3 (3%) IV & V =2 (2%) *Modified Eichenholtz* 0 =9 (9%) I =61 (60%) II =21(21%) III =10 (10%)	mean (SD) = 60.7 (10.6)	Male n =68 (76%) Female n =22 (24%)	Not reported

Table 4-3 Study and Participant Characteristics (continued)

Studies evaluating off-loading which describe monitoring					
Author, year, country, study type	**Inclusion and exclusion criteria**	**Sample size CN classification**	**Participant characteristics**		
			Age yrs.	**Sex**	**Diabetes**
Ruotolo et al (2013) **Italy** Prospective observational study without controls 2006-2011 (4.5yrs)	*Inclusion* Acute onset of swelling, redness, and warmth of the ankle and/or foot, without any bone involvement at standard x-ray. *Exclusion* CN joint and previous or concomitant foot ulceration Bone fractures Foot deformity Peripheral arterial disease.	25 participants *Modified Eichenholtz* 0 =25 (100%) I =0 II =0 III =0	mean (SD) = 58.12 (12.94)	Male n =16 (64%) Female n =9 (36%)	T2DM =19 (76%) T1DM =6 (24%) DM duration mean (SD) =18.87 (10.3)
Saltzman et al (2005) **USA** Retrospective observational case series study without controls 1983-2003 (20yrs)	*Inclusion* Primary diagnosis of CN requiring treatment bony collapse Minimum six month follow up *Exclusion* CN from other causes Patients with diabetes who had fractures that healed in the normal time without evidence of progressive fragmentation, dissolution, or displacement	115 participants 127 feet *Modified Eichenholtz* 0 =5 (4.3%) I =59 (51.3%) II =15 (13%) III =11 (9.6%) IV =6 (5.2%) No Classification =19 (16.5%) Forefoot =15 (%) Midfoot =66 (%) Hindfoot =10 (%)	median (range) =52 (21.1-84.6)	Male n =43 (37%) Female n =72 (63%)	T2DM =84 (74%) T1DM =31 (26%) DM duration median (SD) =21 (0-36)

Table 4-3 Study and Participant Characteristics (continued)

Studies evaluating off-loading which describe monitoring					
Author, year, country, study type	**Inclusion and exclusion criteria**	**Sample size CN classification**	**Participant characteristics**		
			Age yrs.	**Sex**	**Diabetes**
Sinacore (1998) **USA** Prospective case control study 1991-1996 (5ys)	*Inclusion* Acute onset of swelling, redness, and warmth if the ankle of foot requiring medical attention and referrals with a diagnosis of acute CN *Exclusion* Not diagnosed with DM Not referred by an orthopaedic surgeon from the author's medical facility.	30 participants 35 episodes CN Forefoot =(20%) Midfoot =(46 %) Hindfoot =(23%) Ankle =(11%)	Age years mean (SD) =55 (9)	Male n =24 (80%) Female n =6 (20%)	T2DM =21 (71%) T1DM =9 (29%) DM duration mean (SD) =21(12)
Stark et al (2016) **UK** Retrospective observational study without controls 2007-2012 (5yrs)	*Inclusion* Acute CN must have developed within the study period, and the patients must have been managed as an acute CN. *Exclusion* Patients were excluded if an acute CN was deemed unlikely from the history and clinical examination, or if imaging studies were negative or another diagnosis was found to be causative or more likely.	50 participants Forefoot =(11.9%) Mid-foot =(64.3%) Hind-foot =(19.1%) Multiple =(4.8%)	Age years mean (SD) =62.5 (11.7)	Male n =34 (68%) Female n =16 (32%)	T2DM =39 (78%) T2 DM duration median (IQR) =15 (4.5, 20) T2DM HbA1c mean (SD) =64 (20) T1DM =11 (22%) T1DM duration median (IQR) =32 (19.8, 38) T1DM HbA1c mean (SD) =0 (19)

Table 4-3 Study and Participant Characteristics (continued)

Studies evaluating off-loading which describe monitoring					
Author, year, country, study type	**Inclusion and exclusion criteria**	**Sample size CN classification**	**Participant characteristics**		
			Age yrs.	**Sex**	**Diabetes**
Thewjitcharoen et al (2018) Thailand Retrospective observational case series study without controls 2000-2016 (16yrs)	*Inclusion* *P*resence of a hot swollen foot with or without erythema of the overlying skin after the exclusion of conditions resembling CN foot *Exclusion* Not reported	40 participants - 13 with acute CN *Sanders & Frykberg's* I =12.5% II =50% III =27.5% IV =5% V =2.5%	Age years mean (SD) =56.1 (9.2)	Male n =4 (30.8%) Female n =9 (69.2%)	T2DM =12 (92.3%) T1DM =1 (7.7%) DM duration mean (SD) =16.6 (8.3) HbA1c mean (SD) =9.1 (2.3)
Verity et al (2008) Canada Prospective observational study without controls 33month period	*Inclusion* Not reported *Exclusion* Abscess or infection Gross instability that was managed with surgical debridement or stabilisation	21 participants 25 feet *Brodsky* 1 =13 (52%) 2 =2 (8%) 3A =1 (4%) 3B =1 (4%) 4 =7 (28%) 5 =1 (4%) *Modified Eichenholtz* 0 =0 I =8 (32%) II =11 (44%) III =6 (24%)	Age years mean (SD) = 52 (12)	Male n =10 (48%) Female n =11 (52%)	T2DM =12 (57%) T1DM =8 (38%) No diabetes =1 (5%) DM duration mean (SD) =21 (10)

Table 4-3 Study and Participant Characteristics (continued)

Studies evaluating off-loading which describe monitoring					
Author, year, country, study type	**Inclusion and exclusion criteria**	**Sample size CN classification**	**Participant characteristics**		
			Age yrs.	**Sex**	**Diabetes**
Visan et al (2012) Romaninia Prospective observational study without controls 2007-2011 (3yrs 8m)	*Inclusion* Not reported *Exclusion* Not reported	34 participants 42 feet *Modified Eichenholtz* 0 =0 I =29 (69%) II =11 (26%) III =2 (5%)	Age years mean (SD) = Not reported	Male n =28 (67%) Female n =14 (33%)	Not reported
Wukich et al (2011) USA Retrospective cohort study without controls 2005-2009 (5yrs)	*Inclusion* To be included in this study, radiographs taken at the onset of symptoms must not have demonstrated any fractures of the foot or ankle *Exclusion* Not reported	20 participants 22 feet 15 progressed to CN *Modified Eichenholtz* 0 =22 (100%) I =0 II =0 III =0 Forefoot =0 Midfoot =12 Hindfoot =5 Ankle =5 Multiple =5	Participants who did progress to CN. Age years mean=53.5	Not reported	Not reported

Abbreviations
CN Charcot neuroarthropathy
DM Diabetes mellitus
HbA1c Glycated haemoglobin (A1c), mmol/mol
IDDM Insulin dependent diabetes mellitus
NIDDM Non-insulin dependent diabetes mellitus
T1DM Type 1 diabetes mellitus
T2DM Type 2 diabetes mellitus

4.5.3 Techniques used in the monitoring of Charcot neuroarthropathy

Table 4-4 summarises the protocols used to monitor CN. Of the seven studies included in the first group three evaluated MRI for monitoring CN (Schlossbauer *et al.*, 2008; Zampa *et al.*, 2011; Chantelau *et al.*, 2018) . The first study compared dynamic MRI, with gadolinium contrast medium, every three months with foot skin temperature measured with a handheld infrared temperature scanner and midfoot and ankle circumference in 40 participants with CN (Zampa *et al.*, 2011). The authors concluded that contrast medium uptake rate obtained with dynamic-MRI represents a reliable technique for predicting remission in acute CN. Intra and inter-observer agreement for assessment of contrast medium uptake was high: correlation (*k*) = 0.96. The authors reported a 90% agreement between clinical findings and MRI. The mean healing time at clinical examination was 6.8 ±2.3 months and 8.3±2.9 at MRI. In 23% of participants the clinical signs of disease stabilisation were found 3-6 months prior to the stabilisation observed on MRI. The second study retrospectively reviewed the notes and images of 45 episodes of CN over 23 years. They reviewed sequential follow-up MRIs to assess the change in oedema equivalent signal change during treatment for CN with a walking cast. The number of follow-up MRIs per episode of CN ranged from 1-6. They found decreasing oedema-equivalent signal change in 69% (66/95) of follow-up MRIs but reported a combination of physiologic and pathologic fluctuations in oedema equivalent signal change in the remainder of the MRIs (Chantelau *et al.*, 2018). The third study compared bone marrow oedema on MRI at baseline and after 4 months and correlated this to symptoms of CN in 13 participants. There was a statistically significant decrease in bone oedema over 4 months, with a statistically significant correlation between pain and soft tissue oedema and the bone marrow (Schlossbauer *et al.*, 2008).

Table 4-4 Protocols for monitoring Charcot neuroarthropathy

Studies evaluating monitoring				
Author (year)	**Protocol for temperature measurement**	**Protocol for X-ray**	**Protocol for MRI**	**Protocol for other monitoring techniques described**
Armstrong & Lavery (1997)	Device: Exergen Acclimatisation: 15mins Number Sites: 7 Repetitions: NR Frequency: NR Ambient air temperature controlled	No report of it been used	No report of it been used	No report of it been used
Chantelau et al (2018)	Not measured objectively, but rated semi quantitatively by bi-manual comparative palpation, and by inspection	Used no details reported	Standard institution's routines, conventional MRI studies of the foot were commissioned irrespective of an expertise with the diabetic Charcot foot.	Swelling, deformity, joint dysfunction, skin abnormality were not measured objectively, but rated semi-quantitatively by palpation and inspection

Table 4-4 Protocols for monitoring Charcot neuroarthropathy (continued)

Studies evaluating monitoring				
Author (year)	**Protocol for temperature measurement**	**Protocol for X-ray**	**Protocol for MRI**	**Protocol for other monitoring techniques described**
McGill et al (2000)	Device: Dermatemp, Exergen Corporation, Mass, USA Skin temperature of the affected foot was measured at the hottest point. 3 months during the study.	Used at diagnosis	No report of it been used	Quantitative bone scanning. We injected 40 MBq of 99mTcEHDP intravenously, delivering only 11 MRems per scan. A standard of 10±20 MBq was used to decay correct all counts. All images were taken using a low energy all-purpose collimator. Isotope uptake in a standardised rectangular area over the affected foot was quantified for each of the three phases.
Moura-Neto et al (2012)	Device: Minitemp, Raytec Reference Armstrong 1997 for protocol	Frequency: monthly	No report of it been used	No report of it been used

Table 4-4 Protocols for monitoring Charcot neuroarthropathy (continued)

Studies evaluating monitoring				
Author (year)	**Protocol for temperature measurement**	**Protocol for X-ray**	**Protocol for MRI**	**Protocol for other monitoring techniques described**
Schlossbauer (2008)	Used no details reported	No report of it been used	1T Magnetom Harmony scanner (Siemens Medical Solutions, Erlangen, Germany). A dedicated foot and ankle coil was used. T1 fat-suppressed imaging was performed after injection of contrast.	Presence or absence of pain, erythema, oedema,
Wu et al (2012)	No report of it been used	Frequency: 4 weekly	No report of it been used	Doppler spectra of the first dorsal metatarsal arteries in both feet were obtained using a 10 MHz linear ultrasound probe (ATL HDI3000 or HDI5000: ATL, Bothel, Washington). 2 weekly intervals Swelling, warmth and erythema were recorded
Zampa et al (2011)	Device: not stated Technique: hottest point by a hand-held infrared temperature scanner	No report of it been used	Tesla: 1.5 Frequency: 3 monthly Contrast: yes Time: 16±4 minutes	Ankle and midfoot circumference

Table 4-4 Protocols for monitoring Charcot neuroarthropathy (continued)

Studies evaluating off-loading which describe monitoring				
Author (year)	**Protocol for temperature measurement**	**Protocol for X-ray**	**Protocol for MRI**	**Protocol for other monitoring techniques described**
Armstrong et al (1997)	Device: Exergen Reference Armstrong 1997 for protocol	Used no details reported	No report of it been used	No report of it been used
Chantelau (2005)	No report of it been used	Used no details reported	Used - no details reported	Bone technetium scan and CT used in diagnosis
Chantelau & Richter (2013)	Foot temperature – palpated to the contralateral foot	Used: performed as appropriate	T1 weighted, T2 weighted and STIR imaging had been carried out, with or without contrast media, at the discretion of the radiologist in charge. MRI was repeated in each patient for monitoring of the healing process at the discretion of the diabetic foot clinic.	Foot oedema – by inspection and palpation in comparison to the contralateral foot, (photography used) Foot deformity – inspection and palpation in comparison to the contralateral foot (photography used). Depression of longitudinal arch was graded
Christensen et al (2012)	Device: not reported Highest area identified and compared with the identical area on the contralateral foot. Frequency: 2-6weeks	No report of it been used	No report of it been used	Bone scintigram following i.v. injection of pertechnetate used in diagnosis

Table 4-4 Protocols for monitoring Charcot neuroarthropathy (continued)

Studies evaluating off-loading which describe monitoring				
Author (year)	**Protocol for temperature measurement**	**Protocol for X-ray**	**Protocol for MRI**	**Protocol for other monitoring techniques described**
De Souza (2008)	Infrared thermometers, and skin thermistors were not used. Meticulous palpation with the palm and the back of the hand and fingers was used to assess decreased warmth.	Frequency: 2-week intervals early phases of treatment, then less frequently.	No report of it been used	No report of it been used
Dixon et al (2017)	No report of it been used	Used no details reported	Used no details reported	No report of it been used
Fabrin et al (2000)	Device: Thermocouples medical precision thermometer DM 852: Thermocouples, Ellab, Copenhagen). Frequency: 2-6 weeks	Frequency: 6–12 weeks	No report of it been used	No report of it been used
Holmes & Hill (1994)	No report of it been used	Used no details reported	No report of it been used	No report of it been used
O'Loughlin et al (2016)	No report of it been used	No report of it been used	No report of it been used	No report of it been used
Osterhoff et al (2013)	No report of it been used	Used no details reported	MRI used to confirm diagnosis and if uncertainty remained regarding inflammation	Osseous biopsies used to confirm diagnosis

Table 4-4 Protocols for monitoring Charcot neuroarthropathy (continued)

Studies evaluating off-loading which describe monitoring				
Author (year)	**Protocol for temperature measurement**	**Protocol for X-ray**	**Protocol for MRI**	**Protocol for other monitoring techniques described**
Pakarinen et al (2002)	Skin temperature and temperature differences between the affected and non-affected foot were measured	Used no details reported	Diagnostic and follow-up MRIs were performed	No report of it been used
Parisi et al (2013)	Device: not reported Local temperature Every 15 days during the first 12 weeks then monthly	Standardised radiographic evaluations. Every 15 days during the first 12 weeks then monthly	No report of it been used	No report of it been used
Pinzur et al (2006)	No report of it been used	Used no details reported	No report of it been used	Objective measure of water displacement at each visit Clinical assessment of soft tissue swelling (non, mild, moderate, severe) Midfoot stability (stable, moderately unstable, unstable)

Table 4-4 Protocols for monitoring Charcot neuroarthropathy (continued)

Studies evaluating off-loading which describe monitoring				
Author (year)	**Protocol for temperature measurement**	**Protocol for X-ray**	**Protocol for MRI**	**Protocol for other monitoring techniques described**
Renner et al (2016)	Redness and warmth measured by visual inspection and palpation	No report of it been used	Confirmation of CN by magnetic resonance imaging (MRI) (i.e., soft tissue oedema, joint effusion, and/or subchondral bone marrow oedema of involved joints characterized by low signal intensity on T1-weighted images and high signal intensity on T2-weighted images)	No report of it been used
Ruotolo et al (2013)	Device: portable infrared thermometric probe Frequency: 3 weekly Reference Armstrong 1997 for protocol	Used at diagnosis no details reported	Used to confirm healing 1.5T	F-FDG PET/CT scan Scans were examined visually for focal abnormalities, and data generated from the scan were also assessed quantitatively by calculating the maximum standard uptake value Frequency: 3 monthly
Saltzman et al (2005)	No report of it been used	Used no details reported	No report of it been used	No report of it been used

Table 4-4 Protocols for monitoring Charcot neuroarthropathy (continued)

Studies evaluating off-loading which describe monitoring				
Author (year)	**Protocol for temperature measurement**	**Protocol for X-ray**	**Protocol for MRI**	**Protocol for other monitoring techniques described**
Stark et al (2016)	Device: not reported Frequency: 1-2 weeks	Used no details reported	Used no details reported	No report of it been used
Thewjitcharoen et al (2018)	No report of it been used	No report of it been used	No report of it been used	No report of it been used
Verity et al (2008)	Resolution of swelling, erythema, and increased warmth) No details reported Frequency: monthly	Frequency: monthly	No report of it been used	No report of it been used
Visan et al (2012)	No report of it been used	Used no details reported	No report of it been used	No report of it been used
Wukich et al (2011)	No report of it been used	No report of it been used	No report of it been used	No report of it been used

Two studies evaluated infrared thermometry to identify disease remission (Armstrong and Lavery, 1997; Moura-Neto *et al.*, 2012). The first study described in detail the protocol for measuring temperature using the Exergen Model DT 1001®. They controlled for ambient room temperature, allowed a 15 minute acclimatisation period, and measured seven sites on the foot, compared with the contralateral limb as the physiologic control, at monthly intervals (Armstrong and Lavery, 1997). Casting was discontinued based on reduction or absence of clinical signs of inflammation, radiologic signs of healing and when the temperature difference between feet had stabilised with a cut-off point of less than 4°F (2.2°C) difference. The authors report that the choice of the cut-off figure was based on clinical experience The second study referenced the protocol described by Armstrong and Lavery (1997) for measuring temperature but used the Minitemp, Raytec® (Moura-Neto *et al.*, 2012) to monitor temperature. Casting was discontinued when the temperature difference between feet was recorded as less than 2°C.

One study evaluated Doppler spectrum analysis as a novel diagnostic tool for planning treatment. (Wu *et al.*, 2012) The study compared the Doppler spectra of the first metatarsal arteries in both feet using a 10MHz linear ultrasound probe (ATL HDI3000 or HDI5000; ATL, Bothel, Washington). The Doppler spectra in the unaffected limb was triphasic, compared to the affected limb which showed monophasic forward flow. The Doppler spectra analysis was repeated every two weeks in the affected limb until it returned to normal. At this point participants either started weight-bearing or underwent surgical reconstruction of the ankle joint. The authors concluded that Doppler spectra analysis of the foot may be used as a guide to begin weight bearing. They reported a discrepancy between the two monitoring techniques: only four out of 15 people had plain X-rays which showed healing when the foot was healed according to the Doppler Spectra analysis.

In the final study a subset of eight participants from a larger study received three monthly three-phase quantitative bone scans of both feet for a maximum of 12 months. They compared the ratio of isotope uptake between feet, between the affected foot and the tibia and compared isotope uptakes to the clinical indicators of inflammation. There was strong correlation between temperature difference and the ratio of isotope uptake in the affected versus unaffected foot, the perfusion of the affected foot in the dynamic phase and the isotope uptake in the delayed phase of the bone scans (McGill *et al.*, 2000). The study also reported on the change in temperature difference between the affected and unaffected foot from baseline 3.3^0C, at six months 1.3^0C, and at 12 months 0.8^0C noting a progressive decrease over time (McGill *et al.*, 2000).

In the remaining 22 studies, the primary aim was to evaluate the outcomes of CN, but they described the monitoring techniques used (Table 4-4). The most frequent monitoring techniques used was serial X-ray in 16/22 of studies, objective temperature measurement with a handheld infrared monitoring device in 11/22 and MRI with or without contrast media in 7/22 of studies. Protocols for the same technique were not standardised across studies. For example, in studies that used infrared skin temperature measurement to monitor CN, some studies used a cut of <1^{o}C and others <2^{o}C to identify remission. Some studies relied on a combination of different monitoring techniques: 5/22 described two techniques, 4/22 described three techniques and one study used four techniques to monitor CN.

Four studies used advanced radiological methods for diagnostic and/or monitoring: F-FDG PET/CT scanning (Ruotolo *et al.*, 2013), bone scintigram (Christensen *et al.*, 2012), bone biopsies (Osterhoff, Böni and Berli, 2013), and isotope bone scans (Chantelau, 2005). Other monitoring techniques included objective and subjective measures of inflammation by palpating foot temperature, and assessing the presence of swelling (Sinacore, 1998; Chantelau, 2005; de Souza, 2008; Verity *et al.*, 2008; Renner *et al.*, 2016). Another study assessed progression of foot deformity by visual examination, palpation and comparison of serial photographs (Chantelau and Richter, 2013). Objective, serial measures of water displacement and grading of midfoot stability were used to monitor CN in another study (Pinzur, Lio and Posner, 2006).

4.5.4 Sensitivity and specificity of monitoring techniques

Six out of seven studies which evaluated monitoring techniques did not report the sensitivity or specificity. Zampa., et al (2011) reported a high intra and inter observer agreement for the assessment of contrast uptake but did not report the sensitivity of the technique. They reported that the monitoring techniques evaluated could be used as a guide to identify remission, withdraw immobilisation, and begin weight bearing. None of the 22 studies reporting the outcomes of CN reported the specificity or sensitivity of the monitor techniques used to measure when the foot was in remission. Some studies relied on subjective monitoring techniques such as palpation or visual inspection of inflammation to assess for remission in CN.

4.5.5 Financial implications to healthcare providers and clinical feasibility of different techniques

No studies reported the cost of the monitoring used in terms of capital cost to purchase equipment.

4.5.6 Safety considerations, and participant acceptability of different techniques

Ten out of 29 studies used MRI as a monitoring tool for identifying remission of acute CN. Of these, four reported using contrast during the MRI in all or some images at the radiologist's discretion (Schlossbauer *et al.*, 2008; Zampa *et al.*, 2011; Chantelau and Richter, 2013; Ruotolo *et al.*, 2013). A further four studies used advanced methods of radiological imaging which require the use of contrast media (McGill *et al.*, 2000; Chantelau, 2005; Christensen *et al.*, 2012; Ruotolo *et al.*, 2013). Only one of these 14 studies which used contrast specifically reported on the incidence of adverse events from the administration of the contrast, reporting no adverse events. Another study reported using bone biopsy as a diagnostic aid to confirm CN, but this was not used in monitoring. (Osterhoff, Böni and Berli, 2013) They did not report any safety considerations that may be relevant to this technique. X-rays are associated with exposure to ionising radiation, but their potential risk was not discussed in any studies. No safety considerations were reported for objective temperature measurement with a handheld infrared monitoring device or any other clinical methods for monitoring CN. None of the studies reported on participant acceptability of the monitoring techniques used.

Table 4-5 Treatment and Outcomes

Studies evaluating monitoring					
Author (year)	**Monitoring evaluated and treatment**	**Follow-up**	**Outcome – evaluation and time to remission**	**Relapse**	**Frequency and type of complications**
Armstrong & Lavery (1997)	Infrared Dermal Thermometry TCC	mean (SD) =26.6m (7.1)	Mean skin temperature difference for all subjects at initial presentation 8.8 ±2.3°F (range 5.1-14.7) At initial presentation the site of maximum skin temperature gradient correlated to the site of maximum Charcot arthropathy (radiographically) in 92% cases. The site of maximum skin temperature gradient correlated to the site of maximum Charcot arthropathy (radiographically) in 72% of all cases throughout the follow up period. Time to remission – not reported	Relapse - not reported	7.7% new onset ulceration

Table 4-5 Treatment and Outcomes (continued)

Studies evaluating monitoring					
Author (year)	**Monitoring evaluated and treatment**	**Follow-up**	**Outcome – evaluation and time to remission**	**Relapse**	**Frequency and type of complications**
Chantelau et al (2018)	MRI Immobilisation and offloading – cast treatment	19 cases had only 1 follow up scan 11 cases had 2 follow up scans 9 cases had 3 follow up scans 6 cases had 4–6 follow up scans Individuals follow up scans were on average 13 weeks apart (range 35–50 weeks)	Not all patients were followed up until healing 140 reports (45 baseline and 95 MRI follow-up) 69% (66/95) follow up scans showed dependent regression of oedema-equivalent signal change as expected. 31% (29/95) showed stagnant or extending oedema-equivalent signal change. Proportions of follow up scans showing oedema-equivalent signal change regression was independent of the active-stage Charcot foot, severity grade, renal failure, and order of the follow up scans (1st versus 2nd to 6th FUS); all chi2 $p > 0.05$. Estimated duration until 'healing' Grade 0 =25 weeks (approx) Grade 1 =35 weeks (approx)	5 cases	Not reported

Table 4-5 Treatment and Outcomes (continued)

Studies evaluating monitoring					
Author (year)	**Monitoring evaluated and treatment**	**Follow-up**	**Outcome – evaluation and time to remission**	**Relapse**	**Frequency and type of complications**
McGill et al	Temperature measurement Quantitative bone scanning 12 months – rest and contact casting	subset 8 subjects received bone scans	At presentation, the affected foot was 3.3 °C (2.4±4.7) hotter than the unaffected foot. After 6 months there was 1.3 °C (0.5±1.9) difference. After 12 months there was 0.8 °C (0.3±1.6) difference. Correlation ($r = 0.90$, $p < 0.0001$) between temperature difference and the ratio of isotope uptake in the affected: unaffected feet Relationship between the perfusion of the affected foot in the dynamic phase and the isotope uptake in the delayed phase of the bone scans ($r = 0.92$, $p < 0.0001$)	Not reported	Not reported
Moura-Neto et al (2012)	Skin temperature CROW – instructed to weight-bear normally but to restrain from heavy physical work.	1 year	Univariant and multivariant Cox proportional hazard regression analyses for age, sex, diabetes duration, and initial temperature difference showed no influence of any of these factors on the rate or time to consolidation One-year consolidation rate= 25 (89.3%) Mean =6.6months (±2.1) Range =3-12months	No relapses among the 25 patients who progressed to the chronic phase	Not reported

Table 4-5 Treatment and Outcomes (continued)

Studies evaluating monitoring					
Author (year)	**Monitoring evaluated and treatment**	**Follow-up**	**Outcome – evaluation and time to remission**	**Relapse**	**Frequency and type of complications**
Schlossbauer (2008)	MRI and clinical findings Mean interval for follow up MRI =4.2 months Pressure-relieving methods like a strict non-weight bearing in a brace or cast.	4-month follow-up	Bone marrow oedema in affected bones significantly decreased (p<0.001) Signal intensity of bone marrow oedema in STIR imaging showed a significant correlation with the presence of soft tissue oedema and with the presence of pain at clinical evaluation (p<0.05) Erythema and elevated temperature did not show a significant correlation. The presence of bone marrow oedema in the STIR sequence was strongly associated with a corresponding contrast enhancement (p <0.0001)	Not reported	Not reported
Wu et al (2012)	Doppler spectrum analysis. Padded bivalve cast and non-weight bearing	Not reported	Doppler spectrum returned normal Mean =13.6 weeks Range =6-20	1 patient relapsed after 7 weeks	3 pts underwent pan-talar arthrodesis
Zampa et al (2011)	Dynamic MRI TCC	Healing or a max 12 months	Mean healing time Clinical examination =6.8months (±2.3) MRI =8.3months (±2.9) p =<0.0001	Not reported	Not reported

Table 4-5 Treatment and Outcomes (continued)

Studies evaluating off-loading which describe monitoring					
Author (year)	**Monitoring evaluated and treatment**	**Follow-up**	**Outcome – evaluation and time to remission**	**Relapse**	**Frequency and type of complications**
Armstrong et al (1997)	TCC	1yr	Mean =18.5weeks (±10.6) Range =4-46weeks	15% relapsed	9 (25%) underwent corrective surgery for foot deformity
Chantelau (2005)	TCC wherever possible	Until transferred into shoes	*Early referral* Median =3months Range =2-9months *Late referral* Median =5months Range =3.5-14months p =>0.05	Not reported	*Early referral* 1 patient developed gross foot deformity *Late referral* 13 patients developed gross foot deformity 1 skin ulcer 1 malalignment of cast foot healed in supination
Chantelau & Richter (2013)	Removable device	All patients had been followed up until transition to shoes and for variable periods of time thereafter	Stage 0 median (range) =4months (2-8months) Stage 1 median (range) =5months (3.5-14months)	Not reported	9 skin ulcers 1 malalignment the foot healed in supination

Table 4-5 Treatment and Outcomes (continued)

Studies evaluating off-loading which describe monitoring					
Author (year)	**Monitoring evaluated and treatment**	**Follow-up**	**Outcome – evaluation and time to remission**	**Relapse**	**Frequency and type of complications**
Christensen et al (2012)	Removable device	Mean =3.2yrs	Mean (SD) =141 days (±11)	3 pts (5%) had exacerbation 7 pts (12%) had recurrence at 69 days (± 16)	No surgical correction of foot deformity needed
De Souza (2008)	TCC	Mean =5.5yrs Range =1-14yrs	Mean =14weeks Range =4-20weeks	Not reported	Only 1/34 had further anatomical displacement of clinical importance once it had been immobilised in a TCC Ulcers developed in 10 feet after the transfer to orthosis

Table 4-5 Treatment and Outcomes (continued)

Studies evaluating off-loading which describe monitoring					
Author (year)	**Monitoring evaluated and treatment**	**Follow-up**	**Outcome – evaluation and time to remission**	**Relapse**	**Frequency and type of complications**
Dixon et al (2017)	TCC 56%	1 yr. from diagnosis	Mean time until ambulatory in modified shoes =21.3weeks (±11.5)	2 pts a further fracture	1-year diagnosis 17 pts (34%) foot ulcer 1 pt. osteomyelitis 1 pt. underwent amputation All-cause mortality 5%
Fabrin et al (2000)	Immobilization in bed or in a wheelchair weight-off regimen, crutches, therapeutic footwear, soft insoles, control of oedema	Median (range) = 48months (6-114months)	Maintained in most cased for 4-6 months	10 pts with new attacks in the previously affected foot (time to 'new attack' not reported)	7 (6%) developed foot ulcers during a Charcot attack 2 pts underwent major amputation 3 pts underwent corrective surgery for foot deformity 2 pts died during follow-up
Holmes & Hill (1994)	Not reported	Median (range) = 27months (14-70months)	8/20 pts with fractures went on to develop a CN. Range healing CN pts =7-46months	Not reported	1 pt. with CN underwent a major amputation

Table 4-5 Treatment and Outcomes (continued)

Studies evaluating off-loading which describe monitoring					
Author (year)	**Monitoring evaluated and treatment**	**Follow-up**	**Outcome – evaluation and time to remission**	**Relapse**	**Frequency and type of complications**
O'Loughlin et al (2016)	Off-loading was administered in 50% cases. Including rest, TCC, TCI, CROW	Not reported	Not reported	Not reported	38% of pts developed subsequent ulceration 20% pts underwent a major amputation 10% underwent corrective surgery for foot deformity
Osterhoff et al (2013)	TCC	Not reported	Not reported	13 feet (23%) Mean interval recurrence= 27 months (±31) Range =3-102months	Not reported
Pakarinen et al (2002)	TCC	Mean =21 months Range =1-81months	Mean =11 months Range =4-37months	Not reported	2 pts underwent major amputation 12 pts underwent corrective surgery for foot deformity

Table 4-5 Treatment and Outcomes (continued)

Studies evaluating off-loading which describe monitoring					
Author (year)	**Monitoring evaluated and treatment**	**Follow-up**	**Outcome – evaluation and time to remission**	**Relapse**	**Frequency and type of complications**
Parisi et al (2013)	Removable device. Bear weight respecting symptomatic limitations of each case.	Not reported	18weeks	Not reported	Not reported
Pinzur et al (2006)	TCC and then removable device	1-5months after transition into footwear	Treated with TCC Mean 5.8weeks Range =4-10 Then aircast Total treatment time Mean =12 weeks Range =6-16weeks	Not reported	1 Lost to follow-up
Renner et al (2016)	Mixture of TCC and removable devices	1-208 months	Unilateral Mean =20weeks (±21) Bilateral Mean =29weeks (±29)	Not reported	8 pts minor amputation 2 pts underwent a major amputation 4 procedures for corrective surgery for foot deformity

Table 4-5 Treatment and Outcomes (continued)

Studies evaluating off-loading which describe monitoring					
Author (year)	**Monitoring evaluated and treatment**	**Follow-up**	**Outcome – evaluation and time to remission**	**Relapse**	**Frequency and type of complications**
Ruotolo et al (2013)	TCC then removable walker	Return to prescription footwear Mean (SD) =21.75 ±16.7 months	Mean =15.12weeks (±5.45)	No recurrence reported in the follow-up time	Not reported
Saltzman et al (2005)	TCC	Median =3.8yrs Range =0.5–18.5 yrs	The median time wearing an ankle-foot orthosis was 12 months (95% CI; range, 10–13 months) 27 limbs (23%) required long-term use of an ankle-foot orthosis (defined as > 18 months)	Not reported	15 (11.8%) underwent a major amputation 62 (49%) recurrent ulcers 36 (28%) chronically recurrent ulcers 53 corrective surgery procedures performed for foot deformity
Stark et al (2016)	TCC and crutches	5yrs	median time to resolution for the 26 patients initially treated with a TCC was 48 weeks (95% CI: 42.4, 64.4) median time to resolution for the 22 pts initially treated with removable offloading device of 53 weeks (95% CI: 42.5, 64.4)	15 (35%)	4 (8%) or underwent a major amputation 2(4%) died

Table 4-5 Treatment and Outcomes (continued)

Studies evaluating off-loading which describe monitoring					
Author (year)	**Monitoring evaluated and treatment**	**Follow-up**	**Outcome – evaluation and time to remission**	**Relapse**	**Frequency and type of complications**
Thewjitcharoen et al (2018)	TCC	57.1 months after the onset of the CN	Median (range) =5 months (2-10months)	Not reported	5yr mortality 13%
Verity et al (2008)	Removable cast or boot. Limit standing and walking to the minimum	Not reported	Mean =29weeks (±19) Range =6-73weeks No remission in 8 (32%) cases	Not reported	3 feet developed new deformity
Visan et al (2012)	Removable walker	Not reported	Stage 1 4 pts at 3 months 15 pts at 6 months 5 pts after 6 months Stage 2 2 pts at 6 months 4 pts after 6 months Stage 3 1 pt at 8 months	Not reported	3 (8.83%) patients underwent surgery
Wukich et al (2011)	TCC	Median =21.7months mean =23.6 months (±14)	19/20 (95%) diagnosis of CN missed		16/22 (72%) developed a complication 11/22 (50%) required surgical treatment

Abbreviations
CN Charcot neuroarthropathy
CROW Charcot restraining orthotic walker
SD Standard deviation
TCC Total contact cast
TCI Total contact insole

4.5.7 The influence of monitoring techniques on the outcomes of Charcot neuroarthropathy

Treatments and the definitions used to confirm remission and relapse varied between the studies. Time to healing ranged from eight weeks to over one year (Table 4-5). Relapse rates ranged from 0-35% across the studies. The monitoring techniques were poorly reported and inconsistently applied across studies. Four studies did not report which techniques were used to monitor CN.

4.5.8 Update to the systematic review

After duplicates were removed, the updated search identified another 200 papers. A further seven relevant papers were found. One study evaluated a monitoring technique as the primary aim (Berli et al., 2021). In the remaining six, the study's primary aim was to report outcomes of CN, but they also described monitoring techniques used (Jansen et al., 2018; Sebastian et al., 2019; Wanzou et al., 2019; Al-Rubeaan et al., 2020; Gratwohl et al., 2021; Griffiths and Kaminski, 2021). All were retrospectives case control studies of low or very low quality.

The study which evaluated a monitoring technique assessed diagnostic MRI to develop a new MRI scoring system the 'Balgrist Score' to predict treatment times for CN (Berli *et al.*, 2021). Serial MRIs in 65 feet of 56 patients who had previously been diagnosed and received off-loading for CN were blinded and assessed for soft tissue oedema, bone marrow oedema, joint destruction, and fracture. They concluded that a Balgrist score of ≥9 can be used to differentiate between CN that is likely to resolve in < or >90 days. They reported a 'Balgrist score' of ≥9 had a specificity of 72% and a sensitivity of 66% for identifying CN that would take ≥90 days to treat.

The remaining six studies reported the outcomes of CN in Denmark, India, Uganda, Saudi Arabia, Switzerland, and Australia. (Jansen et al., 2018; Sebastian et al., 2019; Wanzou et al., 2019; Al-Rubeaan et al., 2020; Gratwohl et al., 2021; Griffiths and Kaminski, 2021). These studies used a combination of infrared thermography, and plain X-rays to monitor CN. The protocols for infrared thermography were poorly described. The reported times to remission and relapse rates were consistent with the large variations reported in the initial systematic review.

4.6 Discussion

The previous systematic review on assessment, diagnosis and management in CN only included papers between 2002-2012 (Milne *et al.*, 2013), our review search from 1993-2018 and include an additional seven studies (Holmes and Hill, 1994; Armstrong and Lavery, 1997; Armstrong *et al.*, 1997; Sinacore, 1998; Fabrin, Larsen and Holstein, 2000; McGill *et al.*, 2000; Pakarinen *et al.*, 2002) some of which are key reference papers for future studies.

To our knowledge, this systematic review is the first to synthesise the evidence base for monitoring techniques of CN and influences of different techniques for monitoring CN on treatment outcomes. We identified a heterogeneous set of 29 papers: seven specifically evaluated monitoring techniques and a further 22 described the outcomes of CN. It is not possible to conclude whether the monitoring techniques used influences the outcomes of CN. We found no high-quality studies validating the use of monitoring techniques in CN.

The key finding is the lack of a consistent approach to monitoring CN. Common techniques included X-ray, temperature monitoring and MRI. Techniques were poorly described, and where the information was reported there was variability in the devices used and how the technique was applied. It is not clear whether the devices used were validated for the temperature ranges commonly found in feet. Some studies still rely on subjective measures of temperature difference between feet to monitor CN (Sinacore, 1998; de Souza, 2008; Verity *et al.*, 2008; Chantelau and Richter, 2013; Renner *et al.*, 2016; Chantelau *et al.*, 2018).

The first paper included in this review which used temperature measurement for monitoring in CN was published in 1997 (Armstrong and Lavery, 1997). The authors report that the cut-off point of 4^{o}F (2.2°C) for healing was not evidence-based but it appears to have been adopted as the standard for clinical decision making in subsequent studies and guidelines (Milne *et al.*, 2013; National Institute for Health and Care Excellence, 2015). This protocol has not been validated and other studies have not specified sites, repeated measures, or acclimatisation times making evaluation of studies using this technique difficult.

The ‘Balgrist score’ study identified in the update to the systematic review had several limitations (Berli *et al.*, 2021). The score has only been validated for mid-foot and hind-foot CN. The inclusion and exclusion criteria for this study raises several potential issues. Only, half (35/56) of patients included in this review had diabetes. Nine patients were characterised as having peripheral artery disease (PAD), which was not classified by severity. There were a further 11 patients classified

jointly as having either kidney failure or transplantation. The retrospective nature of this study, small sample size and participant characteristics limits the generalisability of these results. Further work is needed to validate this scoring system.

We found a lack of evidence on the sensitivity, specificity, cost-effectiveness, safety, and patient acceptability for all monitoring techniques. There is continued uncertainty about the relationship between monitoring techniques and treatment outcomes.

In the absence of reliable evidence we are unable to recommend any changes to current national (National Institute for Health and Care Excellence, 2015) and international guidance (Milne *et al.*, 2013) which are predominantly based on level IV evidence, i.e. expert opinion.

The strengths of our systematic review include the broad range of inclusion and exclusion criteria for study type. This allowed us to highlight the variability in the current approach to monitoring CN in research as well as clinical practice. Screening and data extraction were completed by two researchers who were experienced podiatrists. Our review also had some limitations: we did not search the grey literature. We limited searches to English language, we acknowledge that this may mean we missed some relevant studies and potentially introduced bias into the review. However, we feel that the impact of this would be relatively small.

In the 1990s it was acknowledged that using subtle changes in skin temperature to inform clinical decisions may not be an accurate way to monitor CN but this is still widely used in clinical practice (Armstrong and Lavery, 1997). Further high-quality research is needed to identify the optimal method of monitoring CN. We recommend that researchers accurately describe the population characteristics at baseline, standardise definitions for diagnosis and outcome measures, and provide detailed protocols for monitoring techniques in future research.

MRI as a monitoring tool for CN is increasingly acknowledged as a potentially more accurate method for monitoring and this is supported by the studies we included in this review (Schlossbauer *et al.*, 2008; Zampa *et al.*, 2011; Chantelau *et al.*, 2018). This warrants further investigation. An ongoing randomised feasibility study aims to explore the feasibility of using serial MRI without contrast to monitor and diagnose remission of CN to decide whether a large-scale study is warranted https://doi.org/10.1186/ISRCTN74101606 (Gooday, *et al.*, 2020b).

The updated search for this systematic review did not add any further evidence to address the uncertainties around the effectiveness of different monitoring techniques used in CN and whether they influence outcomes.

4.7 Conclusion

Multiple techniques have been used to evaluate remission in acute CN, but the quality of published studies to support any one technique is low or very low. Uncertainty therefore remains about the effectiveness of the different monitoring techniques, and whether the different monitoring techniques influence time to remission and recurrence rates. Therefore, we are unable to make recommendations for clinical practice. There is an urgent need for high-quality studies to identify the most accurate, safe, and cost-effective monitoring techniques in CN.

4.8 Summary

This systematic review has provided information to support the design of the next step in this research, the feasibility study. The next two chapters, will report the protocol and results of the feasibility.

5 A feasibility study of serial magnetic resonance imaging to reduce treatment times in Charcot neuroarthropathy in people with diabetes (CADOM). Protocol

5.1 Introduction

The previous chapter reported the results of the systematic review that has been used to inform the design of this feasibility study on the use of serial MRI to reduce treatment times in CN. This is the first of two chapters (chapter 5 and 6) on the feasibility study and reports the details of the study protocol. It is a copy of the published paper (appendix C) (Gooday *et al.*, 2020b). An additional section on the rationale for the chosen outcomes has been incorporated into this chapter. There are minor edits to the chapter to ensure consistency within the thesis. The results of the feasibility study are reported in chapter 6. The methods and findings of the convergent qualitative study are reported in chapter 7.

5.2 Background

CN is a complication of peripheral neuropathy associated with diabetes which most frequently affects the lower limb. It can cause fractures and dislocations within the foot, which may progress to deformity and ulceration. The symptoms include redness, warmth and swelling in the foot and/or leg. This inflammation can lead to fractures in the bones and can damage joints, affecting the shape and function of the foot. It was first described 140 years ago (Charcot, 1868), however it remains a poorly understood and frequently overlooked complication of diabetes (Donegan, Sumpio and Blume, 2013).

Population-based studies have estimated a life time cumulative incidence for CN of 0.4% to 1.3% in people with diabetes, rising to 13% in people at high risk who attend diabetic foot speciality clinics (Armstrong *et al.*, 1997). In 2018 a regional survey of 205,033 people with diabetes in the East Midlands, UK reported a point prevalence of 0.04% (Metcalf *et al.*, 2018). CN is associated with increased length of stay and use of medical resources (Labovitz, Shofler and Ragothaman, 2016).

The aim of treatment is to stop the inflammatory process, relieve pain and maintain foot architecture reducing the risk of future ulceration and amputation (Frykberg and Mendeszoon, 2000). The current international consensus is that the foot should be immobilised in a below knee non-removable cast or boot, with weekly or fortnightly review by healthcare professionals working in specialist multidisciplinary diabetic foot clinics (Rogers *et al.*, 2011). The immobilisation

minimises the potential for any further damage to the foot structure. Immobilisation is continued until remission, defined as the absence of clinical signs of inflammation, measured using skin surface infrared thermography, and plain X-rays showing signs of bone healing and union (Milne *et al.*, 2013).

The evidence base for the treatment of CN is weak. It is based on studies from a few centres which used retrospective designs and case note review methods using small sample sizes, typically in the range of 9-55 participants (Armstrong *et al.*, 1997; Sinacore, 1998; Bates, Petrova and Edmonds, 2006; Pinzur, Lio and Posner, 2006; de Souza, 2008; Stark *et al.*, 2016). Many studies failed to standardise monitoring, treatment, and outcomes, which makes direct comparison between studies difficult.

Studies from the UK have shown a median time to remission of 9-12 months (Bates, Petrova and Edmonds, 2006; Game *et al.*, 2012; Stark *et al.*, 2016). However, US studies report considerably shorter time to remission of 3-5 months (Armstrong *et al.*, 1997; Sinacore, 1998; Pinzur, Lio and Posner, 2006; de Souza, 2008). Studies from Brazil and Germany show remission times of 3-12 months and 3-6 months, respectively (Kimmerle and Chantelau, 2007; Moura-Neto *et al.*, 2012). Shorter treatment times could be related to reported differences in the relapse rates for CN, between 12-33% (Fabrin, Larsen and Holstein, 2000; Christensen *et al.*, 2012; Osterhoff, Böni and Berli, 2013; Stark *et al.*, 2016), but without clear and consistent definitions for remission and relapse this is unknown. There is also variation in the reported annual major amputation rates in people with CN from two different case series from hospitals in the USA: 2.7% and 6.6% (Sinacore and Withrington, 1999; Saltzman *et al.*, 2005).

The reasons for the variation are not understood but could include people's characteristics at the start of the treatment, different techniques for monitoring CN, different protocols for the same monitoring techniques, variations in approach to off-loading, and variability in study design. These could either underestimate or overestimate treatment duration.

Temperature difference between the feet is one of the most frequently used methods to monitor CN. It is recommended in the 2015 National Institute for Health and Care Excellence guidance on diabetic foot problems (National Institute for Health and Care Excellence, 2015). The most recent systematic review (Milne *et al.*, 2013) published in 2013 recommends that immobilisation is continued until the temperature difference between the feet is less than 1-2 °C, and no further

radiological changes on imaging have occurred. However this recommendation is only based on level IV evidence, i.e. case series (Milne *et al.*, 2013). There is variability in the protocols used to measure the temperature difference between the feet. The most detailed protocol for measuring temperature discrepancy requires a 15 minute acclimatisation period, controlled ambient air temperature, and readings collected from nine different places on each foot (Armstrong and Lavery, 1997). In addition, plain X-rays demonstrate damage to the bone and joints rather than disease activity (inflammation).

Studies show inconsistency in the methods for monitoring and monitoring devices used (Armstrong *et al.*, 1997; Fabrin, Larsen and Holstein, 2000; McGill *et al.*, 2000; Hastings *et al.*, 2005; Christensen *et al.*, 2012; Osterhoff, Böni and Berli, 2013; Stark *et al.*, 2016). These factors may overestimate or underestimate the degree of inflammation, so treatment may be discontinued too early or continued for longer than necessary. The presence of simultaneous bilateral foot disease or the absence of a contralateral limb through prior amputation invalidates the use of temperature measurement as a tool for identifying disease remission.

The National Institute for Health and Care Excellence recommends the use of MRI in determining a diagnosis of CN in the early stages of disease when no signs are evident on plain radiology (National Institute for Health and Care Excellence, 2015). However serial MRI is not widely used in routine clinical practice as a tool to monitor for signs of disease remission in CN (Lymbouris, Gooday and Dhatariya, 2020). One prospective study using MRI with contrast reported that mean healing times were associated with contrast uptake assessed at baseline (Zampa *et al.*, 2011). A further two retrospective studies looked at bone marrow oedema. One study reported decreasing bone marrow oedema in 69% of follow up images (Chantelau *et al.*, 2018) and the second study found a significant positive correlation between intensity of bone marrow oedema on MRI and clinical measures (Schlossbauer *et al.*, 2008). This emerging evidence suggests that MRI may be useful for the surveillance of active CN. The findings from MRIs could be adopted as the criterion standard for establishing disease activity and remission.

The use of MRI in monitoring CN therefore needs to be formally evaluated in a study (Chantelau *et al.*, 2018). However, the evidence to support a full randomised controlled study is presently insufficient. We will conduct a randomised feasibility study to understand the proportion of people who meet the eligibility criteria, the number of eligible participants recruited, the number of participants who receive an alternative diagnosis, and the proportion of participants who withdraw. Time to MRI confirmed remission of CN with off-loading treatment (in days) and its

variance will be used to inform sample size in a main study. We will look for opportunities to improve the protocols for monitoring techniques in a future study. We will examine the feasibility of a range of clinical, patient centred, and health economic measures We are using a randomised controlled study as it is considered the gold standard for evaluating efficacy in clinical research (Spieth *et al.*, 2016).

In summary, there is a lack of evidence to support the use of monitoring techniques in CN. Healthcare professionals rely on methods and devices which do not accurately reflect disease progression, and decision making about discontinuing or prolonging immobilisation is challenging. A lack of understanding on people's experiences of living with CN, means their needs and wishes may be neglected with current treatments, and are not being considered when developing new treatment strategies and pathways.

5.3 Aims and objectives

This study aims to explore the feasibility of using serial MRI without contrast in the monitoring of CN to reduce duration of immobilisation of the foot, in order to decide whether a large-scale trial is warranted. We will assess eligibility, recruitment, retention, and withdrawal rates. Time to MRI confirmed remission of CN with off- loading treatment (days), and its variance will be used to inform sample size in a main trial. We will also examine the feasibility of collecting clinical, patient-centred and health economic measures. The convergent qualitative study aims to explore the dimensions of lived experience of CN and the participants' experiences of taking part in the feasibility study

5.4 Methods

5.4.1 Study design

This is a two-arm, open, randomised controlled study, investigating the feasibility of using serial MRI to monitor CN. The study will last for a maximum of 3 ½ years. The study is divided into two phases. Phase one, the active phase, lasted until the CN was in remission, or a maximum of 12 months. Phase two, the follow-up phase, lasted for six months after remission (Figure 5-1). The maximum time a participant was in the study for was 18 months. Figure 5-2 shows the study measures collected during the active phase of the study and Figure 5-3 shows the study measures collected during the follow-up phase of the study.

Figure 5-1 Particpant flow diagram

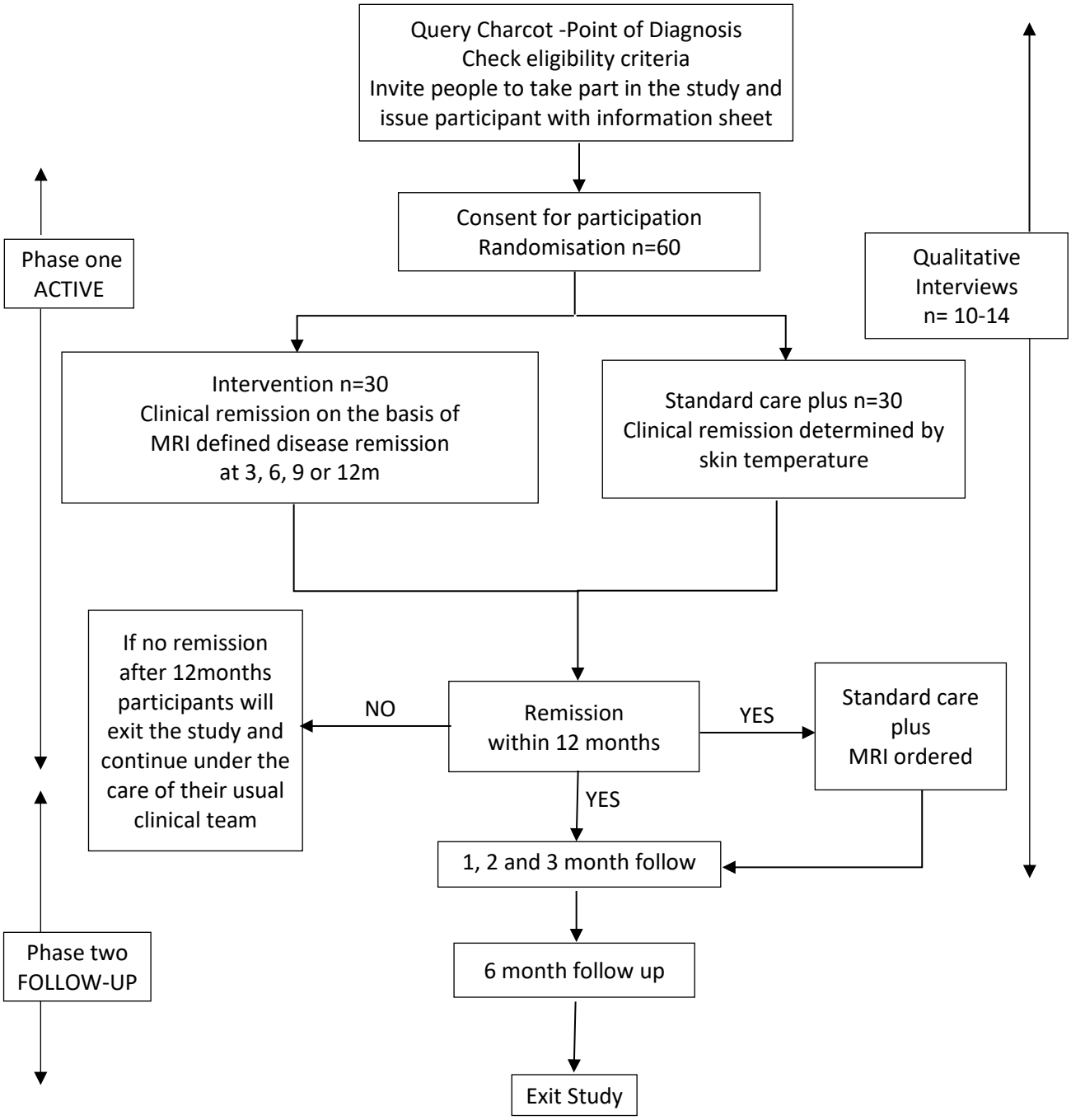


Figure 5-2 Study measures at each visit for participants in the active phase of the study for both standard care plus and intervention arm.

Participants who received an alternative diagnosis during the active phase exited the study and if necessary, they were referred on for follow-up by the appropriate clinical team.

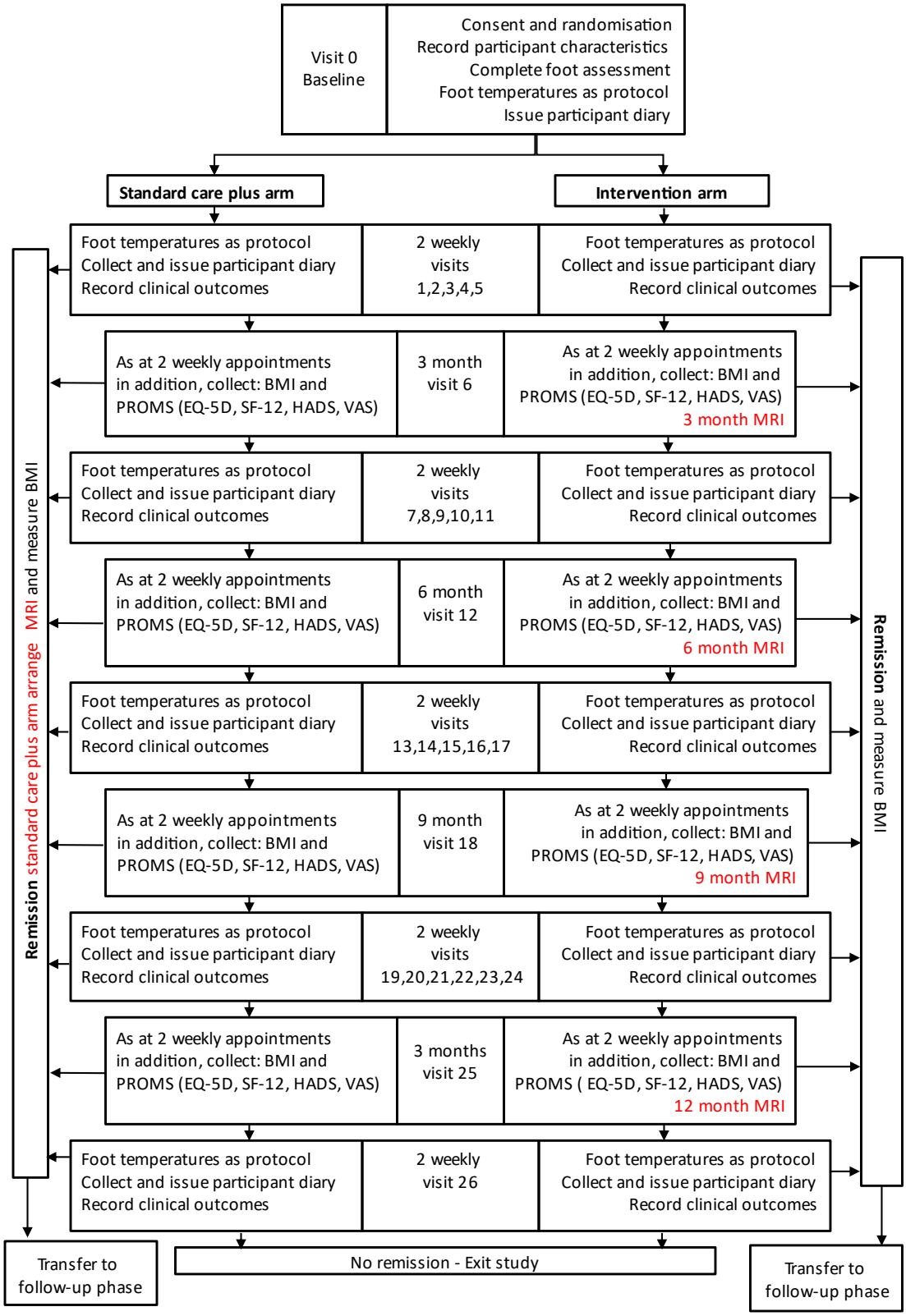
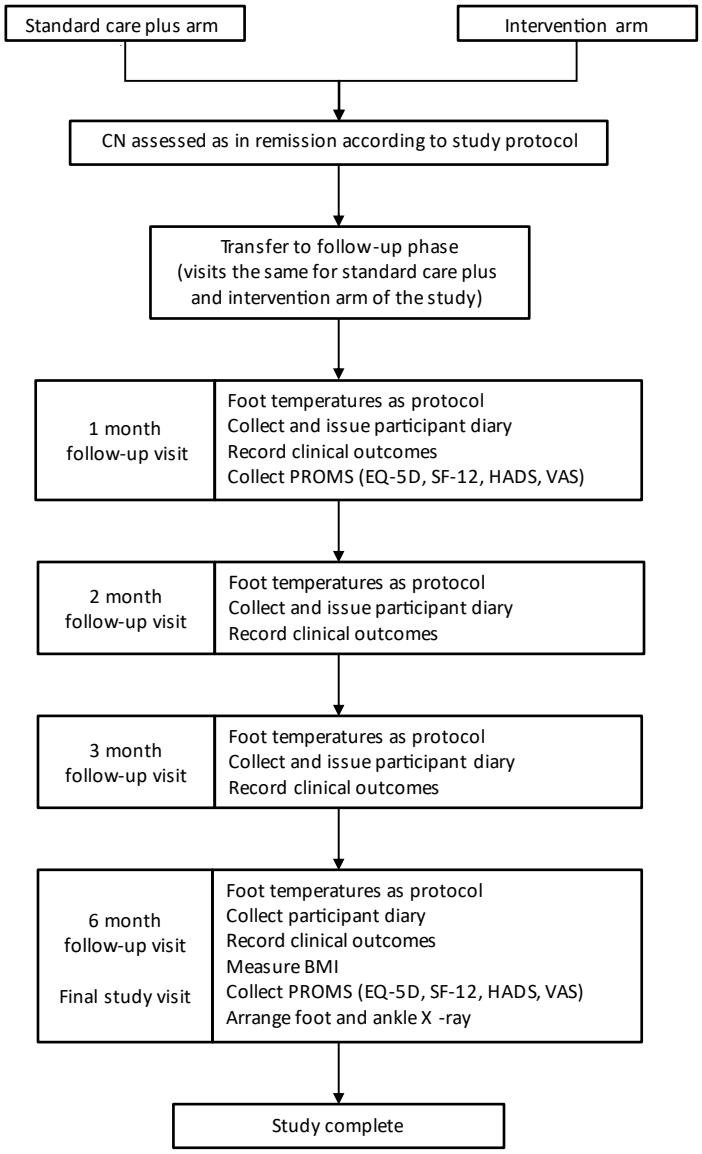


Figure 5-3 Study measures for participants in the follow-up phase of the study



The decision to use an open label design was pragmatic: the MRIs were reported by radiologists and interpreted by the healthcare professionals working in multidisciplinary specialist diabetic foot clinics. As the reporting of MRIs relies on comparison to previous images, this indicates the study arm the participant has been randomised to. A standard MRI protocol was supplied to sites on request, however there was no attempt to standardise the approach to MRI sequencing.

5.4.2 Ethical approval

The study protocol was reviewed and approved by East Midlands - Derby Research Ethics Committee, 04/10/2017, ref: 17/EM/0288. The study approvals for the REC and HRA can be found in appendices D and E.

5.4.3 Study registration

ISRCTN: 74101606. Registered on 6 November 2017.
http://www.isrctn.com/ISRCTN74101606?q=CADom&filters=&sort=&offset=1&totalResults=1&page=1&pageSize=10&searchType=basic-search

5.4.4 Setting

The setting will be multidisciplinary specialist diabetic foot services at five NHS Hospital Trusts in England.

5.4.5 Randomisation

A randomisation scheme has been generated by the study statistician. Allocation was stratified by centre. Participants will be randomised using a web-based randomisation process on a 1:1 basis to: (a) Immobilisation discontinued on the basis of clinical remission determined by skin temperature measurement, which triggers an MRI (standard care plus) or (b) Standard care plus and additionally the serial use of MRI at 3, 6, 9 and 12 months to identify disease remission and thus discontinuation of immobilisation (intervention).

5.4.6 Sample size

As this is a feasibility study a power calculation was not required. An allowance has been made for up to 10-15% of participants to be withdrawn from the study due to an alternative diagnosis. The

sample size will be 60 people with 30 participants per arm, based on recommended sample sizes between 24 – 50 for a feasibility study (Julious, 2005; Sim and Lewis, 2012). We will invite a purposive subsample of 10–14 participants from the feasibility study to take part in the qualitative study.

5.4.7 Inclusion and exclusion criteria

Participants will be people with diabetes as defined by the World Health Organisation (World Health Organisation, 2011) and a suspected or confirmed diagnosis of CN who are attending NHS multidisciplinary specialist diabetic foot services. They will be identified, recruited, and consented by the healthcare professionals working in the foot clinics, these included podiatrists, nurses, and doctors. The full inclusion and exclusion criteria are shown in Table 5-1. The main exclusion criteria were selected because: 1) they are contra-indications to having an MRI scan, 2) bilateral disease prevents temperature comparison with the contra-lateral limb, and 3) co-morbidities may alter people's inflammatory response.

A confirmed diagnosis of CN can take several weeks, so participants will be recruited as early as possible to accurately collect length of time in below knee non-removable cast or boot. If the clinical team decides on an alternative diagnosis during the study, then the participant will exit the study. We anticipate that alternative diagnosis will include infection, gout, arthritis, soft tissue injuries, or deep vein thrombosis. Follow-up care will be provided by the appropriate clinical team.

For the qualitative study, we have identified five participant characteristics which will purposively inform the sampling framework and will seek to maximise variation in sex, age, history of previous foot complications, duration of treatment for the current episode of CN and employment status. In addition to these factors, we will also ensure that participants equally represent both study arms.

Table 5-1 Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Participants who are willing and have capacity to give informed consent.	People who have received a transplant and others receiving immunosuppressant therapy or using long term oral glucocorticoids other than in the routine management of glucocorticoid deficiency. Participants on a low dose of oral glucocorticoids (<10mgs for ≤7 days) are eligible to participate in the study
People with diabetes as diagnosed by the WHO criteria Definition and diagnosis of diabetes_new.pdf (who.int)	Participation in another intervention study on active Charcot
Age 18 years or over	Contra-indication for MRI
New or suspected diagnosis of acute Charcot (no previous incidence of acute Charcot within the last 6 months on the same foot)	Treatment for previous suspected Charcot on the same foot in the last 6 months
Understand written and verbal instructions in English	Suspected or confirmed bilateral active Charcot at presentation
	Active osteomyelitis at randomisation
	Previous contralateral major amputation
	Inability to have an MRI scan
	People receiving palliative care

Abbreviations *WHO World Health Organisation*
MRI Magnetic Resonance Imaging

5.5 Outcomes

We will record participant characteristics and measure a range of feasibility, clinical, patient centred and cost effectiveness outcomes (Table 5-2). The proposed primary outcome for a definitive trial will be time to confirmed remission, recorded as off-loading treatment time measured in days. Clinical outcomes will be assessed to provide an initial efficacy estimate to inform the design of a definitive trial. The safety of the intervention MRI will be assessed

Table 5-2 Feasibility, clinical efficacy and patient reported outcomes

Feasibility outcomes	**Clinical efficacy outcomes**	**Patient reported outcomes**
The proportion of people who meet the eligibility criteria	Number of new ulcerations on the index foot or contralateral foot	Health-related quality of life measured: • Short Form 12 questionnaire (SF-12) • EuroQol-5D-5L questionnaire (EQ-5D-5L)
The number of eligible people recruited	Number of new infections on the index or contralateral foot	Hospital Anxiety and Depression Scale (HADS)
The number of participants in which an alternative diagnosis is made during the active phase of the study	Number of minor and major amputations on the index foot or contralateral at the end of the follow up phase of the study	Pain as assessed by Visual Analogue Scale (VAS)
The proportion of participants that withdraw or are lost to follow up. The term 'withdrawal' encompasses two potential scenarios: withdrawal due to loss of consent or withdrawal due to death	Number and severity of falls (Hopkins Fall Grading System) (Davalos-Bichara *et al.*, 2013)	**Ability to collect resource use data - Patient diary** • Change in employment • Frequency and the amount of time participants received formal/informal care • Number of all healthcare appointments
Statistical parameters of the key outcome measures to inform a sample size calculation for a definitive trial (estimate of effect size)	The number of participants in each arm requiring further intervention for CN (e.g., further immobilisation) within 6 months of remission?	

Abbreviations
EQ-5D-5L *Euroqol 5D*
HADS *Hospital Anxiety and Depression Scale*
SF-12 *Medical Outcomes Short-Form Health Questionnaire*
VAS *Visual analogue scale*

For participants in the standard care plus arm, remission is defined as a temperature difference of ≤ 2°C which is maintained or improves on two separate consecutive occasions for a period of at least four weeks (Milne *et al.*, 2013) or at the discretion of the clinical team when temperature difference is not valid; for example, in the presence of bilateral foot disease. In the standard care plus arm, this will then trigger an MRI. In the intervention arm remission is defined as an absence of subchondral bone marrow oedema on MRI, as reported by a radiologist and the absence of clinical signs and symptoms of CN. The clinical team will interpret the results of the MRI report to determine remission.

The final visit will be six months after remission. During these six months, we will continue to monitor the foot using the standardised assessment of foot temperature for any clinical signs that the CN has relapsed. We have de-fined relapse as a temperature difference of > 2 °C compared to the contralateral foot maintained for two or more occasions or further changes on imaging. The final decision as to whether the CN has relapsed will be at the discretion of the clinical team.

We will explore the feasibility of collecting resource use and quality of life data, to inform the design of the health economics component of a future definitive trial. Data on all primary care and secondary care visits and admissions to hospital will be collected. Time off work and levels of informal care will also be assessed. We will use the qualitative interviews to gain a deeper, more detailed and rounded contextualised understanding of participants' lived experience of CN and of taking part in this study.

5.5.1 Rationale for choice of clinical outcomes

For participants in the standard care arm remission was defined as a temperature difference of ≤2°C which is maintained or improves on two separate consecutive occasions for a period of at least four weeks (Milne *et al.*, 2013) or at the discretion of the clinical team when temperature difference is not valid; for example in the presence of bilateral foot disease. In the standard care plus arm this will then trigger an MRI. In the intervention arm remission was defined as an absence of sub-chondral bone marrow oedema on MRI, as reported by a radiologist and the absence of clinical signs and symptoms of CN. The clinical team will interpret the results of the MRI report to determine remission.

The literature review highlighted the large variation in the reported time to healing for CN in the UK ranging from 3-12months (Game *et al.*, 2012). Therefore, to maximise the number of participants that were likely to go into remission during the study, and therefore have primary outcome data on 'time in cast' the study followed-up participants for a maximum of 12months, which would be the 'active phase' of the study.

We collected data on the type of off-loading participants received and the incidence of clinical outcomes which could be confounders in a future definitive trial. People treated with non-removable devices have been shown to have shorter time to remission than those treated with removable devices (Game *et al.*, 2012). The presence of ulceration, infection and amputation on the study or contralateral limb would invalidate the use of infrared thermography temperature measurement (standard care plus). Finally, the frequency of falls may affect the infrared

thermography temperature measurement and may also influence participants choice over the type of off-loading device they wear and adherence to wearing it, and thus treatment times.

After remission participants were followed-up for a further six months the 'follow-up' phase. The final visit was six months after remission. During these six months we continued to monitor the foot using the standardised assessment of foot temperature for any clinical signs that the CN has relapsed. We defined relapse as a temperature difference of >2°C compared to the contralateral foot maintained for two or more occasions or further changes on imaging. The final decision as to whether the CN has relapsed was at the discretion of the clinical team. It was important to assess whether it was feasible to collect the number of relapses as in a full trial this would be used to compare the specificity of MRI in accurately identifying remission in CN, compared to standard care.

5.5.2 Rationale for patient reported outcomes

Alongside the clinical outcomes it was also important to understand the impact of receiving treatment on people with CN and the potential value of earlier identification of remission on people's experiences and health-related quality of life. Health-related quality of life outcomes are generally collected using patient reported outcome measures in the form of multiple-choice questionnaires or scales. These patient reported outcome measures can be used to measure a variety of different things: 1) health-related quality of life gain after an intervention or procedure, 2) change in health-related quality of life over time or 3) in clinical trials to assess the effectiveness of interventions.

In this study we wanted to understand the feasibility of using a variety of PROMs collected at different time points to make recommendations on which ones and how frequently they should be completed to inform the design of a future definitive RCT. There are a variety generic, neuropathy and foot ulceration patient reported outcome measures that have been used in clinical practice and research to understand the effect of foot complications on health-related quality of life. However, only one patient reported outcome measure has been developed to assess health-related quality of life in CN, which included a modified version of the SF-36, but this tool is yet to validated (Dhawan et al., 2005). As there are no validated PROMs measures for CN, in this study we decided to use internationally validated measures of health-related quality of life. All of the PROMs we used in this study are self-administered to reduce the burden on researchers.

The first measure of health-related quality of life used in this study was the EQ-5D. This is a series of tools that can be used to describe and value people's health (Herdman et al., 2011) (appendix F). This asks people to rate their health 'today'. In England the EQ-5D is the NICE preferred measure of health-related quality of life in adults. In research the EQ-5D can be used to measure health status at different time points, before or after an intervention or overtime. It measures five dimensions of health (Table 5-3). There are two relevant versions of the EQ-5D, the EQ-5D-3L and the EQ-5D-5L. The EQ-5D-3L has three levels of perceived problems which a person can self-report, whereas the EQ-5D-5L has five. Whilst NICE advocates the use of the EQ-5D-3L when preparing case submission for NICE, it does support the use of EQ-5D-5L in prospective clinical studies (National Institute of Health and Clinical Excellence, 2019). However, in this study the EQ-5D-5L was used, and the cross walk methodology used for the analysis (Van Hout *et al.*, 2012).

The second validated measure of health-related quality of life used in this study was the SF-12 (appendix G). The SF-12 is a shortened version of the SF-36 which was developed from the medical outcomes study (Ware and Sherbourn, 1992). In this study participants were already being asked to complete the EQ-5D, therefore I chose to include the SF-12 over the SF-36 to minimise the burden on participants, which I felt may improve data completeness but still provide valid results. The SF-12 uses the same eight domains as the SF-36 to measure the impact of symptoms and disease on people's experiences over the last four weeks (Table 5-3). The results are expressed with two scores: The Physical Component Summary (PCS) Mental Component Summary (MCS).

Table 5-3 Domains for the patient reported outcomes measures

EQ-5D	SF-12	HADS
Mobility	Limitations in physical activities because of health problems	Anxiety
Self-care	Limitations in social activities because of physical or emotional problems	Depression
Usual activities	Limitations in usual role activities because of physical health problem	
Pain/discomfort	Bodily pain	
Anxiety/depression	General mental health (psychological distress and well-being)	
	Limitations in usual role activities because of emotional problems	
	Vitality (energy and fatigue)	
	General health perceptions	

Abbreviations

EQ-5D-5L	*Euroqol 5D*
HADS	*Hospital anxiety and depression scale*
SF-12	*Medical Outcomes Short-Form Health Questionnaire*

The SF-12 and the EQ-5D-5L assess emotional wellbeing, I decide to include another specific measure of depression of anxiety; The Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983) (appendix H). This tool measures the state of anxiety and depression over the 'last few days', and therefore it can be readministered at regular intervals. The analyse of the various patient reported outcomes, will inform recommendations on which ones and the frequency of reassessment that should be used in a future definitive trial.

5.6 Planned interventions

Standard care plus participants will receive standard care for the assessment and management of CN and any other foot problems; alongside this we will collect study measures. If participants have not had a recent diagnostic X-ray or MRI (within the last three weeks) this will be requested. In this study we have standardised the assessment of foot temperature to monitor CN by using the same device, the Thermofocus 01500A3®. Every 14 days the temperature of both feet will be recorded at intervals of 5 minutes, starting at the removal of the off-loading device and up to 15 minutes. The sites where the temperature will be measured are based on the classification tool developed by Sanders and Frykberg (Sanders and Frykberg, 1991). We will classify the stage of the CN using the modified (Shibata, Tada and Hashizume, 1990) Eichenholtz classification tool (Eichenholtz, 1966) and location of the CN (Sanders and Frykberg, 1991) at baseline using anterior/posterior, oblique and lateral weight bearing plain X-rays.

Intervention: In addition to standard care plus, participants in the intervention arm will receive serial MRIs at 3, 6, 9 and 12 months. Intervention participants did not undergo further MRIs once remission was diagnosed, i.e., if remission is diagnosed at 6 months the MRIs at 9 and 12 months will not occur.

5.7 Study procedures

The schedule of enrolment, interventions and assessments is shown in Figure 5-4. After reviewing the patient information sheet (see appendix I) giving written informed consent (see appendix J) participants will attend for visits every 14 days until remission. All visits will take place in or alongside multidisciplinary foot clinics. Wherever possible study measurements and study interventions will coincide with the participant's existing clinic appointments. This will reduce study burden which is likely to help increase recruitment and retention rates. The study protocol

(v1.4, dated 11th June 2020) is based on the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Statement for protocols of clinical trials.

At each visit foot temperatures were measured, and clinical outcomes such as new ulceration, foot infection, and amputation (major and minor) collected. Participants will receive a diary every fortnight to record all health and social care use (appendix K). Patient-reported outcome questionnaires EQ-5D-5L (Euroqol 5D), Medical Outcomes Short-Form Health Questionnaire (SF-12) and Hospital Anxiety and Depression Scale (HADS) measuring health-related quality of life, anxiety and depression will be collected at enrolment and every three months. We will also ask participants to record the pain in their foot/leg recorded on a visual analogue scale (appendix L). Participants will be update on the progress of the study through participants newsletter (appendix M).

Prior to participating in the interviews about the lived experience of CN, participants will receive a further patient information sheet explaining the purpose of the interview and will be asked to complete another consent form. All the qualitative interviews will be carried out by the first author (CG), using a semi-structured approach. The topic guide will include a number of probes designed to prompt the participant to increase the level of detail and depth of the information provided from the participants' own viewpoint. Interviews will last approximately 30-40 minutes in a place of the participant's choosing. The interviews will be audiotaped (with the participant's permission) and transcribed in full to capture language and their own expressions.

During the first wave of the UK COVID-19 pandemic (March-August 2020), approval was granted for sites to post questionnaires to participants and be returned to the sponsor, instead of collection during face-to-face study visits. Participants were informed about this change to the protocol through a study newsletter (appendix N). Where research visits were disrupted due to the COVID-19 pandemic, but clinical visits continued, the study sponsor approved the use of information collected from clinical visits. A list of all the REC/HRA approved protocol amendments can be found in appendix O.

Figure 5-4 Schedule of enrolment, interventions, and assessments

		Active phase* (maximum 12 months)									R	**Follow up phase			
Visit Number		0		6		11		18		26		F1	F2	F3	F4
Month		0		3		6		9		12		1	2	3	6
Enrolment															
Information sheet	*														
Consent		*													
Randomisation		*													
Participant characteristics															
Medical history		*													
HbA1c & eGFR		*													
Foot surgical history		*													
Medications		*													
Classification CN ***		*													
Foot assessment															
Foot pulses		*													
ABPI		*													
10g monofilament		*													
Neurothesiometer		*													
Foot temperatures		*	*	*	*	*	*	*	*	*	*	*	*	*	*
Treatment															
Off-loading/footwear		*	*	*	*	*	*	*	*	*	*	*	*	*	*
Interventions															
MRI (standard care plus)											*				
Serial MRI (intervention)				*		*		*		*					
Clinical outcomes															
Ulceration		*	*	*	*	*	*	*	*	*	*	*	*	*	*
Infection		*	*	*	*	*	*	*	*	*	*	*	*	*	*
Amputation		*	*	*	*	*	*	*	*	*	*	*	*	*	*
Falls		*	*	*	*	*	*	*	*	*	*	*	*	*	*
BMI		*		*		*		*		*	*				*
X-ray															*
Patient reported outcomes															
VAS - pain		*		*		*		*		*		*			*
HADS		*		*		*		*		*		*			*
EQ-5D-5L		*		*		*		*		*		*			*
SF-12		*		*		*		*		*		*			*
Health economic outcomes															
Issue patient diary		*	*	*	*	*	*	*	*	*					
Collect patient diary			*	*	*	*	*	*	*	*	*				
Qualitative research															
Interview			←	—	—	—	—	—	—	—	→				

**Active phase - while the CN is active participants will attend every 14 days, up to a maximum of 26 visits.*

***Follow up phase – once CN is in remission participants will transfer into the follow-up phase for six months.*

****Classification of CN – accordingly to the Sanders and Frykberg and the modified Eichenholtz classification tools*

Abbreviations
ABPI Ankle brachial pressure index
BMI Body mass index
CN Charcot neuroarthropathy
F Follow up visit
eGFR Estimated Glomerular Filtration rate, ml/min
EQ-5D-5L Euroqol 5D
HADS Hospital Anxiety and Depression Scale
HbA1c glycated haemoglobin (A1c), mmol/mol
MRI Magnetic Resonance Imaging
R Remission
SF-12 Medical Outcomes Short-Form Health Questionnaire
VAS Visual analogue scale

5.8 Analyses

The feasibility measures including eligibility, recruitment, retention, and withdrawals will be reported as point estimates with 95% confidence intervals. There is no intention to conduct any formal comparative analyses for these measures, though levels of missing data will be explored with respect to certain baseline characteristics, e.g., age and measures of disease severity. Variability in outcomes (e.g., standard deviation) will be estimated with 95% confidence intervals to inform the sample size calculations for a full-scale study. The primary efficacy outcome, 'time in cast', will be analysed using a Cox Proportional Hazards (PH) regression model. Analyses will be conducted using a modified Intention-To-Treat approach, excluding post-randomisation exclusions from the analysis. Two baseline covariates will be included in the model: 1) off-loading device, removable or non-removable; and 2) Eichenholtz classification, stage 0 or stage 1 (based on clinical and X-ray findings) .Any between-group efficacy analyses will only be exploratory. There are no plans for any interim analyses. The results from the all the clinical, and patient reported outcomes will be reported but will need to be interpreted with caution as this is a feasibility study with small numbers and is not powered to report these outcomes. However, they will give an early indication as to the disease burden for people receiving treatment of CN, and allow comparisons to normal populations, and other medical conditions.

The main purpose of the economic analysis is to inform how the data on costs and effects would be collected within a definitive trial. Thus, we will estimate completion rates and seek to identify big cost drivers, in order to inform this decision. A preliminary cost-effectiveness analysis will also be performed, although the findings will be treated with caution. We will use the crosswalk methodology to calculate the value sets for EQ-5D-5L (Van Hout *et al.*, 2012). As such, we will estimate the mean incremental cost and mean QALY gain associated with the intervention compared to standard care plus.

The qualitative interviews will be analysed using Inductive Thematic Analysis using the six-step model (Braun and Clarke, 2008). The first author (CG) will read all the transcribed interviews to record emerging ideas. The interviews will then be subjected to line-by-line coding using the NVivo data management package. The coding framework will be refined by a second researcher, who will cross-check it against a small sample of transcripts. A modified framework approach will be used to organise the analysis. The coded data will be subjected to a thematic analysis, identifying key categories and themes from the data, ensuring that all participants' responses are adequately captured, and their meaning authentically interpreted. This approach will provide rich descriptions of the data representing accounts of the diverse and personal experiences of people who have taken part in the study and been treated for acute CN.

5.9 Data management and quality assurance

We will set up a Study Management Group to assist with co-ordination and strategic management of the feasibility study. An initial on-site initiation visit will be completed by CG prior to the sites opening. The primary method of data collection by the research teams will be direct online entry of data on to a purpose-designed secure password-protected electronic case record form. The database complies with data protection requirements (European Parliament and Council of the European Union, 2016) on confidentiality and anonymity. Quality management and monitoring procedures were discussed and agreed with the sponsor. Central monitoring was considered appropriate for this study with the option to escalate findings and conduct 'for-cause" on-site triggered monitoring visit if indicated. We will review the completed consent forms and selected data points for quality assurance at each site within a week after randomisation of the first participant. Subsequent monitoring will be completed at six monthly intervals to coincide with the Study Management Group meetings and at the end of data collection.

5.10 Safety reporting

Safety monitoring and reporting of adverse events was discussed and agreed with the sponsor. The study has been assessed as low risk, therefore there was not a Data Monitoring Committee. The intervention consists of increased frequency of MRI scans without contrast, so a pragmatic approach to safety reporting was used. MRI scans will be performed in NHS hospitals under routine clinical protocols. Adverse events resulting from MRI scans will be reported by the

research teams in line with the Hospital Trust's clinical incident reporting policy. A copy of the anonymised incident form will be forwarded to the Chief Investigator (CG) and reviewed by the Study Management Group. All other anticipated events, e.g., ulceration, infection, amputation, pain, falls, and death will be recorded as secondary outcomes.

5.11 Discussion

CN is a poorly understood and under researched complication of diabetes, associated with increased morbidity and mortality compared to people with diabetes without peripheral neuropathy. Evidence is lacking about factors that influence the unexplained variation in treatment times, relapse rates and complications such as ulceration and amputation. We have also identified a lack of evidence to support the efficacy of current monitoring techniques in CN. There is evidence from small studies that MRI may be superior to current methods of monitoring for remission in CN, but this has not been formally evaluated using robust designs. The results of this feasibility study will inform the decision about progressing to a full-sized pragmatic randomised controlled study: the number of sites required, study design, the frequency of MRI monitoring, and the choice of process and outcome measures. The results of this study will be disseminated to researchers, healthcare professionals, people with diabetes and relevant stakeholders through presentations, publications, and social media press releases.

5.12 Conclusion

The study will inform the decision whether to proceed to a full-scale study. It will also allow deeper understanding of the lived experience of CN, and factors that contribute to engagement in management and contribute to the development of more effective patient centred strategies.

5.13 Summary

This chapter has reported the design and protocol for the feasibility study on the use of serial magnetic resonance imaging to reduced treatment times in CN in people with diabetes. The next chapter will report the results from this study.

6 A feasibility study of serial magnetic resonance imaging to reduced treatment times in Charcot neuroarthropathy in people with diabetes (CADOM). Results

6.1 Introduction

The previous chapter described the background and protocol for this feasibility study of serial MRI to reduced treatment times in CN in people with diabetes. This chapter is a copy of the feasibility study results paper which has been submitted for publication and is currently under review. There are minor edits to the chapter to ensure consistency within the thesis.

6.2 Background

CN is a relatively rare but serious complication that can affect people with peripheral neuropathy. It is most commonly diagnosed in people with diabetes, usually affecting the foot and ankle. There is uncontrolled inflammation, bones become weakened, and this can lead to fractures and joint dislocation.

In 2018 a regional survey of 205,033 people with diabetes in the East Midlands, England reported a point prevalence of 0.04% (Metcalf *et al.*, 2018). Population-based studies have estimated a life time cumulative incidence for CN of 0.4% to 1.3% in people with diabetes, and 13% in those attending diabetic foot specialist clinics (Armstrong *et al.*, 1997).

Usual care for people with CN is to offload pressure and immobilise the foot with a non-removable cast or boot (National Institute for Health and Care Excellence, 2015). This aims to stop the inflammatory process, relieve pain, and maintain foot architecture (National Institute for Health and Care Excellence, 2015). Studies from the UK and Brazil show a median time to remission of up to 12 months (Game *et al.*, 2012; Moura-Neto *et al.*, 2012; Stark *et al.*, 2016). Other studies report shorter times to remission: 3-5 months (US) (Pinzur, Lio and Posner, 2006; de Souza, 2008) and 3-6 months (Germany) (Chantelau, Kimmerle and Poll, 2007).

Guidelines for CN management state that off-loading and immobilisation should be continued until the temperature difference between the affected and unaffected foot is ≤2°C, with no further radiological changes on X-ray (Milne *et al.*, 2013). However, this recommendation is based on low quality level IV evidence– i.e., case series.

Skin temperature measured with infrared thermography is recommended as a monitoring technique in CN, as CN involves inflammation of the soft tissue and bone. Skin temperature is a proxy measure of inflammation measured over the site of injury and may not reflect the degree of inflammation within affected bones and/or joints. Plain X-rays show damage to the foot skeleton rather than disease activity and are a measure of foot deformity. In contrast, MRI provides detailed pictures of bone and soft tissue structures and can show abnormalities not evident on plain X-rays (Chantelau and Richter, 2013).

Emerging evidence from case series and observational data suggests that MRI may be useful for monitoring active CN (Schlossbauer *et al.*, 2008; Zampa *et al.*, 2011; Chantelau *et al.*, 2018). Furthermore, that MRIs findings could be adopted as the criterion standard for assessing disease activity and remission. However, evidence supporting a definitive trial is currently lacking. We conducted a study to assess the feasibility and acceptability of serial MRI and recruitment and retention of participants.

6.3 Aims and objectives

This study aims to explore the feasibility of using serial MRI without contrast in the monitoring of Charcot neuroarthropathy to reduce duration of immobilisation of the foot, in order to decide whether a large-scale trial is warranted.

6.4 Methods

Full details of the protocol are published elsewhere (Gooday *et al.*, 2020b). This was a two arm, multicentre, open, randomised controlled feasibility study. Participants were recruited from specialist diabetic foot clinics. The study was divided into two phases. Phase one, the active phase, until the CN was in remission, or a maximum of 12 months. Phase two, the follow-up phase, for six months after the apparent remission of the CN. The study was approved by East Midlands - Derby Research Ethics Committee, 04/10/2017, ref: 17/EM/0288. All participants provided written consent.

6.4.1 Participants – Inclusion and exclusion criteria

Participants were aged over 18 years old with diabetes as defined by the World Health Organisation and with a suspected or confirmed diagnosis of CN. The full inclusion and exclusion criteria are shown in Table 5-1. We decided to exclude people with a previous diagnosis of Charcot neuroarthropathy as new and relapsed cases of Charcot neuroarthropathy may have different healing times. We chose a cut off period of six-months based on the opinion of clinical experts within the trial management team, as we thought that this would ensure that only true news cases of Charcot neuroarthropathy were recruited to the study.

As a confirmed diagnosis of CN can take several weeks, participants were recruited as early as possible to accurately collect the duration of wearing an off-loading device. This was because 'time in cast' is the proposed primary outcome. If the clinical team decided on an alternative diagnosis, the participant exited the study.

6.4.2 Randomisation, blinding and data collection

Eligible participants were randomly assigned using a web-based randomisation process on a 1:1 basis to: (a) Immobilisation discontinued on the basis of clinical remission determined by skin temperature measurement, which triggered an MRI (standard care plus) or (b) Standard care plus and additionally the serial use of MRI at 3, 6, 9 and 12 months to identify disease remission and discontinuation of immobilisation (intervention).

6.4.3 Sample size

As this was a feasibility study a power calculation was not required. An allowance was made for 10-15% of participants to be withdrawn from the study due to an alternative diagnosis. We planned to recruit 60 people with 30 participants per arm, based on recommended sample sizes between 24 – 50 for a feasibility study (Sim and Lewis, 2012).

6.4.4 Study Interventions

Standard care plus participants received usual care for assessment and management of CN. We standardised assessment of foot temperature to monitor CN by using the same device, the Thermofocus 01500A3® (Tecnimed, Varese, Italy). Every 14 days a research team member measured the temperature of both feet at five different sites. Temperatures were collected four

times after removal of the off-loading device: 0, 5, 10, and 15 minutes. In this feasibility study the first reading of ≤2°C at the site overlying the CN was used as the marker for remission.

At remission participants received a study specific MRI.

Intervention: In addition to standard care plus, intervention participants received serial MRIs at 3, 6, 9 and 12 months. They did not receive further MRIs once remission was diagnosed. The median time for remission of Charcot neuroarthropathy is reported as between 3-12 months, therefore we decided that the time to first intervention MRI should reflect the shortest reported median time to remission. As this was a feasibility study, we did not seek to standardise the MRI sequencing protocol.

6.4.5 Study procedures

The schedule of enrolment, interventions and assessments is shown in Figure 5-4. Potential participants were approached when attending their regular foot clinic appointment. After giving written informed consent (appendix J) participants attended visits every 14 days until remission. Participants received usual care for CN regardless of randomisation arm. At each visit foot temperatures were measured, and clinical outcomes such as new ulceration, foot infection, and amputation (major and minor) were collected. Participants received a diary every fortnight to record all health and social care use. Patient-reported outcome questionnaires EQ-5D-5L (Euroqol 5D), Medical Outcomes Short-Form Health Questionnaire (SF-12) and Hospital Anxiety and Depression Scale (HADS)) measuring health-related quality of life, anxiety and depression were collected at enrolment and every three months.

During the first wave of the UK COVID-19 pandemic (March-August 2020), approval was granted for sites to post questionnaires to participants and be returned to the sponsor, instead of collection during face-to-face study visits. Where research visits were disrupted due to the COVID-19 pandemic, but clinical visits continued, the study sponsor approved the use of information collected from clinical visits. The main study protocol deviations are reported in Table 6-1.

Table 6-1 Main study protocol deviations

	Protocol deviations	Implications
1	Disruption to research visit schedule due to COVID-19.	Where research visits were disrupted due to the COVID-19 pandemic, but clinical visits continued, the study sponsor approved the use of information collected from clinical visits. During the first wave of the UK COVID-19 pandemic (March-August 2020), approval was granted for sites to post questionnaires to participants and be returned to the sponsor, instead of collection during face-to-face study visits.
2	Disruption to research radiology imaging due to COVID-19.	During the first wave of the UK COVID-19 pandemic, some hospitals involved in the study stopped or restricted research radiology imaging, reducing the number of completed study MRIs. This may have resulted in either an underestimation or overestimation of the 'time in cast'
3	Preliminary cost-effectiveness analysis not completed	The low completion levels for the patient diary, including a large number of missing data points, and the inability to distinguish between truly missing data or zero values that were not reported means that it was not possible to conduct the preliminary cost effectiveness analysis.
4	Sample size calculation not completed	Disruption caused by the COVID-19 pandemic reduced data and intervention completeness. This means that the current modified ITT Cox regression analysis cannot be relied upon to calculate an accurate simple size.

6.5 Outcomes

We recorded participants' characteristics and measured feasibility, clinical, patient reported, and cost-effectiveness outcomes collected through a patient diary (Table 5-2). The proposed primary outcome for a definitive study will be time to confirmed remission, recorded as off-loading treatment time measured in days. Clinical outcomes were assessed to provide an initial efficacy estimate to inform the design of a definitive study. The safety of the intervention MRI was assessed.

In standard care plus , remission was defined as a temperature difference of ≤2°C between the affected and unaffected foot which was maintained or improved on two separate consecutive occasions for a period of at least four weeks (Milne *et al.*, 2013) or at the discretion of the clinical team when temperature difference was not valid; e.g., in the presence of bilateral foot disease. This triggered a final MRI. In the intervention arm, remission was defined as an absence of sub-chondral bone marrow oedema on MRI. Relapse was defined as a temperature difference of >2°C compared to the contralateral foot maintained for two or more occasions or further changes on imaging.

6.6 Statistical analysis

Descriptive statistics were used to summarise participants' baseline characteristics and feasibility outcomes. All analyses were conducted using an Intention-To-Treat approach. Estimates of outcome variability (e.g., standard deviation) were made with 95% confidence intervals to inform future sample size calculations. The primary efficacy outcome, 'time in cast', was analysed using a Cox Proportional Hazards (PH) regression model. Analyses will be conducted using a modified Intention-To-Treat approach whereby participants identified as post-randomisation exclusions (those participants who were identified as having an alternative diagnose, and therefore failed the inclusion criteria) will be excluded from the modified Intention-To-Teat analysis. All participants with a confirmed diagnosis will be included in the analysis. Two baseline covariates were included in the model: 1) off-loading device, removable or non-removable; and 2) Eichenholtz classification, stage 0, or stage 1 (based on clinical and X-ray findings).

6.7 Results

Five sites in England participated: one in the East of England, two in the East Midlands and two in Yorkshire and Humber. Participant recruitment took place between December 2017 and November 2019. Forty-three participants were randomised, 23 to intervention and 20 to standard care plus.

6.7.1 Participant Characteristics

Baseline characteristics were similar between the two study arms. The mean age (SD) of participants was 59.1 (11.2) years, of whom 29/43 (67.4%) were male; 34/43 (79.1%) had type 2 diabetes (Table 6-2). Mean (SD) diabetes duration was 19 (11.2) years. Table 6-3 shows baseline CN characteristics. 27/43 (62.8%) of participants reported symptoms for >1-month before a consultation with the specialist multidisciplinary foot team. Common self-reported precipitating factors were concurrent ulceration or a recent trip or fall. The most frequent site for the CN was Sanders and Frykberg II (tarso-metatarsal joints). At enrolment 41/43 (95.3%) had an Eichenholtz Classification stage 0 or I. 21/43 (48.8%) participants initially received treatment with a non-removable below-knee device (Table 6-4).

Table 6-2 Baseline participant characteristics

Baseline participant characteristics	All participants		Confirmed diagnosis of Charcot	
	All randomised participants [n=43]	Confirmed diagnosis Charcot [n=30]	Standard care plus (n=16)	Intervention (n=14)
Sociodemographic				
Male n [%]	29 [67.4%]	20 [66.6%]	12 [75.0%]	8 [57.1%]
Age (yrs.) mean ± SD	59.1 ±11.2	59.2 ±10.8	59.2 ±9.4	51.5 ±10.8
Highest education n [%]	n=37	n=27	n=13	
Left school before 16	4 [10.8%]	2 [7.4%]	1 [7.7%]	1 [7.1%]
Stayed in school until 16	11 [29.7%]	8 [29.6%]	4 [30.8%]	4 [28.6%]
Stayed in education until 18	6 [16.2%]	4 [14.8%]	3 [23.1%]	1 [7.1%]
Vocational/occupational qualification	8 [21.6%]	7 [25.9%]	2 [15.4%]	5 [35.7%]
Degree	6 [16.2%]	4 [14.8%]	2 [15.4%]	2 [14.3%]
Masters	1 [2.7%]	1 [3.7%]	1 [7.7%]	0
Doctorate	1 [2.7%]	1 [3.7%]	0	1 [7.1%]
Diabetes and diabetes related complications				
Type 2 diabetes n [%]	34 [79.1%]	22 [73.3%]	12 [75%]	10 [71.4%]
Duration of diabetes (yrs) mean ± SD	19 ±11.2	20.5 ±11.3	24.6 ±13	15.8 ±6.7
HbA1c mmol/mol median [25th-75th IQR]	69 IQR 57-87	77.5 IQR 60-96	73.5 IQR 61-84	77.5 IQR 59-99
eGFR <60 n [%]	13 [30%]	9 [30%]	3 [18.8%]	6 [42.9%]
Type 1 BMI mean ± SD	30.9 ±6.3	32.1 ±5.4	33.8 ±5.9	30.6 ± 5.1
Type 2 BMI mean ± SD	32.5±7.0	32.1 ±6.5	32.2 ±7.7	32.2 ±5.2
Cerebrovascular events n [%]	4 [9.3%]	2 [6.7%]	1 [6.3%]	1 [7.1%]
Cardiovascular events n [%]	10 [23.4%]	6 [20%]	2 [12.5%]	4 [28.6%]
Nephropathy n [%]	11 [25.6%]	9 [30%]	2 [12.5%]	7 [50%]
Retinopathy n [%]	18 [41.9%]	14 [46.6%]	10 [62.5%]	4 [28.6%]
Palpation foot pulses n [%]				
No foot pulses palpable	4 [9.3%]	3 [10%]	1 [6.3%]	2 [14.3%]
One-foot pulse palpable	1 [2.3%]	0	0	0
Two-foot pulses palpable	38 [88.4%]	27 [90%]	15 [93.8%]	12 [85.7%]
Ankle Brachial Index n [%]	n=41	n=28	n=15	n=12
Ankle Brachial Index 0.5-0.79	1 [2.4%]	1 [3.6%]	1 [6.3%]	0
Ankle Brachial Index 0.8-0.99	4 [9.8%]	3 [10.7%]	0	3 [25%]
Ankle Brachial Index 1.0-1.4	31 [75.6%]	22 [78.6%]	13 [81.3%]	9 [75%]1
Ankle Brachial Index >1.4	5 [12.2%]	2 [7.1%]	2 [12.5%]	0

Table 6-2 Baseline participant characteristics (continued)

Baseline participant characteristics	All participants		Confirmed diagnosis of Charcot	
	All randomised participants [n=43]	Confirmed diagnosis Charcot [n=30]	Standard care plus (n=16)	Intervention (n=14)
Monofilament perception n [%]				
-ve at 3/3 sites	33 [76.7%]	24 [80%]	13 [81.3%]	11 [78.6%]
-ve at 2/3 sites	4 [9.3%]	0	0	0
-ve at 1/3 sites	1 [2.3%]	2 [6.7 %]	1 [6.3%]	1 [7.1%]
+ve at all sites n [%]	5 [11.6%]	4 [13.3%]	2 [12.5%]	2 [14.3%]
Hallux (≥25volts)	23 [79.3%]	19 [86.4%]	10 [90.9%]	9 [81.8%]
Previous or current foot complications n [%]				
Previous minor amputation index foot	7 [16.3%]	5 [16.7%]	4 [25%]	1 [7.1%]
Previous minor amputation contralateral foot	5 [11.6%]	4 [13.3%]	3 [18.8%]	1 [7.1%]
History of previous Charcot either foot	6 [14%]	6 [20%]	3 [18.8%]	3 [21.4%]
Ulceration at enrolment on index foot	12 [27.9%]	7 [23.3%]	5 [31.3%]	2 [14.3%]
Ulceration at enrolment on contralateral foot	1 [2.3%]	0	0	0

Abbreviations
BMI Body mass index
eGFR Estimated Glomerular Filtration rate, ml/min
HbA1c Glycated haemoglobin (A1c), mmol/mol

Table 6-3 Baseline Charcot neuroarthropathy characteristics

Charcot characteristics	**All participants**		**Confirmed diagnosis of Charcot**	
Characteristics	**All randomised participants [n=43]**	**Confirmed diagnosis Charcot [n=30]**	**Standard care plus (n=16)**	**Intervention (n=14)**
Location of Charcot n [%]				
Right foot	23 [53.5%]	17 [56.7%]	9 [[56.3%]	8 [57.1%]
Left foot	20 [46.5%]	13 [43.3%]	7 [43.8%]	6 [42.9%]
Duration of signs and symptoms of inflammation prior to diagnosis n [%]				
0-2 weeks	4 [9.3%]	3 [10%]	3 [18.8%]	0
2-4 weeks	12 [27.9%]	6 [20%]	1 [6.3%]	5 [35.7%]
>1 month	20 [46.5%]	17 [56.7%]	10 [62.5%]	7 [50%]
>3 months	6 [14%]	3 [10%]	1 [6.3%]	2 [14.3%]
> 6 months	1 [2.3%]	1 [3.3%]	1 [6.3%]	0
Potential precipitating factors ≤6 months prior to Charcot (participants could have multiple precipitating factors)				
Trip/fall	10	6	1	5
Trauma	9	7	4	3
Limb/foot surgery	2	1	1	0
Ulceration	12	7	4	3
Other suspected cause Charcot	3	1	1	0
Sanders and Frykberg Classification (participants could have multiple sites in the foot at randomisation)				
I	11	7	4	3
II	23	17	7	10
III	8	7	1	6
IV	5	4	1	3
V	0	0	0	0
Unknown	8	5	5	0
Eichenholtz classification n [%]				
Stage 0 - Prodromal	29 [67.4%]	19 [63.3%]	12 [75%]	7 [50%]
Stage I – Developmental	12 [27.9%]	11 [36.7%]	4 [25%]	7 [50%]
Stage II - Coalescence	2 [4.7%]	0	0	0
Stage III - Reconstruction	0	0	0	0

Table 6-4 Off-loading and immobilisation devices provided at enrolment

Off-loading device at baseline n [%]	**All participants**		**Confirmed diagnosis of Charcot**	
	All randomised participants [n=43]	**Confirmed diagnosis Charcot [n=30]**	**Standard care plus (n=16)**	**Intervention (n=14)**
Non-removable device	21 [48.8%]	15 [50%]	9 [56.3%]	6 [42.9%]
Removable device	21 [48.8%]	15 [30%]	7 [25%]	8 [35.7%]
Bespoke Footwear	1 [2.3%]	0	0	0
Additional walking aids provide n [%]				
Crutches/walking sticks	15 [34.9%]	10 [33.3%]	7 [43.8%]	3 [21.4%]
Wheelchair	1 [2.3%]	1 [3.3%]	0	1 [7.1%]

6.7.2 Feasibility Outcomes

6.7.2.1 Eligibility

Participants were approached during routine foot clinic visits. 64/105 (60.9%) potential participants met the eligibility criteria. Nine participants had multiple reasons for ineligibility (Table 6-5). The main reason was a history of CN within the last six months. Of the potentially eligible participants 43/64 (67.2%) agreed to study participation.

Table 6-5 Main reasons for ineligibility

Main reasons for ineligibility *	**Number of participants excluded**
Participants who are unwilling and/or do not have capacity to give informed consent.	21
Absence of new or suspected diagnosis of acute Charcot (no previous incidence of acute Charcot within the last 6 months on the same foot) treated with off-loading	21
Active osteomyelitis at randomisation	8
Contradiction for MRI	8
Treatment for previous suspected Charcot on the same foot in the last 6 months	7
People who have received a transplant and others receiving immunosuppressant therapy or using long term oral glucocorticoids other than in the routine management of glucocorticoid deficiency. People on a low dose of oral glucocorticoids (<10mgs for ≤7 days) are eligible to participate in the study.	6
Suspected or confirmed bilateral active Charcot at presentation	5
People without diabetes as defined by the WHO criteria	3
People receiving palliative care	1
Previous contralateral major amputation	1
Participation in another intervention study on active Charcot	1
Unable to understand written and verbal instructions in English	0
Aged <18 years	0

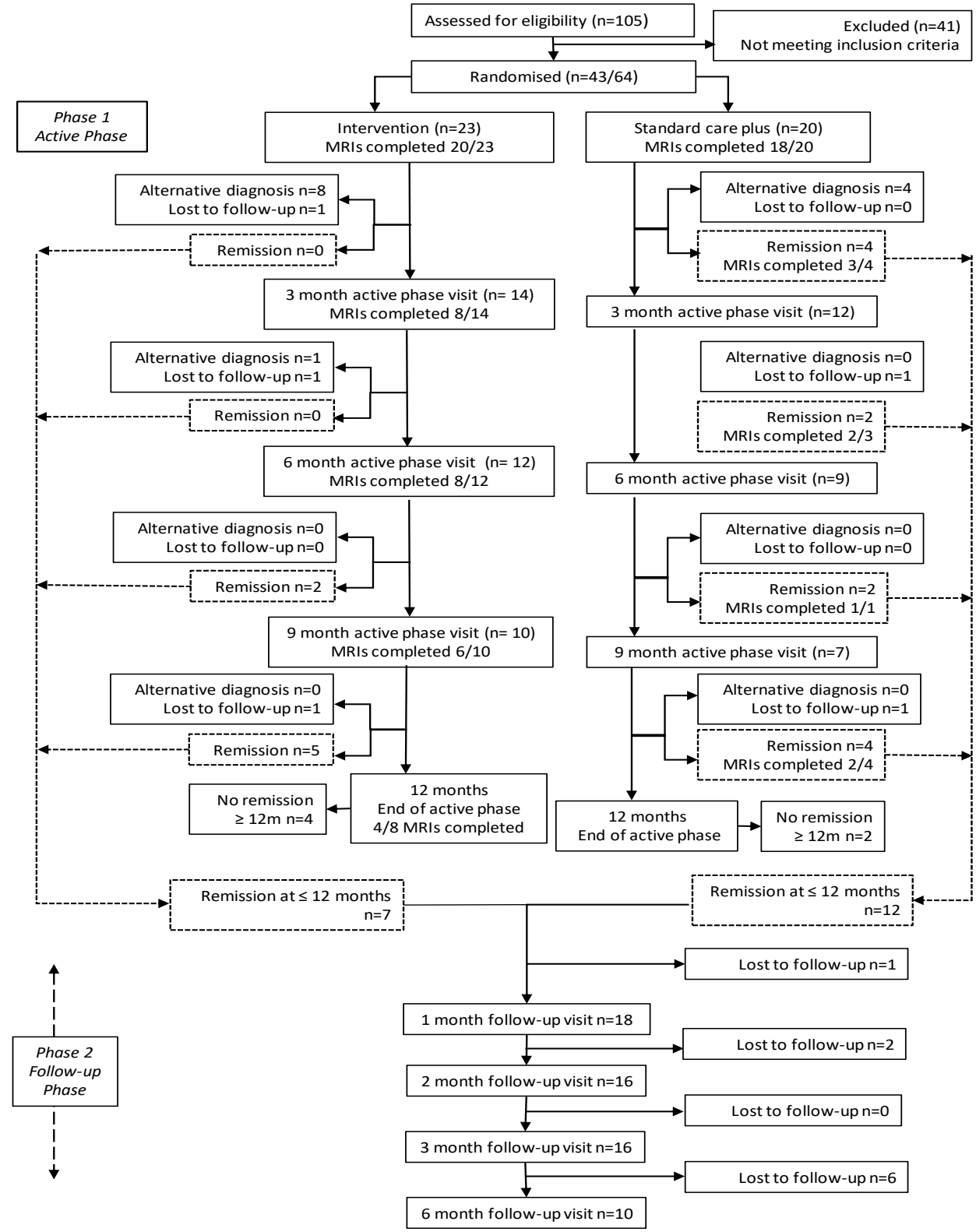
[*]Some participants did not meet more than one eligibility criteria
Abbreviations WHO World Health Organisation
MRI Magnetic Resonance Imaging

6.7.2.2 Participant retention

Figure 6-1 shows the CONSORT diagram. 30/43 (69.7%) participants received a confirmed CN diagnosis, the remaining 13 (30.3%) exited the study due to an alternative diagnosis (3 stress fracture, 2 osteoarthritis, 2 infection, 1 soft tissue injury, 5 not reported). Of the 30 participants with a confirmed CN diagnosis, 19 (63.3%) went into remission, and 5 were lost to follow-up (2 relocated, 2 due to COVID-19 and 1 unknown). Six (20.0%) did not achieve remission at the end of the 12-month active phase. They did not progress into the follow-up phase but were included in analyses. During the six-month follow-up phase, two participants experienced a relapse, one in each study arm.

Figure 6-1 Consort diagram

*



**Participants transferred from the active phase to the follow-up phase of the study once the CN was assessed as in remission. Therefore, the total number of participants decreases over the 12-month active phase. Only participants who achieved remission within the 12-month active phase of the study entered the follow-up phase of the study*

6.7.2.3 Adherence to study procedures

During the active phase, 469/497 (94.4%) of visits not disrupted by COVID-19 pandemic were completed. 438/497 (88.1%) of study visits were completed in the one-week timeframe window 79 visits were partially or completely disrupted by COVID-19 (Table 6-6).

Table 6-6 Number of study visit completed

Visit outcome*	**Active phase n=576**	**Follow-up phase n=80**
Number of completed visits	469 [81.4%]	49 [61.3%]
Number of visits completed within timeframe window**	438 [87%]	36 [60%]
Number of partially completed***	34 [5.9%]	11 [13.8%]
Number of missed visits	28 [4.9%]	1 [1.3%]
Number of missed visits (due to COVID-19)	45 [7.8%]	19 [23.8%]

** For those participants with a confirmed diagnosis of Charcot neuroarthropathy*
*** The study protocol allowed for a one-week window to complete a visit either side of the actual visit due date*
****A partially completed visit occurred where research visits were disrupted due to the COVID-19 pandemic, but clinical visits continued, and information collected from clinical visits was used for the study*

For participants with a confirmed CN diagnosis, 26/31 (83.9%) of MRIs that were not disrupted by COVID-19 pandemic were completed (Table 6-7). It is not known why the remaining five did not go ahead. A further twelve were missed due to changed research radiology priorities during the COVID-19 pandemic. Of the MRIs that went ahead, 16/26 (61.5%) were undertaken within the two-week window; the median time for the remaining ten was 20 days either side of the 14-day window (range -30 to +48 days). Nine non-study MRIs were completed in each study arm; no data are available on which foot they concerned.

Table 6-7 Number of intervention MRIs completed

MRI outcome	**Active phase***				
	0	**3m**	**6m**	**9m**	**12m**
Total completed [%]	13/14 [92.9%]	8/13 [61.5%]	8/12 [66.7%]	6/10 [60%]	4/8 [50%]
Missed MRI [%]	1/14 [7.1%]	4/13 [30.8%]	0	1/10 [10%]	0
Missed [%] (due to COVID-19)	0	1/13 [7.8%]	4/12 [33.3%]	3/10 [30%]	4/8 [50%]
Completed in timeframe window [%]**	NA	6/8 [75%]	4/8 [50%]	4/6 [66.7%]	2/4 [50%]

**Participants randomised to serial MRIs did not undergo a further MRI once remission had been diagnosed. Therefore, the total number of MRIs decreased over the 12-months.*

*** The study protocol allowed for a two-week window to complete the MRI either side of the actual MRI due date*

Abbreviations
MRI Magnetic Resonance Imaging

6.7.3 Clinical and safety outcomes

In this feasibility study there was no statistical difference in the time in off-loading device between the two arms of the study: Hazard Ratio (HR) 0.405 (95% CI 0.140-1.172), p=0.096 (Table 6-8). Participants who were provided with a non-removable device went into remission sooner than those treated with a removable device: HR 0.285 (95% CI 0.107-0.758), p=0.012. The Eichenholtz classification at baseline did not affect time to healing: HR 1.083 (95% CI 0.349-3.362), p=0.890. All 30 participants with a confirmed diagnosis of CN were included in the Cox regression analysis hazard model. This model allows for the data for participants who did not achieve remission within the 12month active phase of the study and those who were lost to follow-up to be included in the analysis but censored.

Table 6-8 Cox regression analysis on time in cast (days)

Enrolment	**Covariates**	**Time in cast (days)**		**p-value**	**Hazard Ratio**	**95.0% CI**	
n=30		**Mean**	**SD**			**Lower**	**Upper**
Randomisation arm	Intervention	292.6	±108.3	0.096	0.405	0.140	1.172
	Standard care plus	235.2	±117.4				
Off-loading device	Non-removable	198.6	±117.8	0.012	0.285	0.107	0.758
	Removable	325.3	±70.3				
Eichenholtz stage	Stage 0	267.5	±108.5	0.890	1.083	0.349	3.362
	Stage I	252.4	±130.4				

One participant in the standard care plus arm was admitted to hospital because of foot complications; no minor or major amputations were reported. Thirty-eight ulcerations were recorded on 19 participants during the active phase, of which 12 were attributed to the off-loading device. Participants reported 84 falls, six required outpatient medical attention, and a further four hospital admissions. No adverse events associated with the intervention (MRI scans) were reported.

It has not been possible to complete the sample size calculation as planned. During the first wave of the UK COVID-19 pandemic, some hospitals involved in this study stopped or restricted

research radiology imaging. Participants in this study were identified as in a 'clinical extremely vulnerable' group and were therefore advised by the UK government not to attend non-essential study visits. Both of these factors reduced data and intervention (MRI) completeness and the clinical and patient reported outcomes that were collected. In addition, some clinical teams decided to transfer participants from non-removable off-loading device to removable off-loading devices to reduce the number of clinical appointments they needed to attend during the COVID-19 pandemic. Removable off-loading devices are associated with longer treatment times than non-removable off-loading devices.

All of these factors may have resulted in either an underestimation or overestimation of the 'time in cast'. It is not possible to know whether both arms of the trial were equally affected. With these limitations the current modified Intention-To-Treat Cox regression analysis on 'time in cast' (measured in days) cannot be relied upon to calculate an accurate sample size for a future definitive trial.

To address these limitations, I plan to carry out a further review of the data to understand the adherence to the study protocol pre, during and post COVID-19, and the potential impact this may have had on the clinical outcome 'time in cast'. I will re-analyse the data using a per protocol analysis to mitigate for the impact of the COVID-19 pandemic on data and intervention completeness, and outcomes. I will review the literature and use a focus group to work with PPI, healthcare professionals, and statisticians to agree the minimally important clinical difference for a reduction in 'time in cast'. This information will then be used in a future sample size calculation.

6.7.4 Patient reported outcomes

For the visits that were conducted face-to-face, completion rates of patient-reported outcome measures were between 71-100% (Table 6-9). The results of the patient-reported outcomes are shown in Table 6-10. Half of the participants reported anxiety and depression scores higher than normal levels. The majority of participants scored (well) below normal levels for the physical component score, and just under half scored (well) below normal for the mental component score are, Kosinski and Keller, 1996). Nearly all participants reported pain and problems with mobility and completing usual activities. The EQ-5D index calculated using the crosswalk mechanism and self-rated health status was lower than that for aged-matched population (Kind, Hardman and Macran, 1999).

Table 6-9 Completion rates of patient reported outcome measures for pain, depression and anxiety and quality of life.

	Active phase (until remission or maximum 12 months) *					**Follow-up phase ****	
	0	**3m**	**6m**	**9m**	**12m**	**1m FU**	**6m FU**
Visits completed	30	26	18	14	7	14	10
VAS – pain							
Completed	30 [100%]	23 [88%]	18 [100%]	11 [79%]	5 [71%]	13 [93%]	9 [90%]
Partially completed	0	0	0	0	0	0	0
Missed at visit	0	3 [12%]	0	3 [21%]	2 [29%]	1 [7%]	1 [10%]
Hospital Anxiety and Depression Scale (HADS) – Anxiety							
Completed	26 [87%]	21 [81%]	18 [100%]	10 [71%]	7 [100%]	12 [86%]	9 [90%]
Partially completed	0	1 [4%]	0	0	0	0	0
Missed during visit	4[13%]	4[15%]	0	4[29%]	0	2[14%]	1 [10%]
Hospital Anxiety and Depression Scale (HADS) – Depression							
Completed	26 [87%]	22 [85%]	17 [94%]	10 [71%]	7 [100%]	13 [93%]	9 [90%]
Partially completed	0	0	1 [6%]	0	0	0	0
Missed during visit	4 [13%]	4 [15%]	0	4 [29%]	0	1 [7%]	1 [10%]
EQ-5D-5L index							
Completed	30 [100%]	23 [88%]	18 [100%]	10 [71%]	5 [71%]	13 [93%]	9 [90%]
Partially completed	0	1 [4%]	0	1 [7%]	0	0	0
Missed during visit	0	2 [8%]	0	3 [21%]	2 [29%]	1 [7%]	1 [10%]
SF-12							
Completed	29 [97%]	23 [88%]	17 [94%]	11 [79%]	6 [86%]	13 [93%]	9 [90%]
Partially completed	1 [3%]	1 [4%]	1 [6%]	0	1 [14%]	0	1 [10%]
Missed during visit	0	2 [8%]	0	3 [21%]	0	1 [7%]	0

**Participants transferred from the active phase to the follow-up phase of the study once the CN was assessed as in remission. Therefore, the total number of participants decreases over the 12-month active phase.*

***Only participants who achieved remission within the 12-month active phase of the study transferred into the follow-up phase of the study.*

Abbreviations

EQ-5D-5L Euroqol 5D
FU Follow up phase
HADS Hospital Anxiety and Depression Scale
SF-12 Medical Outcomes Short-Form Health Questionnaire
VAS Visual analogue scale

Table 6-10 Patient reported outcome measures for pain, depression and anxiety and quality of life.

	Active phase (until remission or max 12 months) *					Follow-up phase**	
	0	**3m**	**6m**	**9m**	**12m**	**1m FU**	**6m FU**
VAS – pain n=	**30**	**23**	**18**	**11**	**5**	**13**	**9**
mean ±SD	18.97 ±29.41	20.70 ±26.02	13.94 ±19.32	12.73 ±19.76	15.60 ±25.58	15.92± 23.69	21.89 ±23.28
Hospital Anxiety and Depression Scale (HADS) n= [%]							
HADS – Anxiety	26	21	18	10	7	12	9
mean ±SD	7.50 ±4.15	7.71 ±5.02	6.89 ±5.41	7.00 ±4.57	6.57 ±4.58	4.25 ±3.62	3.78 ±3.70
Normal score ≤7	13 [50%]	10 [48%]	9 [50%]	6 [60%]	4 [57%]	9 [75%]	7 [78%]
Borderline risk	7 [27%]	5 [27%]	5 [28%]	2 [20%]	1 [14%]	0 [%]	1 [11%]
Intermediate risk	6 [23%]	6 [23%]	4 [22%]	2 [20%]	2 [29%]	3 [25%]	1 [11%]
HADS – Depression	26	22	17	10	7	13	9
mean ±SD	6.69 ±4.27	7.32 ±5.09	6.53 ±5.44	8.30 ±4.37	7.57 ±6.00	4.54 ±4.05	5.00 ±4.47
Normal score ≤7	16 [62%]	14 [64%]	10 [59%]	5 [50%]	3 [43%]	9 [69%]	7 [78%]
Borderline risk	5 [19%]	2 [9%]	3 [18%]	3 [30%]	2 [29%]	3 [23%]	0
Intermediate risk	5 [19%]	6 [27%]	4 [24%]	2 [20%]	2 [29%]	1 [8%]	2 [22%]
EQ-5D-5L n= [%]							
Mobility	30	24	18	11	5	13	9
No problems	1 [3%]	3 [13%]	1 [6%]	0	1 [20%]	2 [15%]	0
Some problems	29 [97%]	21 [88%]	17 [94%]	11 [100%]	4 [8O%]	11 [85%]	9 [100%]
Self-care	30	23	18	11	5	13	9
No problems	15[50%]	7 [30%]	7 [39%]	3 [27%]	2 [40%]	7 [54%]	5 [56%]
Some problems	15 [50%]	16 [70%]	11 [61%]	8 [73%]	3 [60%]	6 [46%]	4 [44%]
Usual activities	30	24	18	10	5	13	9
No problems	2 [7%]	2 [8%]	1 [6%]	0	1 [20%]	2 [15%]	0
Some problems	28 [93%]	22 [92%]	17 [94%]	10 [100%]	4 [80%]	11 [85%]	9 [100%]
Pain/discomfort	30	24	18	11	5	13	9
No problem	6 [20%]	6 [25%]	4 [22%]	3 [27%]	2 [40%]	8 [62%]	3 [33%]
Some problems	24 [80%]	18 [75%]	14 [78%]	8 [73%]	3 [60%]	5 [38%]	6 [67%]
Anxiety/depression	30	24	18	11	5	13	9
No problems	11 [37%]	10 [42%]	7 [39%]	4 [36%]	2 [40%]	8 [62%]	6 [67%]
Some problems	19 [63%]	14 [58%]	11 [61%]	7 [64%]	3 [60%]	5 [38%]	3 [33%]

Table 6-10 Patient reported outcome measures for pain, depression and anxiety and quality of life (continued)

	Active phase (until remission or max 12 months)*					Follow-up phase**	
	0	**3m**	**6m**	**9m**	**12m**	**1m FU**	**6m FU**
Index value	30	23	18	10	5	13	9
Mean ±SD	0.525 ±0.23	0.565 ±0.26	0.531 ±0.24	0.562 ±0.23	0.597 ±0.32	0.68 ±0.19	0.628 ±0.17
Health today	29	24	18	11	5	13	9
Mean ±SD	62.83 ±21.03	66.79 ±22.48	64.89 ±24.83	77.18 ±13.39	71.00 ±28.15	77.77 ±14.35	67.22 ±18.22
SF-12 n= [%]	29	23	17	11	6	13	9
Physical component score (PCS) mean ±SD	37.42 ±7.18	38.44 ±7.43	37.25 ±7.34	39.56 ±5.43	40.48 ±9.0	39.71 ±10.77	34.47 ±8.06
Same or better	5 [17%]	5 [22%]	1 [6%]	2 [18%]	2 [33%]	4 [31%]	2 [22%]
Below	4 [14%]	2 [9%]	6 [35%]	4 [36%]	1 [17%]	2 [15%]	1 [11%]
Well below	20 [69%]	16 [70%]	10 [59%]	5 [45%]	3 [50%]	7 [54%]	6 [67%]
Mental component score (MCS) mean ±SD	45.08 ±11.58	46.44 ±12.6	45.61 ±13.57	43.02 ±12.91	41.04 ±13.05	52.49 ±11.54	35.92 ±10.77
Same or better	15 [52%]	15 [65%]	10 [59%]	6 [55%]	2 [33%]	9 [69%]	6 [67%]
Below	5 [17%]	1 [4%]	0	2 [18%]	0	2 [15%]	1 [11%]
Well below	9 [31%]	7 [30%]	7 [41%]	3 [27%]	4 [67%]	2 [15%]	2 [22%]

**Participants transferred from the active phase to the follow-up phase of the study once the CN was assessed as in remission. Therefore, the total number of participants decreases over the 12-month active phase.*

***Only participants who achieved remission within the 12-month active phase of the study transferred into the follow-up phase of the study.*

Abbreviations

EQ-5D-5L Euroqol 5D
FU Follow up phase
HADS Hospital Anxiety and Depression Scale
SD Standard deviation
SF-12 Medical Outcomes Short-Form Health Questionnaire
VAS Visual analogue scale

6.7.5 Patient diary and cost-effectiveness analysis

To measure levels of informal and formal care the patient diary asked participants to record the level of support they received with completing activities of daily living such as washing, getting dressed, shopping and cleaning. The completion rate for this section of the diary was 435/626 (69.5%). In addition to this participants were also asked to record the details and costs associated with any healthcare appointments they attended. The completion rate for this section of the diary was 314/626 (50.2%). The design of the patient diary (absence of yes/no question) means that it is not possible to tell whether data was truly missing or whether zero values have not been reported. Five participants reported job changes during the study. During the active phase,

participants reported a mean of 18.4 visits per participant. 61.8% of appointments concerned the foot. Nineteen participants reported they needed help on 599 occasions ranging from 5-900 minutes per week. Common tasks requiring help were shopping, cleaning, and bathing.

There was insufficient data to conduct the planned preliminary cost effectiveness analysis. This was because of the low completion rate for the patient diary, which included many missing data points, and the inability to distinguish between truly missing data or zero values that were not reported.

6.8 Discussion

This feasibility study recruited 43 participants with a suspected or confirmed CN diagnosis. Despite not achieving the recruitment target of 60 participants, and study interruptions due to the COVID-19 pandemic, our sample size was sufficiently large enough to draw conclusions about the feasibility of a definitive trial.

Our participants were representative of the wider CN population, with more males, being in their fifties, and diabetes duration of greater than ten years (Petrova, Foster and Edmonds, 2004). In this study the most common site for the CN was Sanders and Frykberg II (tarsometatarsal joints), this is consistent with other studies (Game *et al.*, 2012). The main reason for ineligibility was a previous CN within the last six months. I argue that it is not possible to reduce this as it may affect the results with the inclusion of relapsed CN, which may have different healing times to new cases.

Two-thirds of eligible participants agreed to take part. I recruited similar participant numbers to observational studies on monitoring techniques (Zampa *et al.*, 2011; Moura-Neto *et al.*, 2012; Wu *et al.*, 2012) and recent randomised controlled trials on pharmacological treatment of CN (Das *et al.*, 2019; Petrova *et al.*, 2021). More participants than anticipated were withdrawn from our study due to an alternative diagnosis. This reflects the difficulty in diagnosing CN at Eichenholtz stage 0. During the active phase the attrition rate was 11.6% which is within acceptable limits and does not affect the results of this study (Schulz and Grimes, 2002).

Two-thirds of participants had an Eichenholtz Classification stage 0 at baseline with no changes on X-ray. This highlights the need to use MRI as an adjunct to plain X-rays in CN diagnosis and monitoring. Excluding the effect of COVID-19 pandemic on MRIs, 83.9% intervention MRIs were

completed, and no safety incidents reported. This supports the feasibility, safety, and participants' acceptability of serial MRIs.

During the first wave of the UK COVID-19 pandemic, some hospitals involved in the study stopped or restricted research radiology imaging, reducing the number of completed study MRIs. This may have resulted in either an underestimation or overestimation of the 'time in cast'.

Participants experienced multiple episodes of concurrent ulceration and infection. This highlights the previously recognised limitations of using infrared thermography to monitor CN. If similar findings were replicated in a definitive trial this further justifies the need to use MRI as a monitoring technique for CN. The non-study MRIs that were completed may be contamination, diluting the relationship between intervention and outcome. We do not know whether these MRIs reflected a change in practice due to study participation.

Our participants were considered a 'clinically vulnerable' group and advised by the UK government to only attend essential clinical visits which excluded study visits. Consequently, the end point 'time in cast' and other outcomes were not always collected. Some clinical teams transferred participants from non-removable to removable offloading devices to reduce the number of follow-up appointments. Wearing removable devices is associated with increased time to remission (Game *et al.*, 2012). This may have increased the end point 'time in cast'. We do not have data on whether the two arms of the study were equally affected by this.

The results related to patient-reported outcomes need to be interpreted with caution: this is a feasibility study not powered to detect between-group or longitudinal differences. We showed that receiving treatment for CN has physical, emotional, and socioeconomic ramifications and are results are consistent with others (Raspovic and Wukich, 2014). The minimum clinically important difference for EQ-5D has been estimated to be 0.03 (Coretti, Ruggeri and McNamee, 2014). The increase in EQ-5D scores observed in this study shows that using serial MRI to diagnose CN remission has potential to be cost-effective. We also showed the important and unrecognised burden of informal care for people with CN. In a definitive trial we will seek to capture the cost of this informal care and include this in a cost effectiveness analysis.

6.8.1 Strengths and limitations

The strength of this study is the recruitment of study participants who are representative of the wider population of people living with CN. The COVID-19 pandemic reduced data and intervention completeness and the clinical and patient reported outcomes that were collected. One potential limitation of this study was that MRI sequencing protocol was not standardised; however, this study did not seek to provide a definitive answer as to the efficacy of using serial MRI to diagnosis remission in CN so was not necessary. In a future definitive trial, we will seek to standardise the MRI sequence protocol.

6.9 Conclusion

This study has shown that it is justified and feasible to carry out a fully powered definitive trial to evaluate the effectiveness of MRI in disease monitoring in CN.

6.10 Summary

Chapters 5 and 6 reported the protocol and results for the feasibility study. The next chapter will report the methods and findings of the embedded qualitative study.

7 A qualitative study to explore the participants' lived experience of Charcot neuroarthropathy.

7.1 Introduction

The previous chapter reported the feasibility study results. This chapter reports the aims, methods, findings, and discussion of the convergent qualitative study to understand people's experiences of living with CN. An article based on this chapter has been published (appendix P) (Gooday *et al.*, 2022).

7.2 Background

Chapter 2, the background highlighted what is currently known about the lived experience of CN. Improving our understanding of diabetic foot complications and CN is extremely important given the increasing prevalence of diabetes and diabetic foot disease, which has been shown to cost the NHS in England more than the combined cost of breast, prostate and lung cancers (Kerr *et al.*, 2019). Diabetic foot complications place financial burden on people with diabetes (Fejfarová *et al.*, 2014), their families, and the healthcare sector (Kerr *et al.*, 2019). Diabetic foot complications have also been shown to be associated with increased levels of morbidity and to be potentially life shortening or even life-threatening (Moulik, Mtonga and Gill, 2003).

To date qualitative research around diabetic foot complications has focused on people's experiences of preventing and managing foot ulceration and amputation. The physical and emotional burden of diabetic foot ulceration is considerable: 32% of people are depressed and this is associated with a three-fold greater risk of mortality (Ismail *et al.*, 2007). A qualitative meta-synthesis of 42 papers on the patient's perceptions and experiences of diabetic foot care and ulceration identified several themes: understanding ulceration, prevention, knowledge, attitudes and behaviours, health care experiences, development of ulceration and the effect of ulceration. In this review foot ulceration was found to have significant and long-term effect with physical, social, vocational, psychological, and interpersonal consequences. The importance of the patient's perspective in successfully promoting engagement in the prevention and management of diabetic foot ulceration has been widely recognised (Vileikyte, 2008; McInnes *et al.*, 2011; Vedhara *et al.*, 2014). Interviews with people who have previously experienced a foot ulceration shows they perceived a lack of control over preventing foot complications which, in turn, negatively influences behaviour and emotional responses to the threat of re-ulceration (Beattie, Campbell and Vedhara, 2014). A qualitative study emphasised the importance of

understanding the wider social circumstances to ensure effective support is given to people with foot ulceration or amputation (Delea *et al.*, 2015).

The only evidence about the effect of living with CN comes from quantitative findings about changes in anxiety, depression, and quality of life, rather than understanding people's lived experience. There is a need to understand whether the themes identified in qualitative research into the experience of diabetic foot ulceration are common to both conditions. A systematic review into measures of health-related quality of life in diabetes related foot disease concluded that more in-depth research is needed into the lived experiences of people with CN (Hogg *et al.*, 2012). More in-depth research into the health-related quality of life of people with CN was also recommended in the NICE guidelines, Diabetic foot problems: prevention and management (National Institute for Health and Care Excellence, 2015). To the best of my knowledge there are no published qualitative studies among people living with CN. A more detailed and nuanced understanding of how people live with CN could lead to more effective and constructive relationships between people and healthcare professionals.

In this qualitative study I therefore aimed to explore the expressed thoughts, emotions, and views of people receiving treatment for and living with CN and how this may affect the individual, their families, and their relationships. The objectives are to explore:

1. The perceived effect of CN on day-to-day functional activities.
2. The effect of living with CN on social participation.
3. How receiving treatment for CN may affect people's relationships with family, friends, and colleagues.
4. The effect of these experiences on people's sense of self and self-worth.

7.3 Methods

The background chapter highlighted that there are no published qualitative studies on CN. To address this research gap, this study sought to capture the participants' experiences of living with CN. Data were collected using semi-structured interviews to collect participant's own opinions, thoughts, views, emotions, and practises, and to identify meanings that they may attribute in different CN-related areas of experience:

1. The effect of CN on day-to-day functional activities, employment, leisure pursuits, ability to be physical active, sense of self and self-worth, and social participation.
2. How, receiving treatment for CN may have affected their relationships with family, friends, and colleagues.
3. Whether wearing the cast or boot led to any issues they saw as important to them.
4. What they thought the effect of this current episode of CN would be in the future.

7.3.1 Ethical approval

Health Research Authority and Research Ethics Committee approval for the study was received on 4th October 2017 (appendices D and E); registration no: IRAS 222668.

7.3.2 Topic guide

My previous knowledge and experience as a healthcare professional and researcher, and the literature review findings informed the initial framework for the development of this topic guide (Hunt, 2009). To ensure the topic guide resonated with people, I shared it with people with diabetes who had previous experience of foot complications and CN and with members of a local Public and Patient Involvement in Research Group (PPIRes). I asked for feedback on the wording of the questions and any topics that were missing. The feedback informed small changes to the topic guide: I decided to ask participants' about the reactions of people they met whilst wearing the cast, and why they thought people reacted in these ways. The PPIRes group recommended including a question about participants' experiences of having the MRI. They saw it as important to understand whether the intervention, having an MRI, would be acceptable to people before moving forward to design a full randomised controlled study. A copy of the topic guide can be seen in appendix Q.

7.3.3 Sampling

Participants were able to choose the venue for the interview, either at their hospital to coincide with an appointment or in their own home. I invited a purposive sample of 10-14 participants of the feasibility study who were able to offer maximally varying experiences. The sample size was limited to 10-14 based on recommendations in the literature for strategic and practical reasons of ensuring adequate information power (Malterud, Siersma and Guassora, 2016).

I identified five participant characteristics which purposively informed the sampling framework to maximise variation: gender, age, history of previous foot complications, duration of treatment for the current episode of CN, and employment status.

Although participants were not specifically encouraged to attend the interview with a spouse or family member, some participants were accompanied to the interview. With the participant's agreement they contributed to the discussion.

My initial strategy was to interview participants at the end of the active phase of the feasibility study, once they had gone into remission. However, I realised that this approach would produce a less meaningful sample and inadvertently restrict diversity as it would only include participants' whose foot had healed. It would also rely on participants' ability to accurately recall their thoughts and experiences from diagnosis until remission, which may have been 12 months ago. Participants' may recall things differently when they know that their foot has healed compared to when the outcome is uncertain. To address this issue, I submitted a substantial amendment and updated the protocol, so that new participants in the feasibility study could be interviewed at any point after consenting. The Research Ethics Committee agreed that I could inform participants already involved in the study about the amendment by a study newsletter thus allowing them to be contacted earlier about participating in the interview (appendix R).

Prior to participants completing the informed consent form for the feasibility study, they were asked to consent to being contacted by the research team to discuss the possibility of participating in the interviews. Participants who consented to participate in the interviews were contacted by the study sites either by telephone or asked during study visits if they would still like to be involved in the interviews. During the feasibility study visit participants were given a Patient Information Sheet (appendix S) by researchers at the site specifically designed to inform participants about the interview. On the day of the interview, I obtained written informed consent (appendix T).

7.3.4 Data collection

I carried out all interviews in hospital consultation rooms over six months: August 2019-January 2020. After the participant's consent I audio-recorded the interviews. They were transcribed by an experienced transcriber at the University of East Anglia. I wrote field notes immediately afterm

the interviews. Participant characteristics such as age, employment status, highest qualification and previous history of foot problems were recorded as part of the feasibility study.

7.3.5 Analysis

I used Inductive Thematic Analysis and the six-step model described by Braun and Clarke (2008). I read all the transcribed interviews to record emerging ideas. I then subjected the transcriptions to line-by-line coding using NVivo12. My initial coding framework was refined by a second researcher and cross-checked against a small sample of transcripts. The coded data was subjected to an abductive thematic analysis, identifying key categories and themes from the data (appendix U). This ensured that participants' responses were adequately captured, and their meaning authentically interpreted. To enhance the analysis, I produced a participant newsletter capturing the key themes, with illustrative examples (appendix V) which I posted out to participants asking them to check these findings. I invited participants to post or email any thoughts or feelings about the findings to enable me to gain a deeper understanding of their experience.

7.4 Results

Forty-two of the 43 participants in the feasibility study agreed to be contacted about the qualitative research. I interviewed 14 participants and achieved the recruitment target. All participants chose for the interview to coincide with a pre-arranged study or hospital visit. One participant declined to recording the interview, and in this case, I wrote notes. Interviews lasted approximately 40 minutes.

Five of the 14 participants brought a partner or family member into the interview with them. This presented a different challenge, ensuring that the voice of the participant was not overshadowed by the voice of the person with them. However, it also provided me with an opportunity to understand more about how CN had changed participants' roles and responsibilities within the family and whether this had changed the dynamics of relationships.

Participants' awareness of my clinical role led some of them to ask me to clarify information they had been given or found out about CN and the treatment they received. They also looked to me for reassurance when talking about their own experiences. It was important to try and keep my role as a qualitative researcher and a healthcare professional distinct. I tried to ensure that I did not comment either on the participants' clinical care or the information they had received. Doing

this would have been outside my role as a researcher and may also have undermined my relationship with the clinical and research teams at the different sites.

The individual participant characteristics are shown in Table 7-1 and summarised in Table 7-2. Eight out of the 14 participants were male, and the average age of all the participants was 61. Most (nine out of 14) participants left school at 18 years or earlier. One participant had studied to degree or equivalent level. The remaining four participants reported that they had completed vocational/occupational specific training leading to a professional qualification. Eight participants had retired before their current diagnosis of CN; five were in employment before their diagnosis of CN, with three of these then 'on sick leave'. One person did not work because of their long-term health issues.

Twelve participants were married or lived with a partner, and the remaining two were single, but lived with and cared for an elderly parent. Five participants had caring responsibilities: four lived with and cared for elderly relatives, and one cared for her husband who had recently been diagnosed with cancer and had undergone major surgery. One participant had children living at home full-time.

Three participants interviewed had experienced at least one previous episode of CN. Five participants had previously undergone a minor amputation due to complications of diabetes.

Table 7-1 Baseline characteristics of participants for the qualitative study

	Duration study (days)	Stage of study	Off-loading device	Age	Sex	Working at diagnosis	Highest qualification	Previous minor amputation	Previous Charcot
1	159	Follow-up	Non removable below knee cast	69	M	No	Vocational/occupational specific training leading to professional qualification	No	No
2	205	Active	Non removable below knee cast	48	M	Yes	Stayed at school/college in education until 18	Yes	No
3	163	Follow-up	Non removable below knee cast	56	F	Yes	Stayed at school until 16	No	No
4	261	Active	Removable below knee cast and boot	68	F	No	Stayed at school until 16	No	Yes
5	326	Active	Removable below knee cast and boot	64	M	No	Stayed at school until 16	No	No
6	204	Follow-up	Non removable below knee cast	57	M	Yes	Degree or equivalent	No	No
7	254	Follow-up	Non removable below knee cast	78	M	No	Stayed at school until 16	No	No
8	96	Active	Non removable below knee cast	61	M	Yes	Stayed at school until 16	No	Yes
9	63	Active	Removable below knee cast and boot	61	M	No	Stayed at school/college in education until 18	Yes	No
10	336	Active	Removable below knee boot	45	F	No	Vocational/occupational specific training leading to professional qualification	No	Yes
11	126	Active	Removable below knee cast	63	F	No	Stayed at school until 16	No	No
12	64	Active	Removable below knee boot	70	M	No	Vocational/occupational specific training leading to professional qualification	Yes	No

Table 7-1 Baseline characteristics of participants for the qualitative study (continued)

	Duration study (days)	Stage of study	Off-loading device	Age	Sex	Working at diagnosis	Highest qualification	Previous minor amputation	Previous Charcot
13	71	Active	Removable below knee boot	65	F	Yes	Stayed at school/college in education until 18	Yes	No
14	132	Active	Removable below knee boot	51	F	Yes	Vocational/occupational specific training leading to professional qualification	Yes	No

Table 7-2 Summary of participant baseline characteristics

Baseline participant characteristics	**n=14**
Study details	
Duration of participation in study median [25th-75th IQR]	161 [103.5-241.75]
Intervention arm n [%]	8 [57%]
Sociodemographic	
Male n [%]	8 [57%]
Age (years) mean ± SD	61 ±9.1
Highest education n [%]	
Stayed in school until 16	6 [43%]
Stayed in education until 18	3 [21%]
Vocational/occupational, training/qualification	4 [29%]
Degree	1 [7%]
Non-removable knee- high off-loading device at enrolment (cast or boot)	5 (36%]
Working at diagnosis n [%]	6 [43%]
Previous minor amputation n [%]	4 [29%]
Previous CN n [%]	3 [21%]

7.5 Findings

The interview data were analysed using Inductive Thematic Analysis described by Braun and Clarke (2006). I identified four key themes:

1. 'Trapped at home isolated and missing social life and daily life routines'.
2. 'Disruption to people's roles, responsibilities, relationships, and mobility, which people adapted to try and address and manage'.
3. 'Pain which participants related to the direct or indirect consequences of wearing the cast or boot'.
4. 'Blame for developing CN attributed to themselves and healthcare professionals'.

In this section I will discuss each theme in turn, illustrating them by quotes taken directly selected from the interview transcripts.

7.5.1 Theme 1 – Trapped at home isolated and missing social life and daily life routines.

During the interview participants were asked to discuss how receiving treatment for CN affected their day-to day life. The theme 'trapped at home isolated and missing social life and daily life routines 'was one voiced by all the participants. They said that receiving treatment for CN had disrupted their social life or life routines in a negative way; they described their situation as now trapped at home, isolated and missing the things they used to do before their diagnosis of

CN. This theme encompassed feelings around no longer being able to work or, volunteer, and take part in the leisure activities and social interactions they had enjoyed before their diagnosis. The social isolation resulted from a combination of factors, disability caused by wearing the cast making it more difficult to go out, travelling distances as people could not easily access public transport to visit family and friends who did not live locally, and for a few people a perceived social stigma about being seen out in a cast or boot.

7.5.1.1 Working and volunteering

Being in paid employment provides financial security. Working or volunteering can provide people with access to social networks and can give structure or purpose to people's day. When people are not working or volunteering, they may consider they have lost their identity and it can reduce their social interactions. Both of these factors can decrease people's mental and physical health. This can lead to participants experiencing a loss of status as they think others will think they are less important when they are not working or financially contributing, and thus losing self-esteem. Six participants were working before the diagnosis of CN and one person volunteered as a youth club leader. Four of them had been signed off work following the diagnosis of CN and were not working when we met for the interview. These four participants' work required them to be standing and/or walking for a large part of the day while at work, which meant they could not rest their foot and continue working.

> *"I can't do nothing; can't obviously…can't do stairs or anything. Um, I've had to finish my job because it involved all walking".* P3 female, aged 50-60

The person who volunteered and ran a youth club had resigned as a result of their mobility issues caused by the CN, leading to the club being closed. They experienced this as one of the biggest personal effects of receiving treatment for CN, but they also talked about the guilt and the effect closing the youth club might have on the young people who used to attend.

> *"I co-run a youth club for 27-years. Neither of us are mobile anymore, it's something we just couldn't do and it's something that we absolutely loved, and we missed so much. I'd only done it for the latter 27 but it was the biggest blow of all".* P4 female, aged 60-70

This section focuses on the experiences of these five participants who were currently not working or volunteering. In the first quote the participant reports missing his work and the purpose this gave to his day.

> *"It's the frustration and isolation of the day-to-day things that you can't do. I'm…one of the biggest things has been not being able to work. Especially when you enjoy what you do……. Um, can't wait to get back to work".* P8 male, aged 60-70

In the second quote the participant describes how not going out to work means they are missing the social interaction with colleagues that they associated with being at work, which they felt contributed to their feelings of isolation.

> "*I miss work. I don't miss the job; I miss the colleagues. So, as I say, it's not so much the place, it's the people isn't it".* P3 female, aged 50-60

The effects on their lives when not working varied between participants, depending on the length of time participants had been off work for, the remuneration package their employer provided and their financial commitments. Participants reported that now having financial worries made them stressed, stopped them sleeping and going out as much as they would like too. One participant being interviewed in December mentioned how their new limitations were going to affect the way the family celebrated Christmas. People talked about how they spend less when they did not go to work, not using as much petrol, and not buying newspapers, coffees, and lunches but overall, the main expenses of mortgages, rent and household bills did not change.

> *"I'm not earning any sick pay and I've got a financial…it's put me in a serious financial situation. It's caused a lot of stress, sleepless nights, um…not eating".* P6 male, aged 60-71

One person had started to think about alternative opportunities they could explore to start earning some money but while continuing to rest their foot. They were trying to find a balance between following advice of the healthcare professionals, while managing the impact of living on a reduced income.

> *"If all else fails, I'll see if I can find a little job, I can do…homework, you know piece-work; something that I can do at home".* P13 female, aged 60-70

Participants also worried about the future security of their paid work; their worries were immediate concerns around how much longer their employer would continue to keep their job open for them. One discussed their concern about a future planned meeting with occupational health which could result in their redundancy.

> *"They want me to see occupational health and I'm quite worried about it. Well, you just see what happens when they, cause one of the other managers got…he got laid off, got made redundant cause he had knee issues".* P14 female, aged 50-60

A second participant described his fear of losing his job, and what this might mean for him personally and his family.

> *"I just hope I don't get the phone call to come in and they say, 'here's your cards".* P6 male, aged 60-71

Participants also had long-term concerns over whether they would ever be able to return to the type of work they did before their diagnosis. Two participants said that their healthcare team advised them to consider changing careers when they returned to work, looking for a less active job. For participants who had enjoyed their job, the thought of not being able to return to the same type of role was very disappointing. One participant described how he had managed to work from home, and only went into work for meetings. He acknowledged that he was fortunate that he was able to work from home, as this would not necessarily be an option for other people.

7.5.1.2 Leisure activities

For some people, leisure activities can be important because they allow time to step back from work and normal daily activities. Leisure activities can positively support mental health through reducing stress, improving mood and also have physical health benefits. The theme of missing leisure activities was evident in all the interviews. The leisure activities participants missed varied and included working on allotments, shopping and cooking for pleasure, dancing, DIY, walking for

pleasure including walking dogs and exercising. Five participants reported that they had missed out on planned holidays as a result of being diagnosed. Whether participants could continue taking part in the activities they had enjoyed was dependent on the type of leisure activities they enjoyed doing. More active pursuits such as walking, gardening or exercise were often no longer possible, however participants who enjoyed less active leisure pursuits such as crafting, and reading could continue with these.

Participants firstly talked about the things they could no longer do while wearing the cast or boot, then they discussed how not being able to do the activities they had previously enjoyed made them feel bored and contributed to feelings of low mood.

> *"Some days, an hour feels like a day. It's just the monotony of being within these four walls. You feel like they're closing in. I've gotta get out of here".* P6 male, aged 60-71

The following quote demonstrates how the financial implications of being off work also affected the type and frequency of leisure activities these participants were now able to enjoy.

> *"We can't afford to do it as often as we'd like. So, when we do, do it, we enjoy it. Um…yeah, it's…there's a lot of things that we have to consid…take into consideration".* P6 male, aged 60-71

Participants went on to discuss how they had adapted and changed the things they used to do to try and fill their time and combat these feelings of low mood, frustration, monotony, and boredom. A common activity which participants described replacing work or other leisure activities was watching the television or reading. Participants did not consider watching the television as a good substitute for the activities they have previously enjoyed, it just filled the time.

> *"That's all I do, do, is watch tele really".* P9 male, aged 60-70

Some participants described how they had enjoyed exercising, cycling, swimming, and walking, before developing CN. Participants reported the adaptations they had made to allow them to

maintain some level of physical activity, completing upper body exercises and non-weight bearing cycling, but continue to minimise the time they were walking and/or standing. These participants discussed how they were aware of the importance of physical activity in helping to manage their diabetes.

Although all the participants reported feelings of missing out and isolation, over half of them commented that they knew people in worse situations. They compared themselves to a mixture of different others: people generally, to friends with other health issues and in the following quote to people who they saw sitting in the clinic waiting rooms who they could see had undergone an amputation.

> *"I feel lucky because when I sit out there and I used to say – I'm the only one with all my limbs, they've all got toes and legs missing and I'm the only one that's all there. I'm lucky".* P3 female, aged 50-60

However, the following extract suggest that while participants acknowledged that there were indeed people in worse situations, one person felt that this did not help him, and another person alluded to the unfairness of the situation they found themselves in. While only two participants chose to voice these feelings, they may resonate with other participants who may have chosen not to disclose them for fear of being negatively judged as, e.g., selfish.

> *"there is always somebody worse off than you but it doesn't help, it doesn't help the way…because I know when I…when you lead a normal life, it's just so…it's so… [claps hands] annoying".* P3 female, aged 50-60

7.5.1.3 Social interactions

Social interactions can be important for mental and physical well-being. The participants I interviewed described very diverse experiences of how receiving treatment for CN limited and had negative effects on their contacts with family, friends, and colleagues. What they highlighted depended on whether they had stopped working since being diagnosed, their ability to drive and/or use public transport to get around, the proximity of family and friends and whether they continued to attend clubs or groups. Participants reported that they now planned outings and

that it was more difficult to be spontaneous or gallivant around. They no longer felt they had the energy to do all the things they previously enjoyed doing.

> *"My son went to me, 'are you coming into town?' I went, 'no, I'm going straight home.' Whereas before, I would have gone trotting into town and would have gone shopping with him, but…I found I'm not going out and about like I used to".* P14 female, aged 50-60

Some participants reported that they felt guilty or under pressure from their partners as the restrictions on their mobility also limited their partner's social life. This had put additional strain on their relationship with their partner.

> *"Oh, here's a thing – my wife's on at me because it's limited her social life. The limitations and the future. Um, it's alright saying well, its four months out of your life, but you try telling my wife that".* P9 male, aged 60-70

Eight participants reported that they had been unable to visit family since their diagnosis and wearing the cast or boot. Even travelling relatively short distances to see family caused participants problems. It seemed to be particularly difficult for participants whose family and friends also had restricted mobility due for various reasons. One participant reported being unable to see a family member who was seriously unwell, and not being able to see people in these circumstances was understandably upsetting.

> *"Sometimes I can you know, when you go to bed and you've got things running round your head; you start thinking about things, that's when I could get upset but there's no point. There's just no point. I know I'm nearly crying now but that's because I'm talking about it".* P14 female, aged 50-60

7.5.1.4 Theme summary

Through talking with participants who were currently receiving treatment for CN the theme of 'trapped at home isolated and missing social life and daily life routines' developed. While everyone interviewed expressed some version of these feelings, across the data there were differing nuances often reflecting individuals' different circumstances before diagnosis. Expressions of isolation were mainly associated with 'physical isolation' where the cast or boot

was restricting participants' social interactions. They reported on how this effected casual social interactions, such as meeting and talking to people when out shopping and during formal or planned interactions such as going to work, meeting family, friends or attending clubs. However, one person reported experiencing both 'physical and emotional isolation': they were unable to go out to meet people and their relationship with their partner had broken down as a direct result of their being unable to do the things they used to do, they felt rejected and ostracised within their own home. Being isolated led participants to report feelings of low mood. While not all relationships had broken down, participants with spouses, partners, and children all described how restrictions in their own mobility also affected others in various ways. Realising this contributed to participants' feelings of guilt, and being a burden, sometimes leading to friction in relationships, and to further stress and anxiety for the individuals involved.

Important differences in the experience of participants who had employed work were associated with whether participants were able to continue working while wearing the cast or boot, and perceived current and long-term job security. For those participants who were in paid work before and not after their diagnosis this raised financial implications, and this contributed to feelings of stress and anxiety. Again, here how these effected participants varied, depending on their entitlement to sick pay. For all the participants receiving treatment for CN, resting the foot, and wearing the off-loading cast or boot had led to them feeling isolated and being unable to do the things they previously enjoyed.

7.5.2 Theme 2 – Disruption to people's roles, responsibilities, relationships, and mobility, which people adapted to try and address and manage.

Participants described the numerous, sometimes life-altering changes and adaptations they had made to their lives to manage and minimise the impact of CN, allowing them to continue to live safely, comfortably, and as independently as possible. During the interview participants were asked to describe how they found wearing the cast or boot and consider whether it had caused them any problems. Everyone reported wearing the cast or boot had disrupted their life and made them more reliant on others. They discussed the disruption, and the changes and adaptations they had made and the way these may have changed their personhood and personal identity, and the further effects this had on their relationships with family and friends.

7.5.2.1 Mobility

Being able to be mobile and get out and about can allow participants to live an independent and active life, it can be vital for managing and sustaining work and social interactions. Thirteen of the 14 participants described how wearing the cast or boot restricted their mobility and that this, in turn, presented challenges in going out. The subsequent experiences and consequent further effects of these varied and appeared to be related to how mobile participants had been before their diagnosis. It was often linked back by the participants to previous foot complications or other health problems. This quote demonstrates that some participants felt a strong loss of mobility.

> *"I've gone from being very outgoing to just being at home; I don't do nothing; I don't get around or anything".* P3 female, aged 50-60

The next quote is from someone who had already made several adaptations due to other health conditions including changing his car, having a stair lift fitted and having a personal alarm fitted in the house. For this participant, the CN seemed to have relatively less effect on his mobility.

> *"I'm not shy about asking for help if I need it, so it doesn't really impact on my life, very much, in a major way".* P7 male, aged 70-80

Participants reported that the cast or boot stopped them from driving. Since the diagnosis participants were reliant on family and friends to drive them and felt they had lost their independence. Participants who could no longer drive adapted by trying to use public transport. Everyone who used public transport described problems getting on and off buses, trams and trains when wearing the cast or boot, and thus many participants used taxis to go out, but this was an added expense.

Participants felt wearing the cast or boot made them unsteady and increased their risk of falls. Twelve participants reported unsteadiness and concerns over falling while wearing the cast or boot both inside and outside the house. This quote from one participant highlights how participants accepted the need to wear the cast or boot despite the risks.

> *"I fell at home and then I fell outside A&E cause I had to go there for my eyes to be tested, when I fell outside there. Um, yeah, I just…I know it's got to be on, and I know it's on for a good reason, but it just alters your life completely".* P3 female, aged 50-60

Nine of these twelve participants interviewed reported that they had fallen or tripped at some point while wearing the cast or boot, three reported that a fall had resulted in an assessment in hospital, and one person fractured their elbow. In order to reduce the risk of falling but remain mobile, participants had adapted by using sticks, crutches, frames, wheelchairs, and mobility scooters. They often reported that they went up and down stairs on their bottom and thought all these things made them more reliant on others. Participants who had access to wheelchairs reported they could not go out when they wanted to as they needed someone to push the wheelchair and were reliant on family and friends. They perceived that wearing the cast or boot and using a wheelchair meant that people stared, did not always offer to help them, looked at them differently and talked over them, not to them.

One participant describes how when they are in the wheelchair, they are dependent on others, who may walk away and leave them stranded. They also experienced how the design of market stalls discriminates against people in wheelchairs who are not able to be seen by the stall holder.

> *"If me daughters pushing me and she wants to look at something, she'll just leave me in the middle of the isle. And you know, I know I shouldn't have done it, but I was in the XXX market, fruit and veg stall and it was really high up. The guy kept walking passed me, so, obviously he couldn't see me, so I shout's, 'I'm down here you know.' I was quite rude. And it's not like me to be like that really. [Laughs] I can be rude when I want but not then. He said, 'oh, I dint see you down there.' And you think, you know. What if I hadn't spoken up?".* P3 female, aged 50-60

7.5.2.2 Adapting at home

Maintaining personal independence at home is important for health and wellbeing. All participants reported difficulties in completing everyday tasks while wearing the cast or boot, and relied on family, friends, and paid people to help. Participants reported that they could no longer do basic household jobs such as hoovering. These types of tasks had been taken over by their partners or others in their households.

> *"Shopping, the cleaning, the cooking; everything really. If there weren't nobody there to do my shopping, I'm not eating. It's everyday things that you take for granted that you do".* P3 female, aged 50-60

They described the importance of friends in helping them maintain their independence, and that they would not have managed without their support. Participants used sticks and crutches to improve stability while wearing the cast or boot, but this made relatively simple tasks such as carrying a drink or saucepans when cooking difficult. Participants described that they were able to complete aspects of tasks that did not require them to balance or carry anything, e.g., putting on the washing machine or stripping the bed whilst sitting down but needed support with other aspects, e.g., hanging the washing on the line, and making up the bed. While participants were grateful for help from family and friends, they resented being more reliant on others to help and would have preferred to be able to manage on their own and maintain their independence.

Many participants had decided to make adaptations to their house to help them manage while wearing the cast or boot, and to make life easier in the future should they have further foot problems. They felt that the adaptations had made their home safer for them, made daily tasks easier to carry out, and ensured they maintained their independence. Immediate actions included purchasing anti-slip mats for bathrooms and buying grabbers to pick up things from the floor. Minor changes included purchasing a reclining chair. Some participants had made substantial changes, for instance having bathrooms adapted and fitting a stair lift. One person was in the process of a major house renovation to create open plan living, making their home more accessible for wheelchairs. They worried that in the future they might need a major lower limb amputation and wanted to be prepared. The fear of future amputation was echoed by several participants but only one person reported that they had started making adaptations, specifically to prepare for this.

Participants were adapting to try and make changes to allow them to live more safely and independently. In this study participants report how disruption to what people may consider minor roles and responsibilities such as being able to cook, or clean can have a profound impact on the participants sense of self and mood.

Some participants also considered the long-term consequences of future foot complications and how these might further affect their mobility, employment, and relationships.

7.5.2.3 Caring for others

Four participants had caring responsibilities for elderly parents who lived with them, and a fifth person was caring for her husband who had just undergone surgery. As a result of the CN and wearing the cast or boot, participants now relied on friends and careers to come in and help them meet these responsibilities. All the participants who were providing care for family members were frustrated that they could not care for their parents since their diagnosis: they were at home rather than at work so in theory had more time.

> *"I've got to do what I can do. Which isn't a great deal to be honest, but I do try".* P13 female, aged 60-70

One man felt responsible for putting an extra burden on his wife by asking her to help him as well as look after her father who lived with them. He felt that his father-in-law was quite demanding of his wife's time already, and he did not want to make things worse by increasing these pressures on her.

> *"Because her dad's very, 'I need this, I need this, I need this.' We've got to take him here, got to take him here; it just impounds on it". You see then I feel under pressure because I'm putting pressure on her as well. So, that makes me feel awkward".* P8 male, aged 60-70

7.5.2.4 Relationships

Disruptions due to CN can also considerably affect relationships with family and friends. This could be a result of changes to roles, and responsibilities within the family, or no longer being able to take part in the activities usually enjoyed with family and friends. Twelve participants were married or lived with a partner. Participants generally reported how supportive their partners had been, and how they could not have managed without their help and support. They felt guilty for being a burden and reported that there was occasional friction in some relationships.

Husbands talked about how they could no longer support their wives with tasks such as shopping. They used to help their wives by driving them to the shops and carry the shopping but could no longer do this, and this made them feel guilty. Two male participants talked about ways they tried to make themselves useful by researching on the internet for things the family needed and securing the best deal to save money.

However, this was not the case for everyone. One person described how his relationship with his wife had changed since being diagnosed with CN. He described areas of tension and how he chose to do things that resulted in minimal grief, to make life as easy as possible, so as to not cause trouble between him and his wife.

> *"At the minute, my names mud. I get up at…I actually, have got to the point where…um…I wonder will…cause, her life; she um…gets up. I got up at half five this morning. She came down at twenty past six. I'd washed me foot and that meself but to put the dressing on for me and stuff. Um…I can help…I can't cook as much as I did, which, I love cooking but, I think to meself, is she going to get to the bedroom door before…if she's up before me, before she fires the first bullet".* P9 male, aged 60-70

The majority of participants felt that not only did their partners and spouses provide physical support, but also provided emotional support, without which they would not have been able to cope.

> *"It's just horrible. I'm lucky I had a good one at the side of me, otherwise… [whispers] – I don't know what I'd have done".* P5 male, aged 60-70

Although it was clearly helpful for participants to feel the support of their families, one participant described how he did not share all his concerns with his wife as he did not want to overwhelm her and was trying to protect her but not sharing all his thoughts.

> *"You know, I don't share all my concerns that go through my head, cause if I did, I'd just bombard her with a load".* P8 male, aged 60-70

7.5.2.5 Thinking about the future and long-term implications

Receiving the diagnosis of CN and information around the long treatment times caused feelings of upset and disbelief, participants found it hard to come to terms with the fact that they might need to be in a cast or boot for several months, up to a year. They were concerned about its immediate effect, making changes and adaptations to their current life, but also about what might happen in the future, whether they would ever work again, and the consequences of not earning for several months which may affect their and the family's lifestyle. People reported that with less money they made need to make cutbacks to the household expenditure bill, with less money to spend on the things they enjoy. It may put an increased burden on other family members to make up the lost income and lead to tensions. Participants described being 'absolutely gutted' and 'knocked back'. Some participants felt that they wanted to know the truth about how long it was likely to take to get better. Others felt that being told it could take up to 12 months for the foot to heal was too much to take in and they would rather not have known this. One person felt that they would have recovered quicker if they had had their leg amputated, but then said this was one of their biggest fears.

Both male and female interviewees reported that they were worried about the appearance of the therapeutic shoe they would need when the foot had healed. One male participant reported that he would never walk barefoot again as he did not want people to see the shape of his foot. One person felt that wearing the boot and, in the future, wearing therapeutic shoes was a stigma and signalled them out as disabled and not able to do things normally and that would make them vulnerable, to verbal and physical assault. Participants were worried about getting CN in the other foot or another episode in the same foot.

> *"Will it come back; am I just constantly going to have this stuff; ae they going to have to start hacking away at me foot and taking other bits off? That's the kind of stuff that…".* P2 male, aged 40-50

Participants reported that every time they noticed a pain or change in their foot they thought "could it be happening again" and now needed to be vigilant and could not relax, they constant checked and worried about their foot.

"Is that looking right? Is that the same size as that, is it really? So, total paranoia but I think it's probably better to be vigilant rather than ignore something. I've learnt that lesson the really hard way". P13 female, aged 60-70

7.5.2.6 Theme summary

Thoughts and feelings around 'disruption to people's roles, responsibilities, relationships, and mobility, which people adapted to try and address and manage' appeared to play a pivotal role for participants living with CN and was a powerful theme common to all the participants. The participants reported a range of things they had found difficult to do while wearing the cast or boot and the way in which they had adapted to overcome these. They discussed the frustrations that this had caused them and how this had sometimes negatively affected their mood. The participants reported that their mobility inside and outside the home, the environment in which they lived, family relationships and caring responsibilities had all changed. Often the participants managed a range of underlying health conditions, some but not all related to their diabetes. Participants' health before the diagnosis of CN influenced what level of disruption and the range of adaptations that they found they needed to make, and thus for some participants the consequence of being treated in a cast or boot required a greater level of 'disruption and adaptation' than for others.

Nearly all the participants had made adjustments to help with immediate restrictions caused by while wearing the cast or boot, and in anticipation of future foot problems. Some participants were more easily able to adapt and accept the consequences of wearing the cast or boot. For others it was apparent that the CN and its treatment had significantly undermined their health and wellbeing, and they had struggled to deal with this emotionally. Wearing the cast or boot appeared to be associated with reduced stability in standing and walking and increased risk of falls. Participants talked about how they addressed this risk while trying to minimise their chances of falling by using walking aids. Some participants decided to use wheelchairs and mobility scooters to enable then to remain mobile, go out more, and reduce the risk of falls.

Many participants had caring responsibilities for relatives and being less able to fulfil their role as a carer caused additional stress. Participants described how the dynamics of family relationships had altered with some participants reporting how roles within the household had changed with

husbands and/or children now taking over the housework. Some struggled with no longer being able to support their spouse or partners and felt guilty about not being able to do their fair share of the household chores. Some participants faced possible conflict in their relationships with spouses or partners over the change in roles and responsibilities within the family unit or having less money to spend on the things they have previously enjoyed together. However, on the whole, participants described how supportive friends and family had been but how they could not have managed physical or emotionally without this help and support. It is clear the CN caused participants to have to make both short and potentially long-term changes and adaptations. Some thought that life would never be the same for them.

7.5.3 Theme 3 - Pain which participants related to the direct or indirect consequences of wearing the cast or boot.

Eleven participants mentioned that they experience new and increased pain which continued past their initial diagnosis. They described pain as either direct or indirect pain that they associated with wearing the cast or boot. However, some also discussed other types of foot and leg pain they thought was related to their diabetes but not specifically the CN. The participants interviewed wore a mixture of devices: non-removable and removable casts and below knee walkers. Participants had mixed opinions of which device they felt was more comfortable. This extract from one participant shows how they found the custom-made cast better than the below knee walker boots: they thought that the cast fitted better and was associated with less discomfort.

> *"But you know, the cast…when it was on, I felt that it was supportive and I didn't tend to feel any discomfort or pain, whereas occasionally with the boot, it would move, and I noticed that it tends to be a thing that you really notice. So, yeah, from that aspect, it was more comfortable – it seems weird to say that it was more comfortable in the cast in that respect; it was protected. Well, in some ways the cast is more convenient because of the blasted Velcro".* P6 male, aged 50-60

This participant then mentioned advice that he had received from the podiatrist that some people may be tempted to take off a removable device, whereas this was not possible in a cast. They felt that being in a non-removable device was better as it imposed a level of compliance with

treatment that might not necessarily be followed if it was possible for participants to take the cast or boot of themselves.

> *"I couldn't cheat and take it off, I had to have it on. I gather from the podiatrist that's what some people do – wear it when I'm here and then take it off when they get home. So, you can't really do that type of thing in a cast".* P6 male, aged 50-60

In contrast, other participants described how they enjoyed the benefits of removable devices as they could take them off when resting, sleeping, or bathing. In the next quote one participant describe how choosing to remove the cast or boot is a considered response to try and balance the need for treatment against their own and their family's quality of life.

> *"I was happier with the boot because of course, you can take it off before you go to sleep. With the cast, you find that you might wake yourself up by cluncking…I thrash around in bed all the time and I'm very aware that if I hit the other foot with the boot, I'll wake up".* P7 male, aged 70-80

Whatever device participants were wearing, the narratives highlighted and emphasised how ongoing pain in the foot despite nerve damage and continuing discomfort was a serious issue for some. Some participants felt that cast or boot intensified their nerve pain, they experience in their foot and leg. Some participants described how they now needed to take or increase their pain medication to help control the pain, despite changes to their medication a few participants described ongoing pain. This pain disturbed participants sleep and stopped them doing the things they previously enjoyed like golf, and gardening. This disruption to the things they had previously enjoyed, and ongoing pain contributed to feelings of low mood.

> *"So, sometimes I'm feeling a different kind of pain. Like a really sharp pain right up me foot. My toes tingle and that so…It's just so painful though and it's the medication that needs sorting to get the combination right".* P3 female, aged 50-60

Regardless of the type of device, one of the most pertinent issues raised by participants was that they thought that wearing the cast or boot had caused indirect pain as a result of being off-balance with one leg longer than the other. Because of this, participants reported varying degrees

of back, hip and knee pain. To minimise this pain participants reported that they tried to reduce the time they were on their feet, sometimes this meant they turned down invitations to go out with family and friends, generally they did things more slowly, had to stop what they were doing when the pain came on and take regular rests.

> *"hips hurt while I'm walking. Knees hurt when I'm walking, when they didn't before".* P1 male, aged 60-70

One woman reported that clinical teams had provided a shoe raise for the other leg to minimise the effect of wearing the boot/cast, however she felt that this made her more likely to trip or fall so she preferred to walk without it and tolerate the pain.

7.5.3.1 Theme summary

Pain which participants related to the direct or indirect consequences of wearing the cast or boot was a powerful theme that emerged during the interviews reported by thirteen of the fourteen participants. This study suggests that although CN is a condition associated with nerve damage participants do experience notable pain. Some participants reported that their current pain medication was not adequately managing their symptoms and wanted to discuss this with their health care team. Most of the participants attributed the pain they were experiencing to the cast or boot being worn to protect the foot, rather than to the CN itself. Participants acknowledge that it was important to wear the cast or boot but wanted more support and advice from healthcare professionals on things that they could do themselves to help manage the pain. They suggested strategies they thought would be helpful, including making people more aware of temporary 'shoe raises' that could be purchased to reduce the limb length discrepancy caused by wearing the cast or boot. They also suggest ways in which they thought these types of 'shoe raises' could be improved to make them safer, as although they thought they helped ease the pain, they commented that the current design made people more likely to trip.

7.5.4 Theme 4 - Blame for developing Charcot neuroarthropathy attributed to themselves and healthcare professionals.

Participants attributed blame for the CN developing and progressing both to themselves and to healthcare professionals. They reported self-blame describing how they had not looked after their diabetes, and delayed seeking help when they noticed a problem.

Participants blamed healthcare professionals for a missed or delayed diagnosis and thought that this has contributed to them having to wear a cast or boot longer and changes to their foot shape, which they felt could have been prevented if they had been diagnosed earlier.

7.5.4.1 Personal responsibility

Some participants blamed themselves for developing CN and articulated different reasons for considering it their own fault: doing too much, changing their shoes, not getting help soon enough after noticing a problem, and believing that they should have looked after their diabetes and general health better earlier on. In this quote the participant links the health choices they made about managing their diabetes to developing the CN. They now share their experiences with other people with diabetes, to offer advice on how to reduce the chances of developing diabetes complications.

> *"I wasn't as strict with me insulin and things like that. As I should have been. I know what I've done and yeah; suffering now. I'll lecture anyone now if they tell me that they don't do it themselves".* P14 female, aged 50-60

While all participants reported that they had been advised to rest their foot, some acknowledged that they had not followed this advice completely. Participants were trying to achieve a balance between treatment and their own and their family's quality of life. They did not want to stay at home it became monotonous staring at four walls and were determined to try and get out and about. Some linked lack of improvement in their foot to being more active therefore changed their behaviour and rested their foot more. In this example the participant acknowledges that initially they were doing more than advised by working in the garden.

> *"I still did a bit of gardening; I was still doing things in the garden which I probably shouldn't have done. Then I got to thinking hang on, this is wrong, stop".* P1 male, aged 60-70

Participants may do more than is advised by the healthcare team because they have not fully understood the advice from healthcare professionals, or it can be a conscious or unconscious decision to try and balance treatment, maintain independency and quality of life and continue to do the things they enjoy.

7.5.4.2 Delayed diagnosis

Four participants judged their diagnosis of CN as having been 'missed at crucial times' or 'delayed'. They reported having seen multiple healthcare professionals over a period of several weeks to three months: GPs, practice nurses, physiotherapists, and A&E healthcare professionals. They all reported undergoing various investigations and receiving treatment for other conditions including infection, cellulitis, a blood clot, soft tissue injuries and gout before receiving a diagnosis of CN. They all felt disappointed by the care they had received prior to receiving an accurate diagnosis and thought the delay in having CN specific treatment was likely to have made things worse. Two participants reported they had actually been given advice and or treatment that they now thought was detrimental to the CN and may have caused the foot to deteriorate further. Some participants reported that their foot had already started to change shape before they were seen in specialist diabetic foot clinic.

> *"You see I think to myself if I'd gone to the hospital the first time and someone had knew about it, my Charcot wouldn't be as bad".* P3 female, aged 50-60

One participant described how the delay in getting a diagnosis had caused him a lot of stress: he reported feeling angry and distressed, and this meant that he experienced sleep problems. This participant was pursuing a claim for negligence.

> *"Yeah so, I just felt that I'd been totally neglected from day one, right up until getting here basically".* P8 male, aged 60-70

One pertinent issue that all participants identified with, whether or not they had experienced a possible delayed diagnosis, was general lack of awareness around CN for both people with diabetes and healthcare professionals. In this example the participant acknowledges that diabetes can cause lots of different problems, and people with diabetes have a role to play in knowing about and acting on this information to reduce their risk of complications. They also experienced a lack of awareness around CN from non-specialist healthcare professional and that this contributed to their misdiagnosis and delayed referral on to specialist foot teams. They think it is important to raise awareness among healthcare professionals of CN so that in the future others do not experience a delay in diagnosis or referral.

> *"Charcot foot, I think needs to be talked about a bit more. You know, warnings when you go to clinics. Doctor's need bringing up to speed, because like I say, me practice nurse had never even heard of it and she'd worked in A&E as…so…The doctor that come to see me here and he'd never even heard of it and the gentleman I saw downstairs. There's so many things with diabetes and everything"*. P14 female, aged 50-60

In the next example one of the participants suggests that if people living with diabetes knew more about CN, then they would seek and receive help more quickly, and this would improve outcomes.

> *"There should be more information in leaflets and online about the hot swollen foot and how people should go straight to hospital and be seen quickly. If people are aware, they have a chance to save their foot".* P11 female, aged 50-60

7.5.4.3 Theme summary

This theme's finding has shown ways in which participants felt that more understanding and awareness of CN on the part of both healthcare professionals and people with diabetes is important. This will improve recognition of the signs and symptoms, to ensure prompt treatment and improve outcomes. In some cases, participants felt that their own actions or inactions had contributed to them developing a CN. Some participants blamed themselves as they now judged that if they had taken more care of their diabetes, they would not have developed CN. Others felt if they had sought help earlier then things might not be so bad, treatment times in the cast or boot would have been shorter and their foot may have changed shape less. Participants talked about how a lot of information is given to people when they are diagnosed with diabetes and it is difficult to absorb and remember it all, some of it does not seem relevant at the time.

Several participants thought that if people with diabetes were more aware of the importance of looking after themselves and their diabetes, they may be less likely to develop problems. For participants who thought their diagnosis of CN was initially misdiagnosed by non-specialist healthcare professionals there were feelings of anger and resentment. Participants apportioned blame to the healthcare professionals they had seen who they felt had missed the diagnosis of CN. They thought that the delay in diagnosis was likely to prolong the time they need treatment for and had led to the foot being more deformed, than if it had been treated sooner. For one participant the theme of blame was the overarching focus of the interview.

7.5.5 Overall summary of themes

The analysis of the interviews has identified four themes:

1. 'Trapped at home isolated and missing social life and daily life routines'.
2. 'Disruption to people's roles, responsibilities, relationships, and mobility, which people adapted to try and address and manage'.
3. 'Pain which participants related to the direct or indirect consequences of wearing the cast or boot'.
4. 'Blame for developing CN attributed to themselves and healthcare professionals',

The first three themes interlink to show ways in which receiving treatment for CN has affected participants and their families. The experience of CN and wearing the cast or boot for many months was seen to restrict and undermine participants' ability to do the things they previously enjoyed. Relatedly, and despite making adaptations participants experience becoming more dependent on others for support with all kinds of tasks, from household jobs to going out and about. Unsteadiness, fear of falling and pain from wearing the cast or boot further restricted the types of activities that participants could undertake. They were upset about these restrictions and changes. Although wearing the cast or boot is a physical constriction, the limitations, and changes that it causes had an emotional effect on participants. Participants were frustrated and this led to feelings of low mood, low self-esteem and for one participant desperation. Participants reported feeling guilty that they needed more support from family and friends, and that the restrictions caused by wearing the cast or boot were also affecting their families.

The final theme 'blame' could be subdivided into, firstly, when participants felt their own actions or inactions had led to the CN and, secondly, when they felt healthcare professionals had missed or delayed the diagnosis. Whoever the blame was directed at, it was associated with strong emotions of frustration and sometimes anger.

7.6 Discussion

This study into the lived experience of CN shows the previously unrecognised distinctive and onerous burden of CN experience. Receiving a diagnosis of CN, often without warning, frequently resulted in denial, shock, fear, anger, and resentment. Analysing the semi-structured interview data produced four themes.

The first theme, 'trapped at home isolated and missing social life and daily life routines', highlighted the effects of social isolation whereby participants experienced resting the foot and wearing the cast/boot as restricting their interactions with others.

The second theme, 'disruption to people's roles, responsibilities, relationships, and mobility, which people adapted to try and address and manage', focused on how participants reported being less mobile and more unsteady, which affected their ability to do household chores, shopping, and care for others. This led to experiences of frustration, and loss of control as they had to ask for help with everyday tasks and became more dependent on others. This altered participants' sense of self and affected relationships with family and friends.

The third theme was 'pain which participants related to the direct or indirect consequences of wearing the cast or boot' rather than the CN. They were disappointed and upset that the boot or cast caused pain, and this did not always seem to be discussed and addressed by healthcare professionals during treatment. This pain restricted them further, sometimes affected sleep.

The final theme was 'blame for developing CN attributed to themselves and healthcare professionals. Some of the participants were dissatisfied with the care they received before being referred on to specialist foot clinics, they considered they had been let down, were upset and angry. Many of the participants described how they were frustrated with themselves and wished they had made different long and short-term healthcare choices.

The discussion will consider how far these themes have addressed the aims of this study, how they may have deepened current understanding of the personal experiences of being treated for CN, and how these may have affected participants' social participation and family relationships. Finally, it will consider how these experiences may inform changes in supporting people with diabetes and healthcare professionals to better address experienced challenges of CN.

7.6.1 The experience of Charcot neuroarthropathy

In this study, participants identified several often not-readily-expressed issues that affected their experience of CN. We know from studies exploring the experiences of people with diabetic foot ulceration that the restrictions of resting, wearing an off-loading device and pain (Brod, 1998; Kinmond *et al.*, 2003; Ribu and Wahl, 2004; Bradbury and Price, 2011) can leave people socially isolated. This study has shown that social isolation is also experienced by people receiving

treatment for CN, with participants describing a disconnection from their social networks whether work, family, or leisure. For people with CN, a combination of diabetes, a chronic disease, with disability caused by needing to wear the cast or boot and likely subsequent social isolation could worsen health outcomes for the individual and increase related burden on health and social care services.

Our study has provided deeper insights and context to the quantitative research which shows that CN decreases participants' physical ability to perform tasks (Willrich *et al.*, 2005; Sochocki *et al.*, 2008; Raspovic and Wukich, 2014). It provides specific examples of the kinds of physical limitations participants experience, with an understanding of how participants adapt, and the implications this has on sense of self and relationships. The themes from this study are consistent with the overall theme Price (2004) described for people with diabetic foot ulceration as a 'lifetime of behavioural change', with a life of fear, restrictions, and pain (Kinmond *et al.*, 2003; Ribu and Wahl, 2004) and social, psychological, physical and economic impacts (Brod, 1998). Healthcare professionals need to recognise, understand, and acknowledge the concerns and difficulties individual people face with prolonged periods of resting and wearing the cast or boot.

Isolation, managing disruption, and adapting to this all profoundly affected participants' well-being. In this study, participants described healthcare professionals as focusing on the physical (e.g., cast or boot) and medical issues (e.g., diabetes) associated with the CN while attending less to the emotional impact. In other studies, people with diabetic foot ulceration and amputation have reported their need for additional psychological support. (Fox, 2005; Delea *et al.*, 2015). Yet this study shows clearly that there is still some way to go to meet this need. People with diabetes are already known to experience disproportionately high rates of mental health problems such as depression, and anxiety a diagnosis of CN may make this worse.

As in other studies, participants reported that they felt stigmatised by wearing the cast or boot (Johnson, Newton and Goyder, 2006; Burton, 2007; Paton *et al.*, 2014), expressing concerns over the long-term shape of their foot and their future need for custom made footwear. Providing early opportunities for people to look at the type of shoe or boot they may need once the CN has healed may alleviate some concerns. This could be achieved by putting footwear catalogues in the waiting rooms and advising people that they will be Involved in choosing the style, and design of any future footwear.

7.6.1.1 Families

The effect of CN on participants families is often unrecognised and underestimated. In this study we gained an understanding of the effect of living with and caring for somebody with CN from the perspective of the participant, rather than the experience as described by the family members themselves. There is some evidence on the impact of foot complications on family members from quality-of-life studies, which have specifically explored the experience of the family members who are living with and caring for people with a diabetic foot ulceration. This study has shown consistency between the thoughts and views expressed by participants on impacts on family members in this study and those which are reported by the family members themselves in other studies. These include limitations to social activities, tensions within relationships (Brod, 1998), impaired mobility, frequent hospital visits and fear of amputation (Nabuurs-Franssen *et al.*, 2005). Services that support and encourage people's independence have secondary benefits in improving the emotional health of carers and family relationships (Al-Janabi *et al.*, 2019). If healthcare professionals were able to signpost people with CN and their families to funded or voluntary support services this could increase independence, reduce reliance on family, and in turn reduce any relationship tensions as a consequence of changing roles and responsibilities within the family.

Exploring the effects of CN with future qualitative research with the family members themselves may help all those involved in supporting people with CN to understand participants' reasons behind their treatment decisions. It will highlight what support people need to self-manage their condition as well as possible, improving communication and understanding between people and healthcare professionals should translate into a better experience for people with CN, their spouses, partners, and children and improve outcomes.

7.6.1.2 Pain which participants related to the direct or indirect consequences of wearing the cast or boot.

This study shows that the experience of pain in CN is an important consideration for participants despite nerve damage and this pain has a substantial role in influencing their overall experience. Whatever the reason for the pain, it contributed to the physical and emotional distress they reported. Pain associated with wearing the cast or boot was an important issue for participants and confirms the findings from other studies with people with diabetic foot ulceration where participants experienced pain when using off-loading devices (Brod, 1998; Kinmond *et al.*, 2003; Fox, 2005; Ribu *et al.*, 2007).

7.6.1.3 Blame for developing CN attributed to themselves and healthcare professionals

Individual's experience of blame was the final theme to emerge from analysis. As in other studies among participants with foot ulceration or amputation, participants felt their actions and inactions firstly, around taking care of their feet and secondly, around current and past control of their diabetes had directly led to or slowed down their recovery from foot complications (Beattie, Campbell and Vedhara, 2014; Foster and Lauver, 2014; Delea *et al.*, 2015). In many of these situations, participants engaged in what they regarded at the time as reasonable risk-taking, trying to achieve a balance between quality of life and treatment compliance. Healthcare professionals may risk labelling participants as 'non-compliant' if they do not understand the everyday difficulties people face while wearing an off-loading cast or boot for several months. Healthcare professionals need to develop a relationship with people, and to listen and understand the reasons behind individuals' motivations and choices. At diagnosis of diabetes and if complications arise there needs to be a shared decision-making approach to treatment, discussing the potential benefits or risks and agreeing a patient centred treatment plan, that is jointly reviewed and modified as necessary.

Achieving the balance between education and informing people with diabetes but not overwhelming them is often difficult. A recent systematic review concluded that there is insufficient robust evidence that patient education alone is effective in achieving clinically relevant reductions in foot ulcer risk (Van Netten *et al.*, 2020a). There is a need to develop strategies that move beyond education and actively encourage people to self-manage their diabetes and foot complications using behaviour change techniques such as goal setting and review, self-monitoring, and habit formation. The NICE guidelines – *Diabetic foot problems - prevention and management*, recommended the development and evaluation of educational models and behavioural change interventions to prevent foot complications, and reduce the number of recurrences leading to further foot complications (National Institute for Health and Care Excellence, 2015).

In this study, some participants blamed healthcare professionals for missing the diagnosis of CN, leading them to express anger and frustration. The participants' experiences are consistent with retrospective case series reports from Germany and USA, both showing missed or delayed diagnosis of CN (Chantelau, 2005; Wukich *et al.*, 2011), leading to worse outcomes. Our study is also consistent with studies from the USA and Ireland where participants blamed healthcare

professionals and healthcare systems for causing foot problems to develop and for delays in receiving treatment for foot complications (Feinglass *et al.*, 2012; Foster and Lauver, 2014; Delea *et al.*, 2015).

7.6.2 Recommendations for health and social care professionals and policy makers

The overarching recommendations arising from this study are to increase awareness of CN and to adopt a more holistic approach to supporting individuals living with this condition. Firstly, multidisciplinary diabetic foot teams should be expanded to include professionals with skills to support the profound emotional effect CN has on well-being. Alongside this there is an opportunity to upskill existing multidisciplinary team members to support people in a holistic way. Secondly, healthcare professionals need to identify those people who are experiencing pain, and work with them to find solutions to manage the pain. Thirdly, multidisciplinary foot teams need to develop more formal links with social care professionals and voluntary organisations experienced in supporting people who are unable to work or continue with their caring responsibilities due to sickness. This could help participants navigate social care systems to access additional financial and non-financial support and improve the experience of living with CN. Finally, and importantly there is a need to expand the role of people who are experts by experience in peer support, co-producing patient materials, and involve them in service, and facilities re-design, thus improving the overall patient experience and care provided.

7.6.3 Strengths and limitations

This is the first study to explore the lived experience of CN, and has shown the extensive physical, behavioural, and emotional effects on individuals, their relationships, and families.

Purposeful sampling encouraged study trustworthiness (Patton, 2002), and by a second researcher's independently checking the coding and generation of initial themes. The analysis identifies and highlights the diverse experiences of the participants and seeks to explore and understand the reasons behind the similarities and differences to further enhance the trustworthiness of the study. The sample reflected the known typical characteristics of people who develop CN, increasing the likelihood that the findings of this study will be generalisable to others with CN.

This study has some limitations. Participants were approached by the research sites to take part in the interview, and the sites may have unconsciously or consciously introduced bias into the

sample by selecting participants based on those who were likely to be positive about their clinical care or have strong experiences, either positive or negative.

An independent interviewer may have produced further insights from the participants: as the researcher I was already well known to some participants in my clinical role as part of the multidisciplinary foot team. Participants may have been reluctant to disclose any negative encounters with me for fear of this being shared with the clinical team, and this influencing any future treatment or interaction. To try and address these potential concerns prior to the interviews, I advised participants that what was discussed in the interview was confidential, and that the information would be anonymised before being written up and published. I also completed the interviews at three other sites where I was not known to the participants. However, even at some of the other sites it became apparent that the participants had made judgements about my position as a researcher, my personal knowledge of CN, and my relationships with their own clinical team which may have led them to censor what they chose to disclose to me.

Future studies could use purposive sampling to include a more diverse group of participants from different ethnic, social, and cultural backgrounds. Although the interviews were carried out when participants still received treatment for CN, the time since initial diagnosis was up to six months. This could have introduced an element of recall bias in terms of how participants recounted thoughts and feelings across a six-month period. The interviews produced accounts in conversation, and thus only captured the stories participants shared on that day. Meanings may change over the course of treatment, e.g., whether the foot was responding to treatment with a good outcome. Longitudinal interviews could have allowed a deeper understanding of how participants responded to changes in their foot condition over time.

7.7 Conclusion

This study has provided depth and contextualisation to quantitative evidence, by giving a detailed account of the physical limitations that participants with CN experience, how participants characterise and adapt to them, and what implications they have for people's sense of self, and their relationships. Recognising these has shown that living with and adapting to CN has ramifications that extend beyond the direct limitations imposed by wearing the cast or boot to include physical, social, vocational, and psychological consequences. Participants felt guilty if they

found they needed more support from family and friends. Overall participants expressed frustration with low mood, and low self-esteem.

These physical and emotional effects of CN on participants, their families, and relationships were substantial and sustained. This study has demonstrated the importance of ensuring that policy makers and healthcare professionals ensure that services are developed and redesigned to reflect participants experience of CN. People with CN need to be able to access a wider range of support, not only from their clinical team but also from psychological, and social care services.

7.8 Summary

This chapter has examined and evaluated the methods and findings of the qualitative research. The next and final chapter will be the overall discussion and conclusions of this research.

8 Discussion and conclusion

8.1 Introduction

The aim of this doctorate was to investigate the feasibility of using serial MRI to monitor and diagnose remission in CN and to understand people's experiences of living with CN. The concluding chapter of this thesis will summarise the key results and consider the findings in the context of the current evidence. It will also identify the overall strengths and limitations of the research and implications for health and social care professionals, policy makers, and researchers.

8.2 Summary of findings in the context of the current evidence

This thesis took a mixed methods approach with three different studies: systematic review on monitoring techniques for CN (chapter 4), a feasibility study on the use of serial MRI to identify disease remission in CN (chapters 5 and 6), and a qualitative study to understands people's experiences of CN (chapter 7). This section will briefly overview the findings from the three studies. It will then synthesise the findings of the studies to provide a better understanding of the burden of CN on health and social care providers and individuals.

8.2.1 Systematic review findings

This systematic review reported in chapter 4, identified, and evaluated the evidence base for monitoring techniques used to establish remission in people with diabetes and acute CN. Twenty-nine studies were included in the initial review, and a further seven identified in the update of the review. It found that the current approaches to monitoring CN are primarily based on level 3 and 4 evidence: non-analytical case series and expert opinion. There was a lack of consistency in the types and application of monitoring techniques reported across the studies.

The most frequent monitoring techniques used in these studies was serial X-ray, then temperature measurement with handheld infrared monitoring. This review found that two-thirds of the included studies used MRI to monitor CN. However, the use of MRI in this way to monitor CN has not been formally evaluated and is not included in current guidelines for managing of CN . This review found a lack of evidence on the sensitivity, specificity, cost-effectiveness, safety, and patient acceptability for all monitoring techniques. Therefore, the key recommendation was to carry out further high-quality research to evaluate the different approaches used to monitor CN and identify the optimal approach.

8.2.2 Feasibility study findings

This feasibility study, reported in chapters 5 and 6, examined and evaluated the feasibility of using serial MRI without contrast in the monitoring of CN to examine whether the duration of immobilisation of the foot could be reduced. In order to decide whether a definitive study is feasible and warranted. In line with NIHR guidance about feasibility and pilot studies, this study did not intend to test the efficacy of serial MRI in diagnosing remission in MRI (Eldridge *et al.*, 2016b). The key outcomes of interest in this feasibility study were recruitment, retention, data completeness and intervention safety and acceptability.

The sample size and retention rates were sufficiently large to conclude that a future definitive trial is acceptable and feasible (Schulz and Grimes, 2002; Sim and Lewis, 2012).

This feasibility study showed that a future definitive trial to evaluate the effectiveness of MRI to identify disease remission in CN is warranted, feasible and acceptable, to potential participants, healthcare, and research professionals. The number of completed MRIs and the absence of any safety incidents support the feasibility, safety, and acceptability of serial MRIs as the intervention. In addition, it showed that the use of serial MRI has the potential to be cost-effective (Coretti, Ruggeri and McNamee, 2014).

In this study over half the participants presented with Eichenholtz Classification stage 0 with no changes on plain X-ray (Shibata, Tada and Hashizume, 1990). This means that plain X-rays are less useful for monitoring CN. During the study nearly two-thirds of participants also developed concurrent ulceration and infection. This highlights the previous recognised limitations of using infrared thermography monitoring in CN when there are other reasons for inflammation, and a 'hot foot' (Chantelau and Poll, 2012). It also demonstrated the advisability of using MRI as an alternative or additional monitoring technique.

Time in off-loading device(s) was one of several secondary clinical outcomes investigated to inform the design of a future definitive trial. The signal from this feasibility study does suggest that MRI may extend the time in cast. However, this feasibility study was not powered to detect a difference between the two arms of the study. As this was not an effectiveness study, the observed trend may change in an adequately powered definitive trial. Therefore, at this stage uncertainty remains and the trial is warranted as the sample size cannot exclude the possibility of

a worthwhile effect. There is a need for a high-quality study to answer the question of the effectiveness of MRI in monitoring CN.

8.2.3 Qualitative study findings

This qualitative study reported in chapter 7 aimed to explore the lived experience of CN. It focused on the personal experience of being treated for CN, and its impact on the individual, family members and relationships, and on social participation.

This study identified the previously unrecognised, distinctive, and onerous aspects and life implications of the burden of CN experience. Receiving a diagnosis of CN, often without warning, frequently resulted in denial, shock, fear, anger, and resentment.

This qualitative study showed that living with CN has ramifications for people that extend beyond the physical limitations imposed directly by wearing the offloading device. Overall participants expressed frustration, experiencing low mood, and low self-esteem. These physical and emotional effects of CN on participants, their families, and relationships were substantial and sustained. This indicates that people with CN may need to be able to access a wider range of support beyond their clinical team, to include psychological, and social care services.

8.2.4 Summary of key findings

In summary, these three studies showed the lack of existing evidence to support disease monitoring in CN (systematic review); that a future definitive trial to evaluate MRI is warranted and feasible (feasibility study), and that living with CN has widespread long-term physical, social, emotional, and financial effects on the individual and their families (qualitative study). Table 8-1 provides a summary of the learning from the feasibility and qualitative studies which will be used to inform the design of a future definitive trial.

Table 8-1 Summary of the learning from the feasibility and qualitative studies to inform a future definitive trial

	Learning	**Recommendations for a future definitive trial**
1	The involvement of the public and people living with CN has been fundamental to the success of this research in achieving its aims and objectives.	A future grant application for a definitive trial, will include a PPI representative as a co-applicant and have a larger PPI panel to reflect the different voices of people living with CN.
2	The importance of the biopsychosocial model in health research.	A future definitive will continue to examine and evaluate the burden on CN from both the perspective of healthcare and people with CN.
3	Embedding research within existing care pathways increases levels of recruitment and retention, and data completeness.	The future definitive trial will be designed to be embedded with existing care pathways.
4	More participants than anticipated were withdrawn from the feasibility study due to an alternative diagnosis.	This information will be used to calculate the sample size for a future definitive trial.
5	Non-study MRIs were completed that may contaminate the outcome and dilute the relationship between intervention and outcome.	The potential for contamination of the results with non-study MRIs, will be highlighted to researchers at sites during the site initiation. A future definitive study will seek to capture the reasons for any non-study MRIs completed.
6	Two-thirds of participants had an Eichenholtz Classification stage 0 at baseline with no changes on X-ray. This means that plain X-rays are less useful for monitoring CN.	This supports the need for an alternative monitoring technique.
7	During the study nearly two-thirds of participants also developed concurrent ulceration and infection	This supports the need for an alternative monitoring technique.
8	Just under half of the participants initially received treatment with a non-removable below-knee device. Removable devices are associated with longer treatment times compared to non-removable devices.	In a future definitive trial randomisation will be stratified for the type of off-loading device.
9	In the feasibility study the MRI sequencing protocol was not standardised.	In a future definitive trial, we will seek to standardise the MRI sequence protocol.
10	The feasibility study showed that the use of serial MRI has the potential to be cost-effective.	A health economist will join the research team to support a cost effectiveness analysis in a future definitive trial.

Table 8-2 Summary of the learning from the feasibility and qualitative studies to inform a future definitive trial (continued)

	Learning	**Recommendations for a future definitive trial**
11	The feasibility study used a patient diary to collect levels of informal care, to help inform a cost-effectiveness analysis in a future definitive trial. However, there were many missing data.	Co-produced with PPI an updated patient diary to collect a more complete picture of participants' costs.
12	The feasibility study did not consider the future implementation of the results into healthcare delivery at an early stage.	An implementation focussed qualitative sub-study within the definitive trial could identify specific potential barriers to implementing serial MRI and examine how these could be overcome. I will develop an implementation strategy to promote uptake and adoption of serial MRIs into routine clinical practice.
13	Our participants were considered a 'clinically vulnerable' group and advised by the UK government to only attend essential clinical visits which excluded study visits. Consequently, the end point 'time in cast' and other outcomes were not always collected.	To prepare for the possibility of disruption to study visits in the COVID-19 or another pandemic we will seek to find alternative ways to collect data other than face-to-face study visits.
14	Sites may have unconsciously or consciously introduced bias into the qualitative sample by selecting participants.	An independent person will be asked to randomly select participants to invite to take part in the qualitative interviews rather than asking sites to nominate participants.
15	An independent interviewer completing the qualitative interviews may have produced further insights from the participants.	An independent qualitative researcher will join the research team, to complete the interviews.
16	The time since initial diagnosis to interview was up to six months. This could have introduced an element of recall bias.	Complete initial interviews with people diagnosed with CN as soon as possible after diagnosis.
17	The qualitative interviews produced accounts in conversation, and thus only captured the stories participants shared on that day.	Longitudinal interviews could have allowed a deeper understanding of how participants responded to changes in their foot condition over time.
18	The feasibility and qualitative study both demonstrated the important and unrecognised burden of informal care for people with CN	In a definitive trial we will seek to capture the cost of this informal care and include this in a cost effectiveness analysis. A definitive trial could include a study to explore the experiences of carers supporting people with CN.

8.3 Synthesis of findings from this doctorate

This section will examine and evaluate to what extent the findings of this feasibility and qualitative studies agree, complement, or contradict each other to further the understanding of the burden of CN on people. Convergence in the results from the feasibility and qualitative study will provide a stronger evidence base for the findings and recommendations that have arisen from this doctorate (Polit and Beck, 2008).

This feasibility study collected patient reported outcomes of pain, health-related quality of life and anxiety and depression. The feasibility study was not powered to detect between-group or longitudinal differences. However, the patient reported outcomes can be compared to findings of the qualitative study to look for areas of convergence, discord, and complementarity (Farmer *et al.*, 2006). One consideration in comparing the results of the feasibility study and qualitative study is the inconsistency in the frequency of data collection and timepoints. This feasibility study recorded patient-reported outcomes every three months during the active phase of the trial, and one and six-months post remission. This qualitative study was an account of the stories people shared on the day; ten of the participants were still actively receiving treatment for CN, while the remaining four participants had achieved remission.

8.3.1 Synthesis of findings for pain

This feasibility study found that people with CN reported pain, however the experience of pain varied among participants. A VAS as used in this feasibility study is a one-dimensional measure of the intensity of pain. It does not capture the reasons for the pain experienced, where the pain was felt, and how this affected participants. In order for healthcare professionals to support people to manage their pain it is important for them to recognise and understand the causes and effects of any pain experienced. This qualitative study also identified pain as an important consideration for over three quarters of participants. Participants attributed the pain to the direct or indirect consequences of wearing the cast or boot. Pain associated with wearing the cast or boot was an important issue for most of the participants. This research is consistent with the findings from other studies where participants experienced pain when using off-loading devices to treat diabetic foot complications (Brod, 1998; Kinmond *et al.*, 2003; Fox, 2005; Ribu *et al.*, 2007). The results of this feasibility and qualitative study about the experience of pain are consistent with the qualitative study providing the understanding that the pain was predominately related to wearing the off-loading device rather than the CN itself.

Healthcare professionals need to develop strategies to minimise the pain associated with wearing the offloading cast or boot. One observational study with 25 people at risk of foot ulceration found that ankle-high devices and contra-lateral limb length lifts were associated with increased comfort compared to knee-high devices and no limb length lifts (Crews and Candela, 2018). However, the current recommendations for the treatment of CN are to use below-knee not ankle high devices. Therefore, further work would be needed to assess the effectiveness of ankle-high devices in off-loading and immobilising active CN and preventing foot deformity before recommending a change in practice. The issue of limb length difference brought about by wearing the off-loading cast or boot leading to pain and unsteadiness was raised by participants in this qualitative study. Providing practical information for people with CN on how to overcome this acquired limb length difference and improve their stability is one of the recommendations for healthcare professionals from this study and has previously been raised by other authors (Vileikyte and Crews, 2020).

8.3.2 Synthesis of findings for health-related quality of life

This feasibility study used patient reported outcome questionnaires SF-12 and EQ-5D-5L to collect data on people's health-related quality of life (Ware, Kosinski and Keller, 1996; Herdman *et al.*, 2011). Nearly all participants reported problems with mobility and completing usual activities. This is consistent with previous cross-sectional studies using SF-36 (Pinzur and Evans, 2003; Willrich *et al.*, 2005; Sochocki *et al.*, 2008; Raspovic and Wukich, 2014). The EQ-5D index calculated from the results of the feasibility study was lower than that for aged-matched people (Kind, Hardman and Macran, 1999). This qualitative study found that participants experienced numerous, sometimes life-altering changes and adaptations to manage and minimise the impact of CN. Both the feasibility and qualitative study found that living with CN reduced people's quality of life, this resulted in disruption to their mobility and reduced their ability to complete daily activities.

This qualitative study found that when people were wearing the off-loading cast or boot, they experienced reduced stability in standing and walking and an increased risk of falls. This was consistent with the results of the feasibility study where participants reported falls, some of which required treatment in hospital outpatient departments, and for a few, admission to hospital. This is the first study to report the high frequency and severity of falls people with CN experience while wearing off-loading below knee boot and casts. Cross sectional studies have shown that people with type 2 diabetes and neuropathy have increased risk of falling (Brown *et al.*, 2015;

Timar *et al.*, 2016). Furthermore a systematic review has found that people with diabetes have an increased risk of hip fracture (Janghorbani *et al.*, 2007). Wearing an off-loading cast or boot is known to negatively affect people's stability, and if necessary patients should be provided with additional walking aids to minimise this risk (Jarl *et al.*, 2020). This instability can sometimes means that people are more reluctant to wear off-loading devices (Crews *et al.*, 2016). This could increase the time to remission of the CN .

Given the increased risk of falling, which is exacerbated by the off-loading cast or boot, and the potential for worse outcomes this highlights the need to develop and incorporate effective falls prevention strategies for people with CN. There is some evidence from small observational studies that supervised exercise programmes involving gait, balance and strength training, improves postural control, and can reduce falls risk (Allet *et al.*, 2010; Morrison *et al.*, 2010, 2014). Although the off-loading cast or boot was not the intervention in this feasibility study the findings have raised an important safety concern with wearing off-loading devices which requires further investigation. High-quality studies are needed to develop and implement falls prevention strategies, for people with diabetic neuropathy, and specifically those who are provided with off-loading casts and boots to treat CN, and other diabetes related foot complications. Better stability may also reduce the number of adverse falls events experienced with these types of off-loading devices. If it is possible to address people's anxiety and concerns around the instability caused by the off-loading boot or cast this may lead to greater levels of adherence with these devices and thus improved outcomes of CN (Vileikyte and Crews, 2020).

8.3.3 Synthesis of findings for anxiety and depression

Research exploring the effect of CN on people's emotional wellbeing is lacking. This feasibility study used patient reported outcome questionnaires to collect data on anxiety and/or depression. Half of the participants reported anxiety and depression scores higher than normal levels assessed with the HADS questionnaire and just under half scored (well) below normal for the mental component score of the SF-12 (Zigmond and Snaith, 1983; Ware, Kosinski and Keller, 1996). These results are consistent with the only other study on depression and anxiety in people with CN which also reported high levels of depression and anxiety (Chapman, Shuttleworth and Huber, 2014). The themes identified in the qualitative study help provide understanding as to why people with CN may experience higher levels of anxiety and depression compared to people with diabetes and without CN and normal populations. All four themes identified in this qualitative study contributed to participants' experiences of frustration, low mood, and low self-

esteem. Specifically, participants who were no longer in paid employment as a consequence of their CN, reported losing their identity, reduced social interactions and financial concerns. These findings are consistent with a study by Chapman, Shuttleworth and Huber (2014) who found that patients out of work reported more severe anxiety than those in employment.

8.3.4 Summary of synthesis of findings

In summary, the findings of these feasibility and qualitative studies were consistent as regards participants' experiences of pain, health-related quality of life and anxiety and depression. The findings of the qualitative study provide depth and contextualisation to those of the feasibility study and strengthen the evidence base for the policy, health and social care recommendations reported later in this chapter.

8.4 Strengths and limitations of this doctorate

The strengths and limitations of the individual studies have been reported in their respective chapters. This section will examine the strengths and limitations of the research.

8.4.1 Strengths of the research

8.4.1.1 Developing the research idea and design

The first strength of this research was that it was informed directly by clinical practice, based on the experiences and priorities of healthcare professionals. The research idea originated from my own experiences as a podiatrist working with people with CN, and from discussions with leading experts in the field. Alongside this, the National Institute for Health and Care Excellence recommended further research into CN, specifically when is it safe to stop off-loading in the treatment of acute CN (National Institute for Health and Care Excellence, 2015). The US National Institute of Diabetes, Digestive and Kidney Diseases and the Office of Rare Diseases of the National Institutes, also recommended research into the diagnostic markers of CN (Boulton *et al.*, 2009). Given that the research is directly informed by challenges identified in clinical practice, it is likely to have a positive impact on both healthcare delivery and people living with CN.

The second strength of this research is that it used mixed methods to provide understanding and evidence to reduce the burden of CN by improvements in disease monitoring and to better understand people's experiences. In the feasibility study, the quantitative results from the patient reported outcomes, i.e., health-related quality of life, pain, depression and anxiety, and the

qualitative findings provided additional explanations of people's experiences of living with CN. Mixed-methods research creates a more holistic view of the research question, representing different viewpoints and experiences (Shorten and Smith, 2017). For example, the feasibility study showed that people with CN wearing off-loading devices reported a large number of falls. The qualitative study showed how disruptive wearing the off-loading device can be and how people adapted to wearing the device to reduce their risk of falling. The resulting recommendation for clinical practice is better collaboration with physiotherapy departments and falls prevention strategies on how to mobilise people with CN safely and help them adapt while wearing the off-loading devices.

The third strength of this research was that it was embedded in existing clinical care pathways as recommended in the UK's Government policy paper "Saving and Improving Lives: The Future of UK Clinical Research Delivery" (2021). Participant study visits were designed to align with pre-existing clinical pathways for CN. This reduced the burden on participants as they did not need to attend separate clinic and research visits. The clinical team took responsibility for both clinical care and the research. The screening, identification and consenting of participants, and data collection was completed by healthcare professionals working in the multidisciplinary diabetic foot clinics, supported by clinical research nurses if needed. This meant that the healthcare professionals who approached participants about the research were known to them, thus increasing the number of people who were willing to participate in the research.

The mixed methods research design, embedded within existing care pathways, is likely to be one of the factors that contributed to the high levels of recruitment and retention, and data completeness. It will also increase the external generalisability of the results and should improve the implementation of any recommendations into policy and clinical practice.

8.4.1.2 Building the research team

The third strength of this research was its multi-disciplinary approach. The supervisory and Trial Management Team included people from different disciplines and specialities, and a PPI representative. The research team included a sociologist, behavioural scientist, physicians, podiatrists, radiographer, statistician, and health economist.

The previous section reported how stakeholders and people with diabetes and experience of CN were involved in developing the research idea. Here I will evaluate the advantages and

disadvantages of collaborating with partners from different clinical and non-clinical disciplines in research.

The NIHR recognises the importance of multidisciplinary research teams to address large, complex health and social care problems which span professional and organisational boundaries (National Institute for Health Research, 2022). As in this study multidisciplinary teams can ensure that research questions are meaningful, that the outputs are applicable to patients and health/social care professionals, and that recommendations can and will be implemented. This approach to research offers an opportunity to overcome the 'silo-thinking', which may be associated with a uni-disciplinary approach, or a purely medical model approach to research (Smye and Frangi, 2021). The field of clinical medicine is generally less multidisciplinary, however increasingly health research as a whole is becoming more multidisciplinary as it incorporates public health and social considerations of health (Van Noorden, 2015) The advantage of multidisciplinary research is that different disciplines bring their knowledge and experiences to the research question with different theoretical frameworks, methodologies and analytic approaches (Rutting *et al.*, 2016). The potential challenges or disadvantage of multidisciplinary research can be that different disciplines have different methodologies which can be challenging to integrate. It has been reported that it is sometimes more difficult to get multidisciplinary research recognised, when it is evaluated against purely quantitative research metrics (Rylance, 2015).

My previous training, clinical and research experience was largely defined by the medical model. From a personal perspective, the advantage of working alongside different disciplines has been extending my horizons. The initial idea for my research was a study to understand the feasibility of using serial MRI to identify disease remission in CN. Collaborating with colleagues from sociology and behavioural science highlighted how little is known about people's experiences of CN and influenced my decision to adopt a mixed-methods approach.

As a result of the discussions with multidisciplinary colleagues and PPI feedback reported earlier, I decided to use a biopsychosocial model in this research, rather than a purely medical model. The biopsychosocial model would allow me to examine and evaluate the burden on CN from both the perspective of healthcare and people with CN.

8.4.1.3 Involving people in the design and evaluation of studies

The final strength of my research was patient and public involvement (PPI) in all three proposed areas identified by the NIHR: involvement, engagement, and participation (National Institute for Health Research, 2021a). The next section will report how PPI representatives were specifically involved in this research. It will examine and evaluate the value of PPI input in shaping this research and ensuring robust and relevant findings.

While preparing my NIHR fellowship application, I discussed my research ideas with people with diabetes who attended the multidisciplinary diabetic foot clinic where I worked and who had current or past experience of CN. I then discussed my proposed research with members of the Norfolk Diabetes Patient Support Group and members of the local Patient and Public Involvement in Research Group (PPIRes). The feedback from the groups was positive: everybody thought that a study into CN was really needed, and they would agree to be involved if approached. They also wanted more accurate information on treatment times. They thought that people would be prepared to undergo regular MRIs if the results of this study reduced treatment times. They felt that the additional time in clinic would not be a barrier to being involved. Both the Norfolk Diabetes Patient Support Group and PPIRes expressed concerns that the research did not explore the devasting impact of CN on people diagnosed with the condition. Reflecting on the PPI feedback and advice for the multidisciplinary team lead me to decide to expand the research to include a study to understand people's experiences of living with CN.

Once the research commenced, members of the PPIRes group were asked to review and comment on the study protocol, the patient information sheets and informed consent forms. The PPIRes group provided feedback on changing the language in both the patient information sheet and consent form, to make it clearer, more relevant, and understandable for participants.

Members of the PPRIes group specifically recommended that I 'soften' the wording used to explain the limitations of current approaches to monitoring CN, as this might decrease participant engagement in the standard care arm of the feasibility study. Reflecting on this aspect of the PPI feedback I decided not to significantly change the information in the patient information sheet. Concerns over the standard care arm had not raised by people who had experience of CN. I judged that it was important to adequately describe the limitations of the current approaches to monitoring CN, as this provided the rationale for the study, and I considered that this would not adversely impact on recruitment to the study.

Other concerns included describing potential side effects of plain X-rays as 'cancerous', which may decrease study uptake. Explaining the potential side effects of plain X-rays to research participants, is a specific requirement of the Health Research Authority, and they provide guidance on phrasing risk statements for patient information sheets (Health Research Authority, 2020). While I acknowledged the PPI feedback that the information in the patient information sheet could be perceived as shocking or frightening it was standard text based on the Health Research Authority guidelines and could not be altered.

Finally, members of PPRIes suggested pictures/images to accompany the text in the patient information sheet to illustrate the potential benefits of using MRI over X-ray and a timeline to illustrate the different study stages. I considered this an excellent suggestion, as it had been difficult to adequately describe the potential advantages of MRI over plain X-ray. A pictorial representation would clearly show the difference between the two types of investigations which could complement the text. This could increase participants understand of the rationale behind the study. An improved understanding of the study could result in more people being willing to participate.

One PPI representative, who was an informal carer for someone living with CN, joined the Trial Management Group and contributed to the research based on their own experiences, such as ways to make the feasibility study more acceptable to participants to improve recruitment.

The second way of involving the public in research is engagement. Throughout the feasibility study I provided regular updates to participants through a study newsletter. To improve the credibility of the analysis of the qualitative study, I developed and sent out a study newsletter and asked participants to check the findings. Three participants replied and provided further information on their experiences, thoughts, and emotions of living with CN. These responses provided additional depth to the original interviews but did not affect the overall analysis and interpretation of the findings.

The third and final way in which I plan to engage with PPI is by sharing the results of the studies with the participants and to disseminate the results more widely to organisations which represent people with diabetes, i.e., Diabetes UK. Through sharing the findings of the qualitative study this will enable organisations such as Diabetes UK who offer support to people with diabetes through a helpline, to better train and equip their advisors to be able to assist and help people with CN.

This research has recommended a greater emphasis on supporting people to actively manage their diabetes and foot complications. It has also recommended an improved awareness and recognition to provide support for people with CN who experience isolation, depression and/or anxiety. By promoting the findings of this study to organisation such as Diabetes UK they can campaign for and drive changes to practice to increase the likelihood of the recommendations from this research being adopted and implemented.

In conclusion, PPI involvement throughout the design, data collection, analysis and write-up ensured that the research is relevant to and reflects the priorities of people with CN and diabetes. It has ensured that the research design is sensitive to the needs and preferences of the participants. The involvement of the public and people living with CN has been fundamental to the success of this research in achieving its aims and objectives. In a future grant application for a definitive trial, I will include a PPI representative as a co-applicant and have a larger PPI panel to reflect the different voices of people living with CN.

8.4.1.4 External generalisability

Generalisability in research considers how the findings of a study can be applied to the overall population. Participants of the feasibility study were representative of the wider CN population, with more males, being in their fifties and a diabetes diagnosis more than ten years ago (Petrova, Foster and Edmonds, 2004). The final strength of this study was that it was embedded into clinical practice and participants were recruited by healthcare professionals rather than through an advert. Both factors strengthen the external generalisability of the results.

8.4.2 Limitations of the research

8.4.2.1 Challenges encountered with setting up the feasibility study

This section will examine the barriers reported by sites that prevented them participating in the feasibility study and identify potential solutions that may improve participation in a future definitive trial.

Thirteen potential sites were directly approached about participating in this study. These sites were known to the Trial Management Team and had a good record of participant recruitment and retention to other diabetic foot studies. The study was also publicised through the NIHR Clinical Research Networks. Five sites agreed to participate in the research. The remaining seven found

this an important study and wanted to participate but were unable to. The final site reported being unable to participate due to a conflict of interests with another study they were completing.

The main reason sites reported being unable to participate was associated with funding the excess treatment costs for the serial MRI in the intervention arm. In research, excess treatment costs are the cost that would be incurred if the intervention (i.e. serial MRI) was adopted into routine clinical practice at the end of the research (Department of Health, 2012). In October 2018, during the feasibility study, NHS England introduced a new model for managing excess treatment costs (NHS England, 2018). The resulting complexities and uncertainty over excess treatment cost reimbursement was the main limitation in recruiting more study sites.

Although the feasibility study was adopted on the NIHR portfolio it did not generate any remuneration for the participating sites. While remuneration itself should not affect a site's decision to participate in a trial, practicalities need to be considered such as the funding of additional staff to undertake the research, while not reducing clinical activity. Two sites that were approached identified a lack of capacity within the podiatry department to take on additional workload (collecting and recording outcome measures). One solution in the definitive study would be for the podiatrist to work alongside the NIHR Clinical Research Network funded nurses, who can support the podiatry team in completing additional requirements beyond usual clinical care. At the moment the Clinical Research Network predominately fund nursing posts; they could consider funding Allied Health Professionals to support research activities (National Institute of Health Research, 2018).

This section has identified the challenges associated with embedding research into clinical practice. In order to successfully implement the UK's Government policy paper "Saving and Improving Lives: The Future of UK Clinical Research Delivery" (2021) these structural barriers to embedding research in clinical practice need to be overcome.

8.4.2.2 Completion of the patient diary

The feasibility study used a patient diary to collect levels of informal care, to help inform a cost-effectiveness analysis in a future definitive trial. However, there were many missing data. The qualitative study showed the important role of informal carers in helping people to live with the physical, and psychological effects of CN. If serial MRIs reduce the duration of informal care required, then this is an important economic consideration (Goodrich, Kaambwa and Al-Janabi,

2012). Therefore, a future study will use a modified patient diary to collect a more complete picture of participants' costs. Importantly, it will be co-produced with PPI to ensure the diary is relevant to and reflects the priorities of people with CN and other key stakeholders (Hickey *et al.*, 2018). Greater involvement of PPI in the design of the patient diary should help overcome the limitations of missing data that occurred in this feasibility study.

8.4.2.3 Considerations on how to successfully implement the recommendation from this research into clinical practice

A second limitation of this research was that it did not consider the future implementation of the results into healthcare delivery at an early stage. There are many challenges associated with translating research evidence into clinical practice (Grol and Grimshaw, 2003). Implementation science is a discipline which investigates the social, behavioural, economic, and organisational enablers and barriers for translating research into clinical practice , seeking to develop and evaluate effective implementation strategies (Curtis *et al.*, 2017).

If a future definitive study shows that MRI is more effective in diagnosing remission than current standard care, then this will change the current practice. Including an implementation focussed qualitative sub-study within the definitive trial could identify specific potential barriers to implementing serial MRI and examine how these could be overcome. For instance, such a study could seek views from the immediate diabetic foot team, wider colleagues such as radiologist, radiographers and hospital managers involved in finance and capacity planning. These findings could be used to support the development of a strategy to anticipate and offer solutions to overcome potential barriers to implementing serial MRI to monitor CN in clinical practice.

8.4.3 Summary of the strengths and weakness of this research

In conclusion, this section has examined and evaluated the strengths and limitations of this research. The strengths included the rationale for the study, study design, PPI involvement, multidisciplinary team, and external generalisability. It also reported the limitations in terms of missing data in the patient diary, site recruitment and examined how to increase the likelihood of successful implementation of the evidence of a future definitive trial into clinical practice.

8.5 Implications for policy makers, and health and social care professionals

This section will report the recommendations arising from the findings for policy makers and health and social care professionals. There are three overarching recommendations for policy and practice, which will be discussed in turn.

8.5.1 Increase awareness of Charcot neuroarthropathy among health and social care professionals and people with diabetes

The first recommendation is to increase awareness of CN among health and social care professionals and people with diabetes. Participants of the qualitative study perceived that they had experienced a delay in the diagnosis of CN. They thought that this had contributed to longer treatment times, increased foot deformity and this had contributed to their overall stress and anxiety levels. These experiences of delayed diagnosis were confirmed by the findings of the feasibility study where over half of the participants already had radiological evidence of CN at enrolment, indicating disease progression. The evidence from previous studies confirms that early treatment of CN reduces time to remission and improves outcomes (Chantelau, 2005; Wukich et al., 2011).

Despite national and international guidelines for the assessment and management of diabetic foot complications including CN, this study and other studies have found that people are not being referred on to specialist services soon enough (National Institute for Health and Care Excellence, 2015). This results in worse outcomes for people and increased cost to the healthcare system. Thus, it is important to promote timely and appropriate help seeking among people with diabetes and raise awareness of CN among healthcare professionals.

In the qualitative study, some participants discussed their experience of receiving a diagnosis of diabetes and how they felt overwhelmed with all the information they received. They identified only being able to process what was relevant to their immediate situation. In general, evidence-based structured education is provided for people with newly diagnosed diabetes, as this is part of the Quality and Outcomes Framework of the General Medical Services contract (National Institute for Health and Care Excellence, 2020, 2021). However, ongoing, evidence-based education to support people to develop behavioural and psychological strategies to self-manage their diabetes and foot complications are less widely available (Van Acker and Baker, 2014). These could be provided through face-to-face sessions or digital means (e.g., websites, smartphone applications) and enable long-term self-management of their diabetes at a time and pace that

works for them. Many of these resources already exist, however the challenge continues to ensure that they are person centred and encourage those who are less motivated or capable to engage with this support, then to use this knowledge and information to seek advice and support when needed (Van Netten, Woodburn and Bus, 2020). These resources need to be co-produced with people with diabetes to ensure they are tailored to address cultural differences, among other things. One such programme has been developed by a team at University College London (Murray, 2019).

The challenge is to find ways to ensure that these resources reach the people who can benefit the most from them. This could firstly involve developing partnerships with local community groups, and other social care providers that already have established links with people such as enablement or housing authority services. Secondly, ensuring that the resources are available for individuals who have hearing problems, are deaf, are partially sighted or blind, and people who have no or poor understanding of the English language. Finally offering flexibility in the way education materials are delivered and provided which could include face-to-face sessions with different locations and timings, online material, and leaflets. All of these factors could increase the uptake of and impact of ongoing education to reduce the number of people who develop diabetic foot complications, encourage timely and appropriate health seeking behaviours and encourage people to actively participate in the management of their diabetes.

CN is a relatively rare complication of diabetes and initial symptoms are often non-specific. People are initially seen in a range of settings before being referred to specialist foot clinics. Therefore, it is challenging to successfully raise awareness of this condition among healthcare professionals and reduce the number of delayed diagnosis and referrals. There are evidence-based guidelines on Diabetic foot problems, which include recommendations on the assessment and management of CN (National Institute for Health and Care Excellence, 2015). However, raising awareness of CN among people with diabetes and healthcare professionals is not one of the priority recommendations made in this NICE guideline. This study has shown that guidelines in themselves do not translate into improved experiences for people living with CN. Participants in the qualitative study described strong emotions of frustration and sometimes anger directed at healthcare professionals that they perceived missed or delayed the diagnosis of CN, and this contributed to their stress and anxiety. There are opportunities to increase non-specialists' knowledge and awareness of CN through continued professional development. Clinical guidelines

could include decision trees to help support non-specialist healthcare professional to recognise and then refer suspected cases of CN on to multidisciplinary foot teams without delay.

Given the rarity of CN and the challenges in making a diagnosis based on clinical examination and radiological imaging, there is a need to consider what other opportunities may exist to help screen for and diagnose CN. It is estimated that up to 50% of people with diabetes have neuropathy, however only a small proportion of these develop CN (Goonoo and Selvarjah, 2022). There have been three small studies with between 50-100 participants with CN that have examined whether some people with diabetes may have a genetic predisposition to develop CN (Pitocco *et al.*, 2009; Korzon-Burakowska *et al.*, 2012; Bruhn-Olszewska *et al.*, 2017). These studies have shown that people with diabetes who have neuropathy and develop CN have a higher number of osteoprotegerin (OPG) gene-related candidate genes. There is however a need for further studies to verify these findings. The UK policy paper Genome UK: the future of healthcare sets out a strategy where genomics will be at the forefront of driving improvements in the prevention, diagnosis and treatment of diseases (HM Government, 2020). Genomics represents an opportunity for people with CN, healthcare professionals and researchers to better understand CN and then consider how this genomic evidence can be translate into improvements in prevention, clinical care, and outcomes.

The Office of Rare Diseases of the National Institutes of Health from the USA highlighted the need for a co-ordinated international approach to research into the pathophysiology, and management of CN (Boulton et al., 2009). In the UK a rare disease is defined as a condition which affects less than 1, in 2000 people (Department of Health & Social Care, 2021). The true prevalence of CN is still largely unknown. However, one study from Denmark estimated a 0 - 1 in every 2000 people will develop CN (Svendsen *et al.*, 2021). In the USA figures state that approximately 1 in every 2,500 Americans will experience CN (Amputation Prevention Centers of America, 2022). More recent studies suggest an increase in the numbers of people with CN, but this could be a result of increased awareness, rather than an actual increase in the incidence. This means that CN may not fit the definition of a ‘rare disease’. However, there is definite overlap between the findings and recommendations of this research and the priorities of the UK Rare Disease Framework which are to:

1. Helping patients get a final diagnosis faster.
2. Increasing awareness of rare diseases among healthcare professionals.
3. Better coordination of care.

4. Improving access to specialist care, treatments, and drugs (Department of Health & Social Care, 2021).

This framework highlights the need for national and international collaboration to share knowledge and ideas, and complete high-quality research to ensure the best care and outcomes for people with rare diseases. For CN this could mean the development of an international register with accurate up-to-date data on the incidence of CN, opportunities to examine and evaluate the effectiveness of current and new treatments for CN, and support researchers to identify people with CN will would be willing to participate in research.

8.5.2 Improve awareness and recognition and provide support for people with Charcot neuroarthropathy who experience isolation, depression and/or anxiety

The second recommendation is for healthcare professionals to be able to identify and support people who are experiencing social isolation, depression, or anxiety. The feasibility study found that people with CN reported higher levels of depression and anxiety than age and sex matched controls. This qualitative study findings indicate that people with CN who experience emotional distress, low mood, and low self-esteem will need dedicated psychological support. Participants thought that being disconnected from their social networks was an important reason for these negative emotions.

Individuals, families, health and social care, local authorities and voluntary organisations all need to work together to help reduce the social isolation caused by living with CN (UCL Institute of Health Equality, 2015). This could be achieved by finding solutions to enable people to maintain existing relationships through improved access to technology or transport. Firstly, health and social care professionals could recommend local voluntary organisations who can provide transport to attend meetings. Secondly, they could provide advice on the options available for accessing financial support such as Personal Independence Payment which could be used to cover the cost of using taxis or pay others petrol costs to enable people to go out. Thirdly, signposting individuals to develop new contacts and relationships through peer support groups, voluntary organisations, or a befriending service. For people with CN who experience difficulties in going out, the use of technology to develop social connections may be particularly useful. Finally, health and social care professionals could signpost people with CN to voluntary organisations or local

libraries who can support people to develop IT skills. These organisations may also be able to assist people with temporarily loaning equipment or applying for funding to purchase their own IT equipment to enable them to use technology to maintain and develop social networks, and thus reduce isolation.

The development of a diabetic foot complication increases the likelihood and severity of mental health problems (Chapman, Shuttleworth and Huber, 2014; Hoban *et al.*, 2015). An assessment by healthcare professionals of the emotional consequences of CN on well-being therefore needs to become integral to the clinical appointment . One option may be that people complete recognised patient-reported outcome tools within routine clinical appointments to assess emotional distress, anxiety, and depression. These patient-reported measures could be used to identify people who need additional support and develop shared decision-making about treatment choices and self-management.

There are no validated disease specific patient-reported outcome measures (PROMs) for CN (Hogg *et al.*, 2012). Research is needed to assess whether generic or foot ulceration-specific PROMs could be used for people with CN (Peach and Hinchliffe, 2014). Alongside this, non-specialist healthcare professionals could be trained to recognise and support people who are experiencing emotional distress. This would enable healthcare professionals to identify, refer and signpost people where appropriate to psychological services, volunteer, community, or patient organisations which can provide information and support not just for CN itself, but also on psychological strategies to managing emotional distress.

8.5.3 Actively support people to self-manage their diabetes and foot complications

The third recommendation is that health and social care professionals actively support people with CN to self-manage their diabetes and foot complications. Healthcare professionals need to discuss and identify strategies with people living with CN that balance the need to rest and take weight off the foot against the substantial physical limitations, economic and emotional stresses imposed on people wearing the off-loading device for several months (Vileikyte and Crews, 2020). Healthcare professionals need to be more proactive in providing information about governmental, health and social care, community and voluntary organisations that can provide physical and financial advice and support on how to adapt and maintain personal independence.

This could include voluntary organisations which loan out equipment, or the Citizens' Advice Bureau teams which offer advice on accessing welfare resources.

The results from the feasibility study and qualitative study show that the experience of pain in CN is an important consideration for participants. Pain substantially influences their overall experience of living with CN but is commonly unaddressed in clinical practice. The pain contributed to the common physical and emotional distress participants reported. Clinical teams therefore need to be more aware of and responsive to this aspect of patients experience to ensure that they actively seek to identify people who are experiencing pain. Where relevant healthcare professionals need to work with people to identify person-centred solutions to effectively manage this pain, which in turn would reduce one of the triggers for emotional distress. The introduction of a pain patient reported outcome, as a discussion prompt during foot clinic appointment may be pertinent here. At the initial fitting of the cast or boot, healthcare professionals need to advise or arrange a temporary or permanent raise to the footwear worn on the other leg to address the acquired limb length discrepancy. A limb length lift has been shown to improve the comfort of people with diabetes wearing off-loading devices (Crews *et al.*, 2016). If this does not adequately alleviate symptoms of pain, then other non-medical and medical interventions may need to be discussed with the patient to identify what they consider will be most beneficial to help them manage the pain. Referral to a physiotherapist may support people to develop ways of mobilising while minimising the pain they experience.

General advice about overall good health and diabetes management is to be physically active and maintain a healthy weight (Brownrigg and Ray, 2014). When a diabetic foot complication such as CN develops, this advice changes for the duration of the foot problem. People with CN are advised to be less physically active, rest the foot and are issued with boots or casts which further restrict their mobility, often for many months. For participants in the qualitative study, these recommendations and physical limitations fostered concerns for their overall health and was shown by their emotional distress. One option for clinical teams to address this would be to provide advice, and information on different types of physical activity that can be carried out without the need to stand such as resistance exercise (Reeves, 2020). Physiotherapy departments may have developed similar resources to support other people with other long-term conditions which could be adapted and made available for people with diabetic foot complications.

8.5.4 Summary of implications for policy makers, and health and social care professionals

In summary, the above recommendations highlight the need to develop policy and practice so as to: firstly, support healthcare professionals to adopt and integrate a more patient-centred model of care; secondly, to equip people with behavioural and psychological strategies to better self-manage their condition; finally, that it is essential that people and their families are involved in the co-design, piloting, implementation, and evaluation of any changes to policy and practice.

8.6 Recommendations for future research

This section will consider the recommendations for future research from the feasibility and qualitative study.

8.6.1.1 Primary recommendation

The primary recommendation for future research from this thesis is to conduct a definitive trial to evaluate the use of serial MRI in diagnosing disease remission in CN. The feasibility study identified several considerations and possible adaptions that will need to be examined and evaluated before finalising the design of a future definitive trial.

8.6.1.2 Recommendation to adapt the design of a future definitive trial

Prior to the future definitive trial, a Delphi consensus study will be undertaken to optimise and standardise the intervention serial MRI (Niederberger and Spranger, 2020). Experts from different specialities working with people with CN and in imaging will be invited to participate in an online group to develop a consensus protocol for MRI scanning in CN . Data will also be collected on access to different scanners to ensure that the consensus document is clinical applicable.

The feasibility study showed that the type of off-loading device at baseline had a significant difference on the 'time in cast' ($p=0.012$). This is consistent with other studies which found that CN takes longer to heal in removable devices compared to non-removable (Game *et al.*, 2012). Therefore, in a future study randomisation should be stratified for the type of off-loading device.

In the feasibility study a number of MRIs which were not associated with the study were completed. These may have caused contamination between intervention and control group and diluted any association between intervention and primary outcome. It is not known whether these MRIs reflected a change in practice due to study participation. The potential for contamination of the results with non-study MRIs, will be highlighted to sites during the site

initiation. A future definitive study will seek to capture the reasons for any non-study MRIs completed.

The continuation of the COVID-19 pandemic or another pandemic may disrupt a future study. To prepare for the possibility of this we will seek to find alternative ways to collect data other than face-to-face study visits. This could include additional participant reported outcomes such as the type of off-loading device being used, self-monitored foot temperatures, and outcomes such as ulceration and infection.

8.6.1.3 Recommendations for future qualitative research

The qualitative study only captured those participants' experiences of CN that they shared on the day of the interview. A future definitive trial could include a qualitative sub-study with longitudinal interviews to provide a deeper understanding of how participants responded to successive changes in their foot condition, and physical, socioeconomic, and psychological challenges over time. Such a study could also use purposive sampling to include a more diverse group of participants from different ethnic, social, and cultural backgrounds (Peach and Hinchliffe, 2014). A further qualitative sub-study to explore the experiences of carers supporting people with CN would ensure that the research reflects a biopsychosocial model both for participants with CN and their carers.

As discussed earlier, one of the limitations of this feasibility study was that it did not consider how serial MRI would be implemented into clinical practice. A future definitive trial could also include an implementation qualitative sub-study with healthcare professionals and hospital managers to identify potential barriers to implementing serial MRI in routine practice and examine how these could be overcome (Curtis *et al.*, 2017).

In summary the main recommendation from this research is to carry out a fully powered definitive trial to evaluate the effectiveness of serial MRI in disease monitoring in CN. I plan to conduct this trial as part of a post-doctoral research programme.

8.7 Reflections on my personal development as a clinical academic

This PhD has been the first step towards my aspiration to become an independent researcher with a network of collaborators working towards developing the evidence base to improve the clinical outcomes of people with diabetes and diabetic foot complications.

I completed this PhD part-time, over five years alongside my clinical leadership role. A part-time PhD combining a clinical/academic role is full of challenges, balancing the demands of research and clinical practice. However, I have found that there are some advantages. The two roles complement each other to ensure that the people who I see in clinic are offered treatment based on the best available evidence and that in turn my research reflects the priorities and needs of people with CN. Spending two days a week in my clinical role has allowed me to share the knowledge and experiences I have gained through this PhD with the podiatry team, and hopefully encourage them to develop an interest in research.

This research has given me a greater awareness of the importance and benefits of PPI. Firstly, in identifying research that is relevant to and reflects the priorities of people with CN and diabetes. Secondly, in ensuring that the research design is sensitive to the needs and preferences of the participants.

Prior to beginning this doctorate all my previous training, clinical and research experience has been largely defined by the medical model. Working as part of a multidisciplinary team has extended my horizons. It has encouraged me to adopt a mixed methods approach to research and to investigate the burden of CN from the perspective of healthcare providers and people with CN.

The most daunting and challenging part of this research was the design, data collection, and analysis for the qualitative study. It was a methodological approach I was not familiar with. I was also concerned, despite being a healthcare professional with 25 years' experience, that it was going to put me in situations talking to people with CN that I might not feel completely comfortable with. The support and encouragement of my supervisory team helped me to overcome these anxieties. Completing the qualitative study has been one of the most enjoyable and thought-provoking experiences of this program of research. It has highlighted to me the concerns and challenges people with CN experience with prolonged periods of resting and wearing the cast or boot. As a result of this, I now strive to develop a more effective therapeutic relationship with patients, which reflects and respects people's individual needs and priorities. I

also now encourage other healthcare professionals to reflect on their judgements on people's healthcare and lifestyle choices and support them to adopt and integrate a more patient-centred model of care.

In other work I am involved in I found I have unconsciously become an advocate of exploring and understanding people's experiences to improve the effectiveness of new guidelines and interventions.

I would now like to share my knowledge and experiences with other Allied Health Professionals locally and nationally to support them in developing research skills and aspirations through the 'Shaping Better Practice Through Research: A Practitioner Framework'. On completion of my PhD, I aspire to be appointed to a Consultant Podiatry clinical/academic post in my organisation. I will then apply for a post-doctoral bridging award to prepare an application for a NIHR Clinical Lectureship award.

8.8 Conclusion

To conclude this thesis has contributed to the evidence base to provide understanding and evidence to help reduce the burden of CN by supporting improvements in disease monitoring and to better understand people's experiences.

The systematic review (chapter 4) identified there are multiple techniques, used to evaluate remission in acute CN, however the quality of evidence to support the techniques is low or very low. The review found there is uncertainty about the effectiveness of the different monitoring techniques to diagnose remission in CN, and whether the different monitoring techniques influence time to remission and recurrence rates. The conclusion of the systematic review was that there is a need for high-quality studies to identify the most accurate, safe, and cost-effective monitoring techniques in CN.

The feasibility study (chapters 5 and 6) identified it is possible to recruit and retain participants to a study on the use of serial MRI in the monitoring of CN. It found that the intervention in the feasibility study, serial MRI was achievable, safe, and acceptable. The conclusion of the feasibility study was that a future definitive trial on the use of serial MRI in monitoring CN is warranted, feasible, and acceptable.

The results of the qualitative study (chapter 7) identified that receiving treatment for CN commonly has physical, socio-economic, and psychological consequences, which extend beyond the burden of wearing an offloading device. The physical and emotional effects of living with CN are substantial and sustained, for the individual, and their families. It can be concluded from these studies that health and social care professionals should adopt a more holistic approach to supporting individuals with CN.

If a future definitive study proves that MRI is a more effective way to monitor CN, then this could save the NHS money. People would regain their independence and go back to work sooner. If people are better supported to manage the emotional and physical consequences of CN, then this could improve people's quality of life and wellbeing.

Appendices

A) Published systematic review paper

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RESEARCH ARTICLE

WILEY

Systematic review of techniques to monitor remission of acute Charcot neuroarthropathy in people with diabetes

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Abstract

Aim: The management of acute Charcot neuroarthropathy relies on off-loading which is costly and time-consuming. Published studies have used monitoring techniques with unknown diagnostic precision to detect remission. We performed a systematic review of techniques for monitoring response to offloading in acute Charcot neuroarthropathy.

Materials and Methods: We included studies of off-loading which evaluated or described monitoring techniques in acute Charcot neuroarthropathy. PubMed, EMBASE, CINAHL and Cochrane databases were searched (January1993-July 2018). We extracted data from papers including study design, setting, population, monitoring techniques and treatment outcomes. We also extracted information on the cost, clinical applicability, sensitivity and specificity, safety and participant acceptability of the monitoring techniques.

Results: We screened 1205 titles, 140 abstracts and 45 full-texts, and included 29 studies. All studies were of low quality and at high risk of bias. In seven studies, the primary aim was to evaluate monitoring techniques: three evaluated magnetic resonance imaging, two thermography monitoring, one three-phase bone scanning and one Doppler spectrum analysis. The remaining 22 observational studies reported treatment outcomes and described the monitoring techniques used to assess the Charcot neuroarthropathy. Heterogeneity prevented the pooling of data. Very few studies included data on cost, clinical applicability, sensitivity and specificity, safety and patient acceptability of the monitoring techniques used.

Conclusion: Multiple techniques have been used to evaluate remission in acute Charcot neuroarthropathy but uncertainty remains about their effectiveness. We recommend further research into the influences of different monitoring techniques on treatment outcomes.

KEYWORDS
Charcot neuroarthropathy, monitoring, off-loading, remission, systematic review

1 | INTRODUCTION

Charcot neuroarthropathy (CN) is a complication of peripheral neuropathy associated with diabetes which affects the lower limb. It may be precipitated by minor trauma or other inflammatory insult which the patient does not notice due to insensitivity to pain. When, the patient does not rest the foot, an exaggerated inflammatory response occurs.[1] The symptoms include redness, warmth and swelling in the foot and/or leg. It can cause fractures and dislocations within the foot, which may progress to deformity and ulceration.

The treatment aims to stop the inflammatory process, relieve any pain and maintain foot structure.[2] Treatment for CN is "off-loading" the application of a non-removable plaster or fibreglass cast or boot; this rests and immobilizes the foot and redistributes the weight and pressure from the foot to the leg.[3] Off-loading is continued until remission when there are no longer clinical signs of inflammation, and X-rays are stable with signs of healing.[2]

Globally, evidence suggests significant variation in treatment times. In the United Kingdom, observational studies report treatment times of 9 to 12 months before remission is achieved[4-6] whilst data from the United States[7-10] and other European centres report treatment times of only 4–6 months.[11-14] Several factors could contribute to global variation, include participant characteristics, different techniques for monitoring, different protocols for the same monitoring techniques, variations in approach to off-loading and study design variability.[5]

The current evidence base for the treatment of CN is poor. It is principally based on small retrospective cohort and observational studies of patients attending multidisciplinary foot clinics. Evidence to support the effectiveness of techniques to monitor CN is lacking, and current practice is primarily based on expert opinion.[2] Skin temperature is used because CN involves inflammation of the soft tissue and bone.[17] Skin temperature is however, a proxy measure of inflammation measured on the dorsum of the foot over the site of injury, which may not reflect the degree of inflammation within the affected deeper tissues, bones and/or joints. X-rays show damage to the foot skeleton rather than disease activity and are a measure of foot deformity. Despite these limitations, serial temperature measurements and X-rays remain the most widely used monitoring technique in CN.

Improvements in monitoring CN could reduce treatment times. Lack of evidence to support clinicians in the choice of the type of monitoring and decision thresholds for remission may account for variability in treatment times. To the best of our knowledge, there are no systematic reviews focused on monitoring techniques to identify remission in CN.

Therefore, this systematic review aims to identify the effectiveness of published techniques for monitoring remission in the management of acute CN in patients living with diabetes. The objectives are:

1. To identify the techniques used in the monitoring of CN.
2. To identify the sensitivity and specificity of different techniques used to monitor CN.
3. To identify the financial implications to healthcare providers and the NHS and the clinical feasibility of identified techniques.
4. To identify the safety considerations, and participant acceptability of identified techniques.
5. To identify whether different techniques used for monitoring influence the outcomes of CN.

2 | METHODS

This systematic review adheres to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist.[18] The protocol was prospectively registered in PROSPERO http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018093340(CRD42018093340).[19]

2.1 | Inclusion and exclusion criteria

The inclusion criteria for study design were purposefully wide, based on prior knowledge of research studies on CN. We included randomized controlled trials, preference-controlled trials, and observational studies with or without control group(s). We excluded abstracts, systematic reviews and meta-analyses, studies on surgical and pharmacological management of CN, expert opinion, observations of single case studies and laboratory studies.

We included studies on off-loading which evaluated or reported monitoring techniques in adults with diabetes with a diagnosis of acute CN managed in any setting, including hospital, primary care or community. The control condition included other techniques used to monitor CN or the same technique used differently, for example different protocols for thermographic monitoring.

2.2 | Search strategy

We completed searches in PubMed, Embase, CINAHL, the Cochrane Central Register of Controlled Trials and ClinicalTrials.gov. The searches were restricted to English language, from 1993 to June 2018 and adapted for each database. See Appendix 1 for an example search strategy for PubMed. We used search terms for diabetes, Charcot, neuroarthropathy and osteoarthropathy. We also checked the reference lists of relevant published systematic reviews.

We downloaded all papers identified into EndNote and removed duplicates. Screening was conducted independently by two reviewers (C.G. and K.G.) in all three phases: title, abstract and full-text screening. Reasons for exclusion were recorded during abstract and full text screening. Inter-rater agreement was calculated by the number of papers on which the two reviewers agreed in terms of inclusion and exclusion, divided by the total number of double screened papers. Discrepancies were resolved by consensus (C.G. and K.G.). All records deemed eligible following this consensus process were included for full text assessment or data extraction.

We extracted information on participant characteristics including type of diabetes, duration and HbA1c. We also extracted information

on sensitivity and specificity of the techniques, protocol for application of the technique, costs and feasibility, safety and participant considerations. Finally, we extracted methods of off-loading and clinical outcomes such as time to healing and relapse rates.

The first author (C.G.) extracted data from all included papers. The completed data extraction sheets were independently validated by a second reviewer (K.G.) against the papers. Given the wide range of study designs included, data synthesis was narrative.

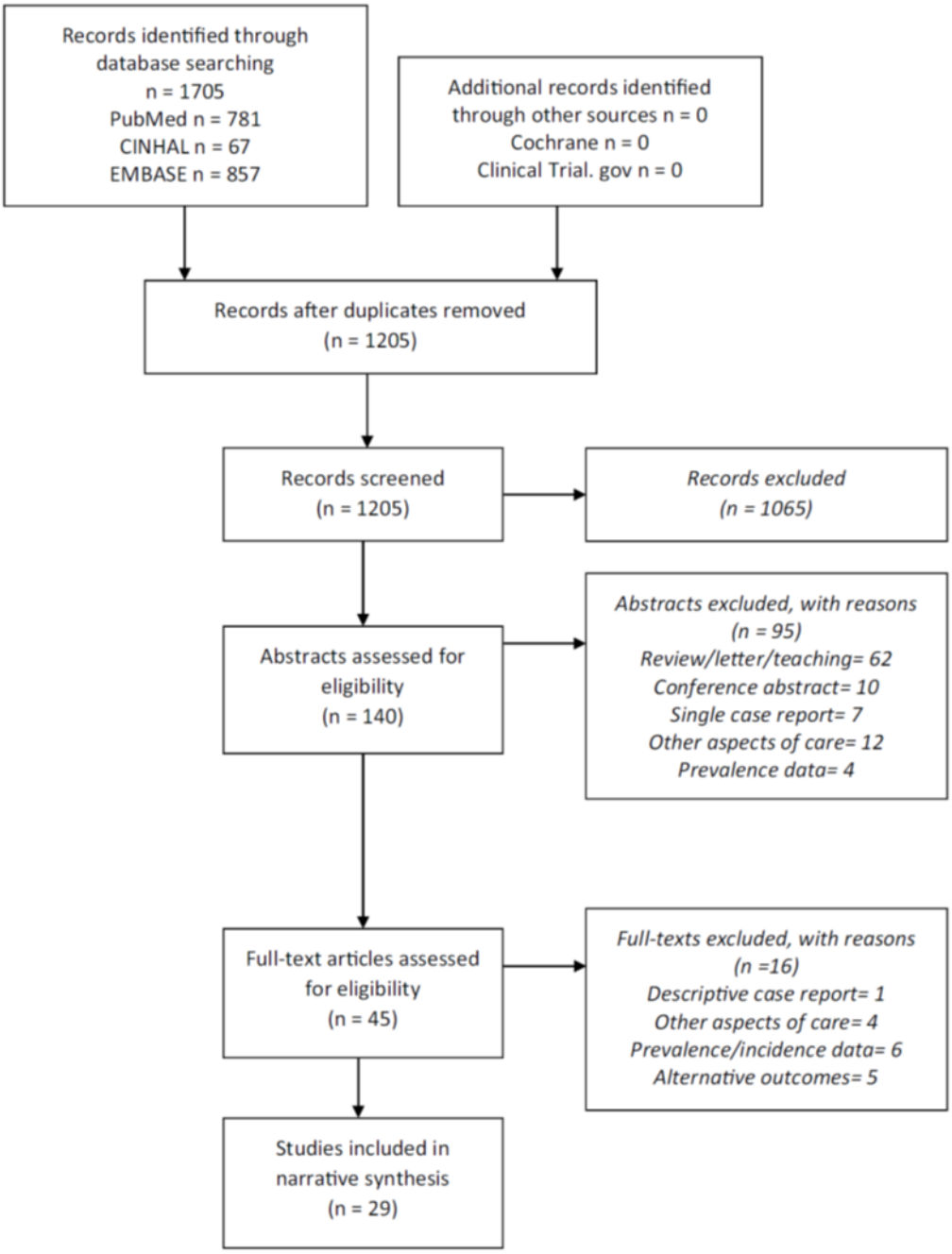

FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses diagram

3 | RESULTS

3.1 | Search results

After removal of duplicates, we identified 1205 papers (Figure 1) and excluded 1065 during title screening. During abstract screening we excluded 95/140 papers, most exclusions concerned reviews, papers describing other aspects of care and conference abstracts. Inter-rater agreement during title screening was 94.1% (1134/1205), and 81.4% (114/140) during abstract screening 87% (39/45). Forty-five full text papers were screened; most common exclusion reasons were that studies described other aspects of care, and outcomes or were epidemiological reports.

TABLE 1 Included studies and evidence grades

Studies evaluating monitoring	Evidence grading
Armstrong et al.[38]	Level 3
Chantelau et al.[21]	Level 3
McGill et al.[22]	Level 3
Moura-Neto et al.[23]	Level 3
Schlossbauer et al.[24]	Level 3
Wu et al.[25]	Level 3
Zampa et al.[11]	Level 3
Studies evaluating off-loading which describe monitoring	**Evidence grading**
Armstrong et al.[10]	Level 3
Chantelau.[12]	Level 2
Chantelau and Richter.[26]	Level 3
Christensen et al.[13]	Level 3
de Souza.[8]	Level 3
Dixon et al.[27]	Level 3
Fabrin et al.[14]	Level 3
Holmes and Hill.[28]	Level 3
O'Loughlin et al.[29]	Level 3
Osterhoff et al.[30]	Level 2
Pakarinen et al.[31]	Level 3
Parisi et al.[32]	Level 3
Renner et al.[15]	Level 2
Ruotolo et al.[16]	Level 3
Pinzur et al.[9]	Level 3
Saltzman et al.[33]	Level 3
Sinacore.[7]	Level 3
Stark et al.[6]	Level 3
Thewjitcharoen et al.[34]	Level 3
Verity et al.[35]	Level 3
Visan et al.[36]	Level 3
Wukich et al.[37]	Level 2

We included 29 papers (Table 1). We used the Scottish Intercollegiate Guidelines Network criteria for assigning level of evidence. Three papers were case control and one a cohort study, that is, level 2 studies. The remaining 25 were level 3, non-analytic case series. Ten studies were prospective and the remaining 19 retrospective reviews of medical records. All included studies were of low or very low quality.

3.2 | Study and participant characteristics

Eight studies were conducted in the United States, four studies in Germany, and two in Denmark, Switzerland, Italy, and Brazil (Table 2). In total, 1132 participants were included across all studies with 1239 episodes of CN. Mean sample size was 39 (±27 range 13-115). The studies collected data for between 4 months and 23 years.

The mean age of participants was reported in 20 studies and ranged from 52 to 62.5 years old. Participants' sex was reported in 26 studies: 56% (614/1095) who experienced an episode of acute CN in these studies were male (range 4-68). Twenty-three studies clearly reported the type of diabetes. 67.7% (598/896) of participants with acute CN had a diagnosis of type 2 diabetes (range 5-84). The mean duration of all types of diabetes ranged from 13.0 to 24.5 years. Any data reported on severity and anatomical location of the CN are reported in Table 2.

We divided the studies into two groups. In the first group, the evaluation of monitoring techniques was the study's primary aim, so likely to report data to address the first four objectives on the efficacy and acceptability of the techniques.[11,21-25,38] In the second group, the study's primary aim was to report outcomes of CN but they may also describe monitoring techniques used, thus providing data to answer our fifth objective on whether monitoring techniques influence outcomes.[6-10,12-16,26-37]

3.3 | Techniques used in the monitoring of CN

Table 3 summarizes the protocols used to monitor CN. Of the seven studies included in the first group, three evaluated magnetic resonance imaging (MRI) for monitoring CN.[11,21,24] The first study compared dynamic MRI, with gadolinium contrast medium, every 3 months with foot skin temperature measured with a handheld infrared temperature scanner and midfoot and ankle circumference in 40 participants with CN.[11] The authors concluded that contrast medium uptake rate obtained with dynamic-MRI represents a reliable technique for predicting remission in acute CN. Intra- and inter-observer agreement for assessment of contrast medium uptake was high: correlation (k) = 0.96. The authors reported a 90% agreement between clinical findings and MRI. The mean healing time at clinical examination was 6.8 ± 2.3 months and 8.3 ± 2.9 at MRI. In 23% of participants, the clinical signs of disease stabilization were found 3 to 6 months prior to the stabilization observed on MRI. The second study retrospectively reviewed the notes and images of 45 episodes of CN over 23 years.

TABLE 2 Study and patient characteristics

Studies evaluating monitoring						
				Participant characteristics		
Author, year and country of study	Study design and time frame for data collection	Inclusion and exclusion criteria	Sample size and CN classification	Age	Sex	Diabetes
Armstrong and Lavery (1997) USA	Retrospective observational study without controls 1993-1994 (2 years)	*Inclusion* Diagnosis of DM Acute CN *Exclusion* Osteomyelitis Extending to bone Chronic CN Open reduction of fracture	39 participants *Sanders & Frykberg's* I = 2.6% II = 64.1% III = 25.6% IV = 7.7% V = 0%	Age years mean (SD) = 59 (9.5)	Male n = 20 (51%) Female n = 19 (49%)	T1DM n = 1 (2.6%) T2DM n = 38 (97.4%) DM duration mean (SD) = 16.5 (4.9)
Chantelau et al (2018) Germany	Retrospective observational study without controls 1994 to 2017 (23 years)	*Inclusion* Active stage CN based on typical clinical and MRI findings *Exclusion* Cases with skin defects or infections Non-compliant patients Insufficient clinical documentation	37 participants 45 feet *Modified Eichenholtz* 0 = 17 (38%) I = 28 (62%) II = 0 III = 0	Age years median (range) = 59 (37-81)	Male n = 21 (57%) Female n = 16 (43%)	T2DM = 19 (51%) T1DM = 17 (46%) No diabetes = 1 (3%)
McGill et al (2000) Australia	Prospective observational study with controls Time frame not reported	*Inclusion* Acute unilateral CN *Exclusion* Not reported	17 participants 8/17 participants received bone scans every 3 months maximum 12 months	Age years median (IQR) = 58.5 (53.5-65.5)	Not reported	T2DM = 13 (75%) T1DM = 4 (25%) DM Duration median (IQR) = 13.5 (7-19.5)
Moura-Neto et al (2012) Brazil	Prospective observational study without controls 2007-2009 (3 years)	*Inclusion* Acute Charcot foot *Exclusion* Not reported	28 participants Brodsky 1 = 71.40% 2 = 17.90% 3A = 0% 3B = 0% 4 = 10.7% 5 = 0%	Age years mean (SD) = 58.8 (11.7)	Male n = 14 (50%) Female n = 14 (50%)	T2DM n = 28 (100%) DM duration mean (SD) = 14.3 (5.1)
Schlossbauer (2008) Germany	Prospective observational study without controls Time frame not reported	*Inclusion* Acute clinical signs of CN *Exclusion* Foot ulcers Previous foot surgery Fractures Apparent deformity	13 participants *Modified Eichenholtz* 0 = 13 (100%) I = 0 II = 0 III = 0	Age years mean = 61.2	Male n = 20 (51%) Female n = 19 (49%)	T1DM n = 7 (54%) T2DM n = 5 (38%) Idiopathic neuropathy n = 1 (8%) DM duration mean = 20.5

(Continues)

TABLE 2 (Continued)

Studies evaluating monitoring							
Author, year and country of study	**Study design and time frame for data collection**	**Inclusion and exclusion criteria**	**Sample size and CN classification**	**Participant characteristics**			
				Age	**Sex**	**Diabetes**	
Wu et al (2012) Taiwan	Prospective observational study without controls 2001-2009 (8 years)	*Inclusion* Acute Charcot foot *Exclusion* Undergone no previous evaluation or treatment	15 participants Brodsky 1 = 40% 2 = 27% 3A = 13% 3B = 7% 4 = 13% 5 = 0%	Age years mean (range) = 55.6 (28-76)	Male n = 7 (47%) Female n = 8 (53%)	T1DM n = 4 (27%) T2DM n = 11 (73%) DM duration mean (range) = 22.2 (13-34)	
Zampa et al (2011) Italy	Prospective observational study without controls 2001-no end date reported	*Inclusion* Acute Charcot foot *Exclusion* Not reported	40 participants Forefoot = 12.5% Mid-foot = 80% Hind-foot = 7.5%	Age years mean (SD) =58.3 (13)	Male n = 22 (55.5%) Female n = 18 (45.5%)	T1DM n = 17 (42.5%) T2DM n = 23 (57.5%) DM duration mean (SD) = 19.1 (12.1) HbA1c mean (SD) = 8.9	
Studies evaluating offloading which describe monitoring							
Armstrong et al (1997) USA	Retrospective observational study without controls 1991-1994 (3 years)	*Inclusion* Acute Charcot foot *Exclusion* Concomitant osteomyelitis Chronic CN Bilateral CN Open reduction of fracture	55 participants 60 feet *Sanders & Frykberg's* I = 3% II = 48% III = 34% IV = 13% V = 2%	Age years mean (SD) = 58.6 (8.5)	Male n = 27 (49%) Female n = 28 (51%)	T1DM n = 1 (2%) T1DM duration = 12 T2DM n = 54 (98%) T2DM duration mean (SD) = 15.9 (5.7)	
Chantelau (2005) Germany	Case control study 1997-2004 (7 years)	*Inclusion* Clinical signs of CN. Selected if fractures were undetected on first plain X-ray after onset of symptoms or presumed OA changes in only one WB joint *Exclusion* Previous CN on the same foot Active ulceration Patients defaulting from clinic before complete healing	24 participants Unable to summarize from paper	Age years; early initiation treatment group mean (range) = 61 (44-73) Age years; late initiation treatment group mean (range) = 52 (28-73)	Male n = 13 (54.2%) Female n = 11 (45.8%)	T1DM n = 8 (33%) T2DM n = 16 (77%) DM duration median early initiation treatment group (range) = 25 (3-53) DM duration median late initiation treatment group (range) = 14 (3-32)	
Chantelau and Richter (2013) Germany	Retrospective observational cohort study without controls	*Inclusion* Cases treated and followed up by the diabetic foot clinic until healing *Exclusion*	59 participants 71 feet Forefoot = 18 (25%) Midfoot = 48 (68%)	T1DM Age years median (range) = 55 (48.5-59.5)	Male n = 30 (50.1%)	T2DM n = 35 (59%) T2DM duration median (range) = 10 (5-19)	

TABLE 2 (Continued)

	2000-2012 (12 years)	Cases with coexisting plantar ulceration or possible septic skeletal pathology	Hindfoot = 5 (7%) *Modified Eichenholtz* 0 = 27 (38%) I = 44 (62%) II = 0 III = 0	T2DM Age years median (range) = 62 (56-59)	Female n = 29 (49.9%)	T1DM n = 24 (40.1%) T1DM duration median (range) = 32 (25.5-41)
Christensen et al (2012) Denmark	Retrospective observational study without controls 2000-2005 (5 years)	*Inclusion* Persistent swelling of the foot and an increase skin temperature of more than 2°C with spontaneous onset over a few days or following minimal trauma or sudden overuse of the feet *Exclusion* Not reported	56 participants Forefoot = 15 (26.8%) Midfoot = 31 (55%) Heel = 3 (5%) Ankle = 7 (12.5%)	Age years mean (SD) = 58.3 (11.6)	Male n = 33 (59%) Female n = 23 (41%)	T2DM = 32 (57%) T2DM duration mean (SD) = 17.1 (7.8) T1DM = 24 (43%) T1DM duration mean (SD) = 34.4 (13) DM duration mean (SD) = 24.5 (13.6) HbA1c mean (SD) = 8.9 (1.7)
De Souza (2008) USA	Retrospective observational study without controls 1998-2006 (18 years)	*Inclusion* Charcot of the foot and ankle *Exclusion* Irregular attendance Noncompliance Inadequate/lost radiographs Inadequate follow up	27 participants 34 feet *Brodsky* *1 = 17* *2 = 8* *3A = 7* *3B = 0* *4 = 0* *5 = 0*	Not reported	Male n = 6 (22%) Female n = 21 (78%)	T2DM = 17 (65%) T1DM = 9 (35%)
Dixon et al (2017) New Zealand	Retrospective observational case series study without controls 2000-2014 (14 years)	*Inclusion* Not reported *Exclusion* Not reported	41 participants	Age years mean (range) = 54 (34-73)	Male n = 28 (68%) Female n = 13 (32%)	T2DM = 31 (76%) T1DM = 10 (24%) DM duration median (range) = 15 (1-47) HbA1c median (range) = 70 (36-178)
Fabrin et al (2000) Denmark	Retrospective observational case series study without controls 1984-1994 (10 years)	*Inclusion* 107 patients presenting a red, hot swollen foot with spontaneous onset who exhibited radiological evidence of osteoarthropathy. Eight patients with typical Charcot rocker bottom deformity that had developed over a period of some months in adult life with radiological evidence of Charcot *Exclusion* Deformities caused by bone fractures related to accidents were not included	115 participants 140 feet	Age years median (range) = 54 (27-80)	Male n = 59 (51%) Female n = 56 (46%)	T2DM = 21 (18%) T2DM duration median (range) = 8 (0-19) T1DM = 94 (82%) T1DM duration median (range) 22 (0-50) HbA1c median (range) = 9.4 (5.6-14)
Holmes and Hill (1994)	Retrospective observational	*Inclusion* Fracture/dislocations of the foot and ankle	18 participants		Male n = 11 (61%)	T1DM = 1 (6%) T2DM = 17 (94%)

(Continues)

TABLE 2 (Continued)

USA	case series study without controls 1985-1990 (4 years 6 m)	*Exclusion* Not reported	20 fracture/dislocations Forefoot = 2 (10%) Mid-foot = 7 (35%) (including base second metatarsal) Hind-foot = 5 (25%) Ankle = 6 (30%)	Age years mean (range) = 55 (38-78)	Female n = 7 (39%)	
O'Loughlin et al (2016) Ireland	Retrospective observational case series study without controls 2006-2012 (6 years)	*Inclusion* Not reported *Exclusion* Not reported	40 participants	Age years mean (SD) = 58 (10)	Male n = 27 (68%) Female n = 13 (32%)	T1DM = 11 (27%) T2DM = 29 (73%) DM duration mean (SD) = 15 (9) HbA1c mean (SD) = 65 (16)
Osterhoff et al (2013) Switzerland	Retrospective case control study 2005-2012 (7 years 6 m)	*Inclusion* Diagnosed with acute CN; Echienholz's stages 0-2. Non-diabetes related CN included in the analysis *Exclusion* Echienholz's stage 3 at diagnosis Follow up <3 months after casting Immunosuppressive or osteoactive medication Post-arthrodesis of the foot before the onset of CN Amputation proximal to the Lisfranc joint during treatment	52 participants 57 feet *Sanders & Frykberg's* I = 10 (18%) II = 30 (53%) III = 13 (23%) IV = 3 (5%) V = 1 (2%)	Age years mean (SD) = 59 (11)	Male n = 36 (69%) Female n = 16 (31%)	Not reported
Pakarinen et al (2002) Finland	Retrospective observational case series study without controls 1994-2000 (6 years)	*Inclusion* Not reported *Exclusion* Not reported	32 participants 36 feet *Sanders & Frykberg's* I = 5 (%) II = 31 (%) III = 0 (%) IV = 3 (%) V = 1 (%) 11% more than 1 area involved *Modified Eichenholtz* I = 29 (80.5%) II = 2 (5.5%) III = 5 (14%)	Not reported	Male n = 22 (69%) Female n = 10 (31%)	NIDDM = 19 (59%) NIDDM duration mean (range) = 14 (1-28) IDDM = 13 (41%) IDDM duration mean (range) = 28 (8-58) HbA1c mean = 9.4%
Parisi et al (2013) Brazil	Prospective observational study without controls 2004-2009 (5 years)	*Inclusion* Patient with type 2 diabetes CN Eichenholtz stages I and II without previous treatment Abnormalities in the neuropathy evaluation Endocrinology follow-up Compliance with the proposed treatment protocol Regular follow-up with the institution's social services. *Exclusion*	22 participants	Age years mean (range) = 56 (47-64)	Male n = 7 (32%) Female n = 15 (68%)	T2DM = 22 (100%) DM duration mean (range) = 13 (8-25)

TABLE 2 (Continued)

		Presence of plantar foot ulcer at initial evaluation Preceding surgical procedure on affected foot Preceding osteomyelitis Presence of rheumatological and immunological diseases or alcoholism Patients on haemodialysis Contralateral limb amputation Pregnancy Cognitive impairment				
Pinzur et al (2006) USA	Prospective observational study without controls Time frame not reported	*Inclusion* First occurrence of CN as diagnosed by the original Eichenholtz criteria ≥40 years age Diabetes CN localized to the mid-foot Peripheral neuropathy Deformity within defined criteria No more than 1 superficial ulcer ≤3 cm Also, radiographic angle criteria *Exclusion* Pacemaker or defibrillator Full thickness foot ulcer or exposed bone History of osteomyelitis in the involved foot Inflammatory arthritis, malignancy, dialysis, oral corticosteroid therapy during the 6 months before entry Organ transplant Prior foot surgery for infection Contralateral amputation Pregnancy or lactating	10 participants (1 dropped out before completion of treatment)	Age years mean (range) = 58.2 (39-72)	Male n = 4 (44%) Female n = 5 (56%)	DM duration mean (range) = 16.4 (7-30)
Renner et al (2016) Switzerland	Retrospective case control 2002-2012 (10 years)	*Inclusion* T1DM or T2DM Peripheral neuropathy *Exclusion* Immunosuppressive or osteoactive medication Osteodestructive bone pathologies Osteomyelitis Idiopathic osteoarthropathy	90 participants 101 feet *Sanders & Frykberg's* I = 12 (12%) II = 35 (35%) III = 13 (13%) IV = 6 (6%) V = 2 (2%) I & II = 6 (6%) II & III = 1 (1%)II & IV = 24 (24%)III & IV = 3 (3%)IV & V = 2 (2%) *Modified Eichenholtz* 0 = 9 (9%) I = 61 (60%) II = 21(21%)	Age years mean (SD) = 60.7 (10.6)	Male n = 68 (76%) Female n = 22 (24%)	Not reported

(Continues)

TABLE 2 (Continued)

			III = 10 (10%)			
Ruotolo et al (2013) Italy	Prospective observational study without controls 2006-2011 (4.5 years)	*Inclusion* Acute onset of swelling, redness and warmth of the ankle and/or foot, without any bone involvement at standard X-ray. *Exclusion* Charcot joint and previous or concomitant foot ulceration Bone fractures Foot deformity Peripheral arterial disease.	25 participants *Modified Eichenholtz* 0 = 25 (100%) I = 0 II = 0 III = 0	Age years mean (SD) = 58.12 (12.94)	Male n = 16 (64%) Female n = 9 (36%)	T2DM = 19 (76%) T1DM = 6 (24%) DM duration mean (SD) = 18.87 (10.3)
Saltzman et al (2005) USA	Retrospective observational case series study without controls 1983-2003 (20 years)	*Inclusion* Primary diagnosis of CN requiring treatment of bony collapse Minimum 6-month follow-up *Exclusion* CN from other causes Patients with diabetes who had fractures that healed in the normal time without evidence of progressive fragmentation, dissolution or displacement	115 participants 127 feet *Modified Eichenholtz* 0 = 5 (4.3%) I = 59 (51.3%) II = 15 (13%) III = 11 (9.6%) IV = 6 (5.2%) No Classification = 19 (16.5%) Forefoot = 15 (%) Midfoot = 66 (%) Hindfoot = 10 (%) Ankle = 22 (%) No Classification = 4 (%) (2 pts had 2 sites)	Age years median (range) = 52 (21.1-84.6)	Male n = 43 Female n = 72 (60.5%)	T2DM = 84 (74%) T1DM = 31 (26%) DM duration median (SD) = 21 (0-36)
Sinacore (1998) USA	Prospective case control study 1991-1996 (5 years)	*Inclusion* Acute onset of swelling, redness and warmth if the ankle of foot requiring medical attention and referrals with a diagnosis of acute CN *Exclusion* Not diagnosed with DM Not referred by an orthopaedic surgeon from the author's medical facility.	30 participants 35 episodes CN Forefoot = (20%) Midfoot = (46%) Hindfoot = (23%) Ankle = (11%)	Age years mean (SD) = 55 (9)	Male n = 24 (80%) Female n = 6 (20%)	T2DM = 21 (71%) T1DM = 9 (29%) DM duration mean (SD) = 21 (12)
Stark et al (2016) UK	Retrospective observational study without controls 2007-2012 (5 years)	*Inclusion* Acute CN must have developed within the study period, and the patients must have been managed as an acute CN. *Exclusion* Patients were excluded if an acute CN was deemed unlikely from the history and clinical examination, or if imaging studies were negative or another diagnosis was found to be causative or more likely.	50 participants Forefoot = (11.9%) Mid-foot = (64.3%) Hind-foot = (19.1%) Multiple = (4.8%)	Age years mean (SD) = 62.5 (11.7)	Male n = 34 (68%) Female n = 16 (32%)	T2DM = 39 (78%) T2 DM duration median (IQR) = 15 (4.5, 20) T2DM HbA1c mean (SD) = 64 (20) T1DM = 11 (22%) T1DM duration median (IQR) = 32 (19.8, 38)

TABLE 2 (Continued)

						T1DM HbA1c mean (SD) = 70 (19)
Thewjitcharoen et al (2018) Thailand	Retrospective observational case series study without controls 2000-2016 (16 years)	*Inclusion* Presence of a hot swollen foot with or without erythema of the overlying skin after the exclusion of conditions resembling Charcot foot *Exclusion* Not reported	40 participants – 13 with acute CN *Sanders & Frykberg's* I = 12.5% II = 50% III = 27.5% IV = 5% V = 2.5%	Age years mean (SD) = 56.1 (9.2)	Male n = 4 (30.8%) Female n = 9 (69.2%)	T2DM = 12 (92.3%) T1DM = 1 (7.7%) DM duration mean (SD) = 16.6 (8.3) HbA1c mean (SD) = 9.1 (2.3)
Verity et al (2008) Canada	Prospective observational study without controls 33 month period	*Inclusion* Not reported *Exclusion* Abscess or infection Gross instability that was managed with surgical debridement or stabilization	21 participants 25 feet *Brodsky* *1 = 13 (52%)* *2 = 2 (8%)* *3A = 1 (4%)* *3B = 1 (4%)* *4 = 7 (28%)* *5 = 1 (4%)* *Modified Eichenholtz* 0 = 0 I = 8 (32%) II = 11 (44%) III = 6 (24%)	Age years mean (SD) = 52 (12)	Male n = 10 (48%) Female n = 11 (52%)	T2DM = 12 (57%) T1DM = 8 (38%) No diabetes = 1 (5%) DM duration mean (SD) = 21 (10)
Visan et al (2012) Romaninia	Prospective observational study without controls 2007-2011 (3 years 8 m)	*Inclusion* Not reported *Exclusion* Not reported	34 participants 42 feet *Modified Eichenholtz* 0 = 0 I = 29 (69%) II = 11 (26%) III = 2 (5%)	Age years mean (SD) = Not reported	Male n = 28 (67%) Female n = 14 (33%)	Not reported
Wukich et al (2011) USA	Retrospective cohort study without controls 2005-2009 (5 years)	*Inclusion* To be included in this study, radiographs taken at the onset of symptoms must not have demonstrated any fractures of the foot or ankle *Exclusion*	20 participants 22 feet 15 progressed to CN *Modified Eichenholtz* 0 = 22 (100%) I = 0 II = 0 III = 0 Forefoot = 0 Midfoot = 12 Hindfoot = 5 Ankle = 5 Multiple = 5	Participants who did progress to CN. Age years mean = 53.5	Not reported	Not reported

Abbreviations: CN, Charcot neuroarthropathy; DM, diabetes mellitus; IDDM, insulin dependent diabetes mellitus; IQR, interquartile range; MRI, magnetic resonance imaging; NIDM, non-insulin dependent diabetes mellitus; SD, standard deviation; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

TABLE 3 Protocols for monitoring CN

Author (year)	Protocol for temperature measurement	Protocol for X-ray	Protocol for MRI	Protocol for other monitoring techniques described
Studies evaluating monitoring				
Armstrong and Lavery (1997)	Device: Exergen Acclimatization: 15 minutes Number Sites: 7 Repetitions: NR Frequency: NR Ambient air temperature controlled	No report of it been used	No report of it been used	No report of it been used
Chantelau et al (2018)	Not measured objectively, but rated semi quantitatively by bi-manual comparative palpation, and by inspection	Used; no details reported	Standard institution's routines, conventional MRI studies of the foot were commissioned irrespective of an expertise with the diabetic Charcot foot.	Swelling, deformity, joint dysfunction, skin abnormality were not measured objectively, but rated semi-quantitatively by palpation and inspection
McGill et al (2000)	Device: Dermatemp, Exergen Corporation, Mass, USA Skin temperature of the affected foot was measured at the hottest point. 3 months during the study.	Used at diagnosis	No report of it been used	Quantitative bone scanning. We injected 40 MBq of 99mTcEHDP intravenously, delivering only 11 MRems per scan. A standard of 10 ± 20 MBq was used to decay correct all counts. All images were taken using a low energy all purpose collimator. Isotope uptake in a standardized rectangular area over the affected foot was quantified for each of the three phases.
Moura-Neto et al (2012)	Device: Minitemp, Raytec Reference Armstrong 1997 for protocol	Frequency: monthly	No report of it been used	No report of it been used
Schlossbauer (2008)	Used no details reported	No report of it been used	1T Magnetom Harmony scanner (Siemens Medical Solutions, Erlangen, Germany). A dedicated foot and ankle coil was used. T1 fat-suppressed imaging was performed after injection of contrast.	Presence or absence of pain, erythema, oedema
Wu et al (2012)	No report of it been used	Frequency: 4 weekly	No report of it been used	Doppler spectra of the first dorsal metatarsal arteries in both feet were obtained using a 10 MHz linear ultrasound probe (ATL HDI3000 or HDI5000: ATL, Bothel, Washington). 2 weekly intervals Swelling, warmth and erythema were recorded

TABLE 3 (Continued)

Author (year)	Protocol for temperature measurement	Protocol for X-ray	Protocol for MRI	Protocol for other monitoring techniques described
Studies evaluating monitoring				
Zampa et al (2011)	Device: not stated Technique: hottest point by a hand-held infrared temperature scanner	No report of it been used	Tesla: 1.5 Frequency: 3 monthly Contrast: yes Time: 16 ± 4 minutes	Ankle and midfoot circumference
Studies evaluating off-loading which describe monitoring				
Armstrong et al (1997)	Device: Exergen Reference Armstrong 1997 for protocol	Used; no details reported	No report of it been used	No report of it been used
Chantelau (2005)	No report of it been used	Used; no details reported	Used; no details reported	Bone technetium scan and CT used in diagnosis
Chantelau & Richter (2013)	Foot temperature – palpated to the contralateral foot	Used: performed as appropriate	T1 weighted, T2 weighted and STIR imaging had been carried out, with or without contrast media, at the discretion of the radiologist in charge. MRI was repeated in each patient for monitoring of the healing process at the discretion of the diabetic foot clinic.	Foot oedema – by inspection and palpation in comparison to the contralateral foot, (photography used) Foot deformity – inspection and palpation in comparison to the contralateral foot (photography used). Depression of longitudinal arch was graded
Christensen et al (2012)	Device: not reported Highest area identified and compared with the identical area on the contralateral foot. Frequency: 2-6 weeks	No report of it been used	No report of it been used	Bone scintigram following i.v. injection of pertechnetate used in diagnosis
De Souza (2008)	Infrared thermometers, and skin thermistors were not used. Meticulous palpation with the palm and the back of the hand and fingers was used to assess decreased warmth.	Frequency: 2 week intervals early phases of treatment, then less frequently.	No report of it been used	No report of it been used
Dixon et al (2017)	No report of it been used	Used; no details reported	Used; no details reported	No report of it been used
Fabrin et al (2000)	Device: Thermocouples medical precision thermometer DM 852: Thermocouples, Ellab, Copenhagen). Frequency: 2-6 weeks	Frequency: 6-12 weeks	No report of it been used	No report of it been used
Holmes and Hill (1994)	No report of it been used	Used; no details reported	No report of it been used	No report of it been used
O'Loughlin et al (2016)	No report of it been used	No report of it been used	No report of it been used	No report of it been used

(Continues)

TABLE 3 (Continued)

Studies evaluating off-loading which describe monitoring				
Osterhoff et al (2013)	No report of it been used	Used; no details reported	MRI used to confirm diagnosis and if uncertainty remained regarding inflammation	Osseous biopsies used to confirm diagnosis
Pakarinen et al (2002)	Skin temperature and temperature differences between the affected and non-affected foot were measured	Used; no details reported	Diagnostic and follow-up MRIs were performed	No report of it been used
Parisi et al (2013)	Device: not reported Local temperature Every 15 days during the first 12 weeks then monthly	Standardized radiographic evaluations. Every 15 days during the first 12 weeks then monthly	No report of it been used	No report of it been used
Pinzur et al (2006)	No report of it been used	Used; no details reported	No report of it been used	Objective measure of water displacement at each visit Clinical assessment of soft-tissue swelling (non, mild, moderate, severe) Midfoot stability (stable, moderately unstable, unstable)
Renner et al (2016)	Redness and warmth measured by visual inspection and palpation	No report of it been used	Confirmation of CN by magnetic resonance imaging (MRI; ie, soft tissue oedema, joint effusion and/or subchondral bone marrow oedema of involved joints characterized by low signal intensity on T1-weighted images and high signal intensity on T2-weighted images)	No report of it been used
Ruotolo et al (2013)	Device: portable infrared thermometric probe Frequency: 3 weekly Reference Armstrong 1997 for protocol	Used at diagnosis no details reported	Used to confirm healing 1.5T Pre-contrast T1WTSE Ax, T2WTSE Ax, T2WFFE SAG, T2 STIR COR, T1 SPIR AX: Post-contrast T1WTSE AX, T1 SPIR AX, T1 SPIR SAG optional.	F-FDG PET/CT scan Scans were examined visually for focal abnormalities, and data generated from the scan were also assessed quantitatively by calculating the maximum standard uptake value Frequency: 3 monthly
Saltzman et al (2005)	No report of it been used	Used; no details reported	No report of it been used	No report of it been used
Sinacore (1998)	Reduction in swelling, a decrease in local skin/tissue temperature and reduced skin erythema.	Used; no details reported	No report of it been used	No report of it been used
Stark et al (2016)	Device: not reported Frequency: 1-2 weeks	Used; no details reported	Used; no details reported	No report of it been used
Thewjitcharoen et al (2018)	No report of it been used	No report of it been used	No report of it been used	No report of it been used

TABLE 3 (Continued)

Studies evaluating off-loading which describe monitoring					
Verity et al (2008)	Resolution of swelling, erythema and increased warmth) No details reported Frequency: monthly	Frequency: monthly	No report of it been used		No report of it been used
Visan et al (2012)	No report of it been used	Used: no details reported	No report of it been used		No report of it been used
Wukich et al (2011)	No report of it been used	No report of it been used	No report of it been used		No report of it been used

They reviewed sequential follow-up MRIs to assess the change in oedema equivalent signal change during treatment for CN with a walking cast. The number of follow-up MRIs per episode of CN ranged from 1 to 6. They found decreasing oedema-equivalent signal change in 69% (66/95) of follow-up MRIs but reported a combination of physiologic and pathologic fluctuations in oedema equivalent signal change in the remainder of the MRIs.[21] The third study compared bone marrow oedema on MRI at baseline and after 4 months, and correlated this to symptoms of CN in 13 participants. There was a statistically significant decrease in bone oedema over 4 months, with a statistically significant correlation between pain and soft tissue oedema and the bone marrow oedema over the same timescale.[24]

Two studies evaluated infrared thermometry to identify disease remission.[23,38] The first study described in detail the protocol for measuring temperature using the Exergen Model DT 1001. They controlled for ambient room temperature, allowed a 15 minute acclimatization period, and measured seven sites on the foot, compared with the contralateral limb as the physiologic control, at monthly intervals.[38] Casting was discontinued based on reduction or absence of clinical signs of inflammation, radiologic signs of healing and when the temperature difference between feet had stabilized with a cut-off point of less than 4°F (2.2°C) difference. The authors report that the choice of the cut-off figure was based on clinical experience The second study referenced the protocol described by Armstrong and Lavery[38] for measuring temperature but used the Minitemp, Raytec[23] to monitor temperature. Casting was discontinued when the temperature difference between feet was recorded as less than 2°C.

One study evaluated Doppler spectrum analysis as a novel diagnostic tool for planning treatment.[25] The study compared the Doppler spectra of the first metatarsal arteries in both feet using a 10 MHz linear ultrasound probe (ATL HDI3000 or HDI5000; ATL, Bothel, Washington). The Doppler spectra in the unaffected limb were triphasic, compared to the affected limb which showed monophasic forward flow. The Doppler spectra analysis was repeated every 2 weeks in the affected limb until it returned to normal. At this point, participants either started weight-bearing or underwent surgical reconstruction of the ankle joint. The authors concluded that Doppler spectra analysis of the foot may be used as a guide to begin weight bearing. They reported a discrepancy between the two monitoring techniques: only four out of 15 patients had X-rays which showed healing when the foot was healed according to the Doppler Spectra analysis.

In the final study, a subset of eight participants from a larger study received three monthly three-phase quantitative bone scans of both feet for a maximum of 12 months. They compared the ratio of isotope uptake between feet, between the affected foot and the tibia and compared isotope uptakes to the clinical indicators of inflammation. There was strong correlation between temperature difference and the ratio of isotope uptake in the affected vs unaffected foot, the perfusion of the affected foot in the dynamic phase and the isotope uptake in the delayed phase of the bone scans.[22] The study also reported on the change in temperature difference between the affected and unaffected foot from baseline 3.3°C, at 6 months 1.3°C, and at 12 months 0.8°C noting a progressive decrease over time.[22]

TABLE 4 Treatment and outcomes of CN

Studies evaluating monitoring					
Author (year)	**Monitoring evaluated and treatment**	**Follow-up**	**Outcome – evaluation and time to remission**	**Relapse**	**Frequency and type of complications**
Armstrong and Lavery (1997)	Infrared dermal thermometry TCC	Mean (SD) = 26.6 m (7.1)	Mean skin temperature difference for all subjects at initial presentation 8.8 ± 2.3°F (range 5.1-14.7) At initial presentation the site of maximum skin temperature gradient correlated to the site of maximum Charcot arthropathy (radiographically) in 92% cases. The site of maximum skin temperature gradient correlated to the site of maximum Charcot arthropathy (radiographically) in 72% of all cases throughout the follow up period. Time to remission – not reported	Relapse – not reported	7.7% new onset ulceration
Chantelau et al (2018)	MRI Immobilization and offloading – cast treatment	19 cases had only 1 follow up scan 11 cases had 2 follow up scans 9 cases had 3 follow up scans 6 cases had 4–6 follow up scans Individual follow up scans were on average 13 weeks apart (range 35-50 weeks)	Not all patients were followed up until healing 140 reports (45 baseline and 95 MRI follow-up) 69% (66/95) follow up scans showed dependent regression of oedema-equivalent signal change as expected. 31% (29/95) showed stagnant or extending oedema-equivalent signal change. Proportions of follow up scans showing oedema-equivalent signal change regression was independent of the active-stage Charcot foot, severity grade, renal failure and order of the follow up scans (1st vs 2nd to 6th FUS); all chi2 $P > 0.05$. Estimated duration until 'healing' Grade 0 = 25 weeks (approx) Grade 1 = 35 weeks (approx)	5 cases	Not reported
McGill et al	Temperature measurement Quantitative bone scanning 12 months – rest and contact casting	subset 8 subjects received bone scans	At presentation, the affected foot was 3.3°C (2.4 ± 4.7) hotter than the unaffected foot. After 6 months there was 1.3°C (0.5 ± 1.9) difference.	Not reported	Not reported

TABLE 4 (Continued)

Studies evaluating monitoring					
Author (year)	**Monitoring evaluated and treatment**	**Follow-up**	**Outcome – evaluation and time to remission**	**Relapse**	**Frequency and type of complications**
			After 12 months, there was 0.8°C (0.3 ± 1.6) difference. Correlation (r = .90, P < .0001) between temperature difference and the ratio of isotope uptake in the affected: unaffected feet Relationship between the perfusion of the affected foot in the dynamic phase and the isotope uptake in the delayed phase of the bone scans (r = .92, P < .0001).		
Moura-Neto et al (2012)	Skin temperature CROW – instructed to weight-bear normally but to restrain from heavy physical work.	1 year	Univariant and multivariant Cox proportional hazard regression analyses for age, sex, diabetes duration and initial temperature difference showed no influence of any of these factors on the rate or time to consolidation One-year consolidation rate = 25 (89.3%) mean = 6.6 months (±2.1) Range = 3-12 months	No relapses among the 25 patients who progressed to the chronic phase	Not reported
Schlossbauer (2008)	MRI and clinical findings Mean interval for follow up MRI = 4.2 months Pressure-relieving methods like strict non-weight bearing in a brace or cast.	4 month follow-up	Bone marrow oedema in affected bones significantly decreased (P < .001) Signal intensity of bone marrow oedema in STIR imaging showed a significant correlation with the presence of soft tissue oedema and with the presence of pain at clinical evaluation (P < .05) Erythema and elevated temperature did not show a significant correlation. The presence of bone marrow oedema in the STIR sequence was strongly associated with a corresponding contrast enhancement (P < .0001)	Not reported	Not reported
Wu et al (2012)	Doppler spectrum analysis. Padded bi-valve cast and non-weight bearing	Not reported	Doppler spectrum returned normal mean = 13.6 weeks range = 6-20	1 patient relapsed after 7 weeks	3 pts underwent pan-talar arthrodesis

(Continues)

TABLE 4 (Continued)

Studies evaluating monitoring					
Author (year)	**Monitoring evaluated and treatment**	**Follow-up**	**Outcome – evaluation and time to remission**	**Relapse**	**Frequency and type of complications**
Zampa et al (2011)	Dynamic MRI TCC	Healing or a max 12 months	Mean healing time Clinical examination = 6.8 months (±2.3) MRI = 8.3 months (±2.9) *P* = <.0001	Not reported	Not reported
Studies evaluating off-loading which describe monitoring					
Armstrong et al (1997)	TCC	1 year	mean = 18.5 weeks (±10.6) range = 4-46 weeks	15% relapsed	9 (25%) underwent corrective surgery for foot deformity
Chantelau (2005)	TCC wherever possible	Until transferred into shoes	*Early referral* median = 3 months range = 2-9 months *Late referral* median = 5 months range = 3.5-14 months *P* = > .05	Not reported	*Early referral* 1 patient developed gross foot deformity *Late referral* 13 patients developed gross foot deformity 1 skin ulcer 1 malalignment of cast foot healed in supination
Chantelau and Richter (2013)	Removable device	All patients had been followed up until transition to shoes and for variable periods of time thereafter	Stage 0 median (range) = 4 Months (2-8 months) Stage 1 median (range) = 5 months (3.5-14 months)	Not reported	9 skin ulcers 1 malalignment the foot healed in supination
Christensen et al (2012)	Removable device	Mean = 3.2 years	Mean (SD) = 141 days (±11)	3 pts (5%) had exacerbation 7 pts (12%) had recurrence at 69 days (±16)	No surgical correction of foot deformity needed
De Souza (2008)	TCC	Mean = 5.5 years Range = 1-14 years	Mean = 14 weeks Range = 4-20 weeks	Not reported	Only 1/34 had further anatomical displacement of clinical importance once it had been immobilized in a TCC

TABLE 4 (Continued)

Studies evaluating monitoring					
Author (year)	**Monitoring evaluated and treatment**	**Follow-up**	**Outcome – evaluation and time to remission**	**Relapse**	**Frequency and type of complications**
					Ulcers developed in 10 feet after the transfer to orthosis
Dixon et al (2017)	TCC 56%	1 year from diagnosis	Mean time until ambulatory in modified shoes = 21.3 weeks (±11.5)	2 pts a further fracture	1-year diagnosis 17 pts (34%) foot ulcer 1 pt. osteomyelitis 1 pt. underwent amputation All-cause mortality 5%
Fabrin et al (2000)	In the case of excessive swelling, a few days of immobilization in bed or in a wheelchair (sometimes in the hospital) was necessary to reduce the oedema. The routine treatment was a weight-off regimen involving 2 crutches and foot protection involving therapeutic footwear with a rigid bottom and pedal arch supports. Fitted individually with soft insoles moulded from functional imprints when necessary. Control of oedema was managed with an elastic bandage followed by compression stockings and sometimes assisted by diuretics.	Median (range) = 48 months (6-114 months)	Maintained in most cased for 4-6 months	10 pts with new attacks in the previously affected foot (time to 'new attack' not reported)	7 (6%) developed foot ulcers during a Charcot attack 2 pts underwent major amputation 3 pts underwent corrective surgery for foot deformity 2 pts died during follow-up
Holmes and Hill (1994)	Not reported	Median (range) = 27 months (14-70 months)	8/20 pts with fractures went onto develop a CN. Range healing CN pts = 7-46 months	Not reported	1 pt. with CN underwent a major amputation
O'Loughlin et al (2016)	Off-loading was administered in 50% cases. Including rest, TCC, TCI, CROW	Not reported	Not reported	Not reported	38% of pts developed subsequent ulceration

(Continues)

TABLE 4 (Continued)

Studies evaluating monitoring					
Author (year)	**Monitoring evaluated and treatment**	**Follow-up**	**Outcome – evaluation and time to remission**	**Relapse**	**Frequency and type of complications**
					20% pts underwent a major amputation 10% underwent corrective surgery for foot deformity
Osterhoff et al (2013)	TCC recurrence = 27 months (±31) range = 3-102 months	Not reported Not reported	Not reported	13 ft (23%) Mean interval	
Pakarinen et al (2002)	TCC	Mean = 21 months Range = 1-81 months	Mean = 11 months Range 4-37 months	Not reported	2 pts underwent major amputation 12 pts underwent corrective surgery for foot deformity
Parisi et al (2013)	Removable device. Bear weight respecting symptomatic limitations of each case.	Not reported	18 weeks	Not reported	Not reported
Pinzur et al (2006)	TCC and then removable device	1-5 months after transition into footwear	Treated with TCC mean = 5.8 weeks range = 4–10 Then aircast Total treatment time mean = 12 weeks range = 6-16 weeks	Not reported	1 Lost to follow-up
Renner et al (2016)	Mixture of TCC and removable devices	1-208 months	Unilateral mean = 20 weeks (±21) Bilateral mean = 29 weeks (±29)	Not reported	8 pts minor amputation 2 pts underwent a major amputation 4 procedures for corrective surgery for foot deformity
Ruotolo et al (2013)	TCC then removable walker	Return to prescription footwear Mean (SD) = 21.75 ± 16.7 months	Mean = 15.12 weeks (±5.45)	No recurrence reported in the follow-up time	Not reported
Saltzman et al (2005)	TCC	Median = 3.8 years Range = 0.5-18.5 years	The median time wearing an ankle-foot orthosis was 12 months (95% CI; range, 10-13 months)	Not reported	15 (11.8%) underwent a major amputation 62 (49%) recurrent ulcers

TABLE 4 (Continued)

Studies evaluating monitoring					
Author (year)	**Monitoring evaluated and treatment**	**Follow-up**	**Outcome – evaluation and time to remission**	**Relapse**	**Frequency and type of complications**
			27 limbs (23%) required long-term use of an ankle-foot orthosis (defined as >18 months)		36 (28%) chronically recurrent ulcers 53 corrective surgery procedures performed for foot deformity
Sinacore (1998)	TCC with crutches and advice to partial weight bear	1 month after cessation of casting	Mean = 86 days (±45) Range = 22-224	4 (13%) within first month after the initial casting period	Not reported
Stark et al (2016)	TCC and crutches	5 years	Median time to resolution for the 26 patients initially treated with a TCC was 48 weeks (95% CI: 42.4, 64.4) Median time to resolution for the 22 pts initially treated with removable offloading device of 53 weeks (95% CI: 42.5, 64.4)	15 (35%)	4 (8%) or underwent a major amputation 2(4%) died
Thewjitcharoen et al (2018)	TCC	57.1 months after the onset of the CN	Median (range) = 5 months (2-10 months)	Not reported	5 years mortality 13%
Verity et al (2008)	Removable cast or boot. Limit standing and walking to the minimum	Not reported	Mean = 29 weeks (±19) range = 6-73 weeks No remission in 8 (32%) cases	Not reported	3 feet developed new deformity
Visan et al (2012)	Removable walker	Not reported	Stage 1 4 pts at 3 months 15 pts at 6 months 5 pts after 6 months Stage 2 2 pts at 6 months 4 pts after 6 months Stage 3 1 pt at 8 months	Not reported	3 (8.83%) patients underwent surgery
Wukich et al (2011)	TCC	Median 21.7 months mean 23.6 months (±14)	19/20 (95%) diagnosis of CN missed		16/22 (72%) developed a complication 11/22 (50%) required surgical treatment

Abbreviations: CROW, Charcot restraining orthotic walker; MRI, magnetic resonance imaging; Pt, patient; Pts, patients; TCC, total contact cast; TCI, total contact insole.

In the remaining 22 studies, the primary aim was to evaluate the outcomes of CN but they described the monitoring techniques used (Table 3). The most frequent monitoring techniques used was serial X-ray in 16/22 of studies, objective temperature measurement with a handheld infrared monitoring device in 11/22 and MRI with or without contrast media in 7/22 of studies. Protocols for the same technique were not standardized across studies. For example, in studies that used infra-red skin temperature measurement to monitor CN, some studies used a cut of <1°C and others <2°C to identify remission. Some studies relied on a combination of different monitoring techniques: 5/22 described two techniques, 4/22 described three techniques and one study used four techniques to monitor CN.

Four studies used advanced radiological methods for diagnostic and/or monitoring: F-FDG PET/CT scanning,[16] bone scintigram,[13] bone biopsies[20] and isotope bone scans.[12] Other monitoring techniques included objective and subjective measures of inflammation by palpating foot temperature, and assessing the presence of swelling.[7,8,12,15,25] Another study assessed progression of foot deformity by visual examination, palpation and comparison of serial photographs.[26] Objective, serial measures of water displacement and grading of midfoot stability were used to monitor CN in another study.[9]

3.3.1 | Sensitivity and specificity of different techniques used to monitor CN

Six out of seven studies which evaluated monitoring techniques did not report the sensitivity or specificity. Zampa et al[11] reported a high intra and inter observer agreement for the assessment of contrast uptake but did not report the sensitivity of the technique. They reported that the monitoring techniques evaluated could be used as a guide to identify remission, withdraw immobilization, and begin weight bearing. None of the 22 studies reporting the outcomes of CN reported the specificity or sensitivity of the monitor techniques used to measure when the foot was in remission. Some studies relied on subjective monitoring techniques such as palpation or visual inspection of inflammation to assess for remission in CN.

3.3.2 | Financial implications to healthcare providers and clinical feasibility of different techniques

No studies reported the cost of the monitoring used in terms of capital cost to purchase equipment.

3.3.3 | Safety considerations, and participant acceptability of different techniques

Ten out of 29 studies used MRI as a monitoring tool for identifying remission of acute CN. Of these, four reported using contrast during the MRI in all or some images at the radiologist's discretion.[11,16,24,26]

A further four studies used advanced methods of radiological imaging which require the use of contrast media.[12,13,14,22] Only one of these 14 studies which used contrast specifically reported on the incidence of adverse events from the administration of the contrast, reporting no adverse events. Another study reported using bone biopsy as a diagnostic aid to confirm CN, but this was not used in monitoring.[20] They did not report any safety considerations that may be relevant to this technique. X-rays are associated with exposure to ionizing radiation, but their potential risk was not discussed in any studies. No safety considerations were reported for objective temperature measurement with a handheld infrared monitoring device or any other clinical methods for monitoring CN. None of the studies reported on participant acceptability of the monitoring techniques used.

3.3.4 | The influence of monitoring techniques on the outcomes of CN

Treatments and the definitions used to confirm remission and relapse varied between the studies. Time to healing ranged from 8 weeks to over 1 year (Table 4). Relapse rates ranged from 0% to 35% across the studies. The monitoring techniques were poorly reported and inconsistently applied across studies. Four studies did not report which techniques were used to monitor CN.

4 | DISCUSSION

The previous systematic review on assessment, diagnosis and management in CN only included papers between 2002 and 2012,[2] our review searched from 1993 to 2018 and include an additional seven studies[7,10,14,22,28,31,38] some of which are key reference papers for future studies.

To our knowledge, this systematic review is the first to synthesize the evidence base for monitoring techniques of CN and influences of different techniques for monitoring CN on treatment outcomes. We identified a heterogeneous set of 29 papers: seven specifically evaluated monitoring techniques and a further 22 described the outcomes of CN. It is not possible to conclude whether the monitoring techniques used influences the outcomes of CN. We found no high-quality studies validating the use of monitoring techniques in CN.

The key finding is the lack of a consistent approach to monitoring in CN. Common techniques included X-ray, temperature monitoring and MRI. Techniques were poorly described, and where the information was reported there was variability in the devices used and how the technique was applied. It is not clear whether the devices used were validated for the temperature ranges commonly found in feet. Some studies still rely on subjective measures of temperature difference between feet to monitor CN.[7,8,15,21,24,25]

The first paper included in this review which used temperature measurement for monitoring in CN was published in 1997.[38] The authors report that the cut-off point of 4°F (2.2°C) for healing was

not evidence-based but it appears to have been adopted as the standard for clinical decision making in subsequent studies and guidelines.[2,39] This protocol has not been validated and other studies have not specified sites, repeated measures, or acclimatization times making evaluation of studies using this technique difficult.

We found a lack of evidence on the sensitivity, specificity, cost-effectiveness, safety and patient acceptability for all monitoring techniques. There is continued uncertainty about the relationship between monitoring techniques and treatment outcomes.

In the absence of reliable evidence, we are unable to recommend any changes to current national[39] and international guidance[2] which are predominantly based on level IV evidence, that is, expert opinion.

The strengths of our systematic review include the broad range of inclusion and exclusion criteria for study type, which allowed us to describe the variability in the current approach to monitoring CN in research as well as clinical practice. Screening and data extraction were completed by two researchers who are experienced podiatrists. Our review also had some limitations: we did not search the grey literature. We limited searches to English language, we acknowledge that this may mean we missed some relevant studies and potentially introduced bias into the review. However, we feel that the impact of this would be relatively small.

In the 1990s, it was acknowledged that using subtle changes in skin temperature to inform clinical decisions may not be an accurate way to monitor CN[20] but this is still widely used in clinical practice. Further high quality research is needed to identify the optimal method of monitoring CN. We recommend that researchers accurately describe the population at baseline, standardize definitions for diagnosis and outcome measures, and provide detailed protocols for monitoring techniques in future research.

MRI as a monitoring tool for CN is increasingly acknowledged as a potentially more accurate method for monitoring and this is supported by the studies we included.[11,21,24] This warrants further investigation. An ongoing randomized feasibility study aims to explore the feasibility of using serial MRI without contrast in the monitoring of CN to decide whether a large-scale trial is warranted https://doi.org/10.1186/ISRCTN74101606.[40]

5 | CONCLUSION

Multiple techniques have been used to evaluate remission in acute CN, but the quality of published studies to support any one technique is low or very low. Uncertainty therefore remains about the effectiveness of the different monitoring techniques, and whether the different monitoring techniques influence time to remission and recurrence rates. Therefore, we are unable to make recommendations for clinical practice. There is an urgent need for high-quality studies to identify the most accurate, safe and cost-effective monitoring techniques in CN.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

C.G. is the NIHR Clinical Doctoral Fellow. C.G., K.G., F.G., J.W., F.P. and W.H. made substantial contributions to the conception and design of the review. C.G. and K.G. screened the papers. C.G. extracted data from all the included papers. K.G. validated data extraction. C.G. drafted the manuscript. All authors critically reviewed and revised the manuscript for important intellectual content. All authors read, amended and approved the final manuscript.

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APPENDIX A: SEARCH STRING PUBMED

Query	Items found
Search ((((((charcot joint[MeSH Terms]) OR charcot)) OR neuroarthropathy) OR osteoarthropathy)) AND ((diabetes) OR diabetes [MeSH Terms]) Filters: Publication date from 1993/01/01 to 2018/07/24; Humans; English	784
Search ((((((charcot joint[MeSH Terms]) OR charcot)) OR neuroarthropathy) OR osteoarthropathy)) AND ((diabetes) OR diabetes [MeSH Terms]) Filters: Humans; English	952
Search ((((((charcot joint[MeSH Terms]) OR charcot)) OR neuroarthropathy) OR osteoarthropathy)) AND ((diabetes) OR diabetes [MeSH Terms]) Filters: Humans	1204
Search ((((((charcot joint[MeSH Terms]) OR charcot)) OR neuroarthropathy) OR osteoarthropathy)) AND ((diabetes) OR diabetes [MeSH Terms])	1345
Search ((((charcot joint[MeSH Terms]) OR charcot)) OR neuroarthropathy) OR osteoarthropathy	11 189
Search osteoarthropathy	3292
Search neuroarthropathy	465
Search (charcot joint[MeSH Terms]) OR charcot	8067
Search (diabetes) OR diabetes[MeSH Terms]	633 535
Search charcot joint[MeSH Terms]	1604
Search charcot	7192
Search diabetes[MeSH Terms]	392 176
Search diabetes	633 535

B) Search strategy for systematic review

1993-June 2018

Query	Items found
Search ((((((charcot joint[MeSH Terms]) OR charcot)) OR neuroarthropathy) OR osteoarthropathy)) AND ((diabetes) OR diabetes[MeSH Terms]) Filters: Publication date from 1993/01/01 to 2018/07/24; Humans; English	784
Search ((((((charcot joint[MeSH Terms]) OR charcot)) OR neuroarthropathy) OR osteoarthropathy)) AND ((diabetes) OR diabetes[MeSH Terms]) Filters: Humans; English	952
Search ((((((charcot joint[MeSH Terms]) OR charcot)) OR neuroarthropathy) OR osteoarthropathy)) AND ((diabetes) OR diabetes[MeSH Terms]) Filters: Humans	1204
Search ((((((charcot joint[MeSH Terms]) OR charcot)) OR neuroarthropathy) OR osteoarthropathy)) AND ((diabetes) OR diabetes[MeSH Terms])	1345
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Search neuroarthropathy	465
Search (charcot joint[MeSH Terms]) OR charcot	8067
Search (diabetes) OR diabetes[MeSH Terms]	633535
Search charcot joint[MeSH Terms]	1604
Search charcot	7192
Search diabetes[MeSH Terms]	392176
Search diabetes	633535

C) Published feasibility protocol paper

Gooday et al. Pilot and Feasibility Studies (2020) 6:85
https://doi.org/10.1186/s40814-020-00611-3

Pilot and Feasibility Studies

STUDY PROTOCOL Open Access

A randomised feasibility study of serial magnetic resonance imaging to reduce treatment times in Charcot neuroarthropathy in people with diabetes (CADOM): a protocol

Catherine Gooday[1,2*], Frances Game[3], Jim Woodburn[4], Fiona Poland[1], Erika Sims[5], Ketan Dhatariya[2], Lee Shepstone[6] and Wendy Hardeman[1]

Abstract

Background: Charcot neuroarthropathy is a complication of peripheral neuropathy associated with diabetes which most frequently affects the lower limb. It can cause fractures and dislocations within the foot, which may progress to deformity and ulceration. Recommended treatment is immobilisation and offloading, with a below knee non-removable cast or boot. Duration of treatment varies from six months to more than 1 year. Small observational studies suggest that repeated assessment with magnetic resonance imaging improves decision-making about when to stop treatment, but this has not been tested in clinical trials. This study aims to explore the feasibility of using serial magnetic resonance imaging without contrast in the monitoring of Charcot neuroarthropathy to reduce duration of immobilisation of the foot. A nested qualitative study aims to explore participants' lived experience of Charcot neuroarthropathy and of taking part in the feasibility study.

Methods: We will undertake a two-arm, open study and randomise 60 people with a suspected or confirmed diagnosis of Charcot neuroarthropathy from five NHS, secondary care multidisciplinary Diabetic Foot Clinics across England. Participants will be randomised 1:1 to receive magnetic resonance imaging at baseline and remission up to 12 months, with repeated foot temperature measurements and X-rays (standard care plus), or standard care plus with additional three-monthly magnetic resonance imaging until remission up to 12 months (intervention). Time to confirmed remission of Charcot neuroarthropathy with off-loading treatment (days) and its variance will be used to inform sample size in a full-scale trial. We will look for opportunities to improve the protocols for monitoring techniques and the clinical, patient-centred and health economic measures used in a future study. For the nested qualitative study, we will invite a purposive sample of 10–14 people able to offer maximally varying experiences from the feasibility study to take part in semi-structured interviews to be analysed using thematic analysis.

(Continued on next page)

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(Continued from previous page)
Discussion: The study will inform the decision whether to proceed to a full-scale trial. It will also allow deeper understanding of the lived experience of Charcot neuroarthropathy, and factors that contribute to engagement in management and contribute to the development of more effective patient-centred strategies.

Trial registration: ISRCTN, ISRCTN74101606. Registered on 6 November 2017.

Keywords: Charcot neuroarthropathy, Diabetes, MRI, Temperature monitoring, X-ray, Patient experience, Feasibility study

Background

Charcot neuroarthropathy (CN) is a complication of peripheral neuropathy associated with diabetes which most frequently affects the lower limb. It can cause fractures and dislocations within the foot, which may progress to deformity and ulceration. The symptoms include redness, warmth and swelling in the foot and/or leg. This inflammation can lead to fractures in the bones and can damage joints, affecting the shape and function of the foot. It was first described 140 years ago [1]; however, it remains a poorly understood and frequently overlooked complication of diabetes [2].

Population-based studies have estimated a life time cumulative incidence for CN of 0.4 to 1.3% in people with diabetes, rising to 13% in people at high risk who attend diabetic foot speciality clinics [3]. In 2018, a regional survey of 205,033 people with diabetes in the East Midlands, UK, reported a point prevalence of 0.04% [4]. CN is associated with increased length of stay and use of medical resources [5].

The aim of treatment is to stop the inflammatory process, relieve pain and maintain foot architecture and so reduce the risk of future ulceration and amputation [6]. The current international consensus is that the foot should be immobilised in a below knee non-removable cast or boot, with weekly or fortnightly review by healthcare professionals working in specialist multidisciplinary diabetic foot clinics [7]. The immobilisation minimises the potential for any further damage to the foot structure. Immobilisation is continued until remission, defined as the absence of clinical signs of inflammation, measured using skin surface infra-red thermography and X-rays showing signs of bone healing and union [8].

The evidence base for the treatment of CN is weak. It is based on studies from a few centres which used retrospective designs and case note review methods using small sample sizes, typically in the range of 9–55 participants [3, 9–13]. Many studies failed to standardise monitoring, treatment and outcomes, which makes direct comparison between studies difficult.

Studies from the UK have shown a median time to remission of 9–12 months [9, 13, 14]. However, US studies report considerably shorter time to remission of 3–5 months [3, 10–12]. Studies from Brazil and Germany show remission times of 3–12 months and 3–6 months, respectively [15, 16]. Shorter treatment times could be related to reported differences in the relapse rates for CN, between 12 and 33% [13, 17–19], but without clear and consistent definitions for remission and relapse, this is unknown. There is also variation in the reported annual major amputation rates in people with CN from two different case series from hospitals in the USA—2.7% and 6.6% [20, 21].

The reasons for the variation are not understood but could include people's characteristics at the start of the treatment, different techniques for monitoring CN, different protocols for the same monitoring techniques, variations in approach to off-loading and variability in study design. These could either underestimate or overestimate treatment duration.

Temperature difference between the feet is one of the most frequently used methods to monitor CN. It is recommended in the 2015 National Institute for Health and Care Excellence guidance on diabetic foot problems [22]. The most recent systematic review [8] published in 2013 recommends that immobilisation is continued until the temperature difference between the feet is less than 1–2 °C, and no further radiological changes on imaging have occurred. However, this recommendation is only based on level IV evidence, i.e. case series [8]. There is variability in the protocols used to measure the temperature difference between the feet. The most detailed protocol for measuring temperature discrepancy requires a 15-min acclimatisation period, controlled ambient air temperature and readings collected from nine different places on each foot [23]. In addition, plain X-rays demonstrate damage to the bone and joints rather than disease activity (inflammation).

Studies show inconsistency in the methods for monitoring and monitoring devices used [13, 17–19, 23–25]. These factors may overestimate or underestimate the degree of inflammation, so treatment may be discontinued too early or continued for longer than necessary. The presence of simultaneous bilateral foot disease or the absence of a contralateral limb through prior amputation invalidates the use of temperature measurement as a tool for identifying disease remission.

The National Institute for Health and Care Excellence recommends the use of MRI in determining a diagnosis of CN in the early stages of disease when no signs are evident on plain radiology [22]. However, serial MRI is not widely used in routine clinical practice as a tool to monitor for signs of disease remission in CN [26]. One prospective study using MRI with contrast reported that mean healing times were associated with contrast uptake assessed at baseline [27]. A further two retrospective studies looked at bone marrow oedema. One study reported decreasing bone marrow oedema in 69% of follow-up images [28], and the second study found a significant positive correlation between intensity of bone marrow oedema on MRI and clinical measures [29]. This emerging evidence suggests that MRI may be useful for the surveillance of active CN. The findings from MRIs could be adopted as the criterion standard for establishing disease activity and remission.

The use of MRI in monitoring CN therefore needs to be formally evaluated in a trial [30]. However, the evidence to support a full randomised controlled trial is presently insufficient. We will conduct a randomised feasibility study to understand the proportion of people who meet the eligibility criteria, the number of eligible participants recruited, the number of participants who receive an alternative diagnosis and the proportion of participants who withdraw. Time to MRI confirmed remission of CN with off-loading treatment (in days), and its variance will be used to inform sample size in a main trial. We will look for opportunities to improve the protocols for monitoring techniques in a future trial. We will examine the feasibility of a range of clinical, patient centred, and health economic measures. We are using a randomised controlled trial as it is considered the gold standard for evaluating efficacy in clinical research [31].

As part of the feasibility study, we will carry out a qualitative study to further the understanding of people's experiences of living with CN and the factors that contribute to people's engagement in their treatment. Previous qualitative studies have demonstrated the importance of people's perspectives in order to promote engagement in the prevention and management of diabetic foot ulcerations [32–34]. What may be people's views and experiences of CN is an under-researched area [35]. In the UK treatment times for CN are between 9–12 months [14], which is longer than those for foot ulceration, where treatment times are no more than 12 weeks for half of the people [36]. This means that evidence on people's experiences of foot ulceration may not transfer to CN.

In summary, there is a lack of evidence to support the use of monitoring techniques in CN. Healthcare professionals rely on methods and devices which do not accurately reflect disease progression, and decision-making about discontinuing or prolonging immobilisation is challenging. A lack of understanding of people's experiences of living with CN means their needs and wishes may be neglected with current treatments, and are not being considered when developing new treatment strategies and pathways.

Aim and objectives

This study aims to explore the feasibility of using serial MRI without contrast in the monitoring of CN to reduce duration of immobilisation of the foot, in order to decide whether a large-scale trial is warranted. We will assess eligibility, recruitment, retention and withdrawal rates. Time to MRI confirmed remission of CN with off-loading treatment (days), and its variance will be used to inform sample size in a main trial. We will also examine the feasibility of collecting clinical, patient-centred and health economic measures. The nested qualitative study aims to explore the dimensions of lived experience of CN and the participants' experiences of taking part in the feasibility study.

Methods

Study design (Fig. 1)

This is a two-arm, open, randomised controlled trial investigating the feasibility of using serial MRI to monitor CN. The study will last for a maximum of 3½ years. The study is divided into two phases: phase one, the active phase, will last until the CN is in remission or a maximum of 12 months, and phase two, the follow-up phase, will last for six months after remission (Fig. 1). The maximum time a participant will be in the trial is 18 months.

The decision to use an open label design was pragmatic: the MRIs will be reported by radiologists and interpreted by the healthcare professionals working in multidisciplinary specialist diabetic foot clinics. As the reporting of MRIs relies on comparison to previous images, this will indicate the trial arm the participant has been randomised to.

The trial has been reviewed and approved by East Midlands-Derby Research Ethics Committee, April 10, 2017, ref 17/EM/0288.

Setting

The setting will be multidisciplinary specialist diabetic foot services at five NHS Hospital Trusts in England.

Randomisation

A randomisation scheme has been generated by the trial statistician. Allocation will be stratified by centre. Participants will be randomised using a web-based randomisation process on a 1:1 basis to (a) immobilisation discontinued on the basis of clinical remission and determined by skin temperature measurement, which triggers an MRI (standard care plus) or (b) standard care

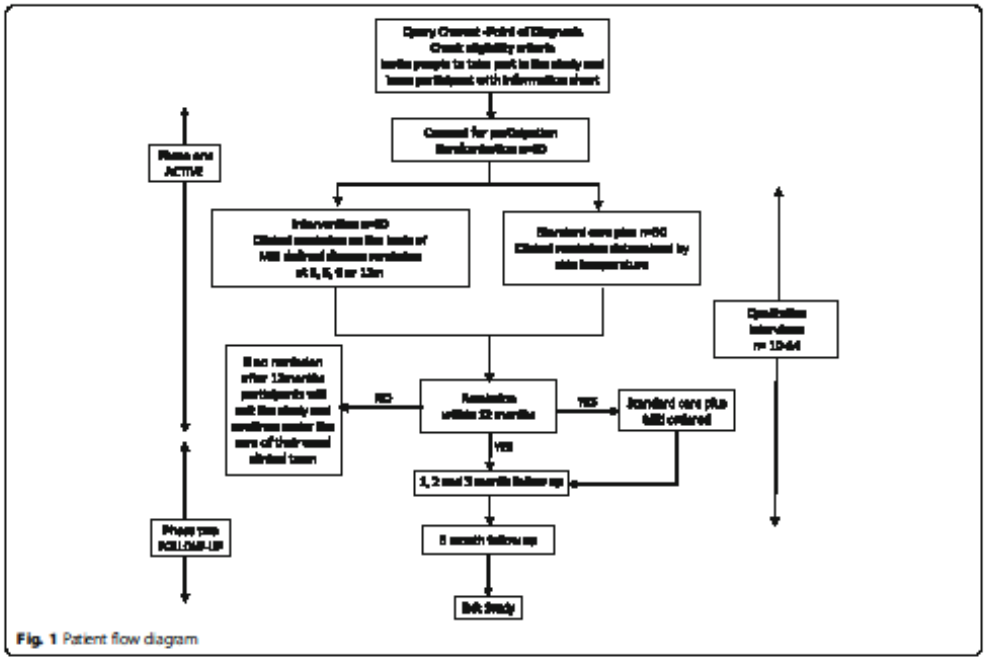

Fig. 1 Patient flow diagram

plus and additionally the serial use of MRI at 3, 6, 9 and 12 months to identify disease remission and thus discontinuation of immobilisation (intervention).

Sample size

As this is a feasibility study, a power calculation is not required. An allowance has been made for up to 10–15% of participants to be withdrawn from the study due to an alternative diagnosis. The sample size will be 60 people with 30 participants per arm, based on recommended sample sizes between 24 and 50 for a feasibility study [37, 38]. We will invite a purposive subsample of 10–14 participants from the feasibility study to take part in the qualitative study.

Participants—inclusion and exclusion criteria

Participants will be people with diabetes as defined by the World Health Organisation [39] and a suspected or confirmed diagnosis of CN who are attending NHS multidisciplinary specialist diabetic foot services. They will be identified, recruited and consented by the healthcare professionals working in the foot clinics, and these will include podiatrists, nurses and doctors. The full inclusion and exclusion criteria are shown in Table 1. The main exclusion criteria were selected because (1) they are contra-indications to having an MRI scan, (2) bilateral disease prevents temperature comparison with the contra-lateral limb, and (3) co-morbidities may alter people's inflammatory response. A confirmed diagnosis of CN can take several weeks, so participants will be recruited as early as possible to accurately collect length of time in below knee non-removable cast or boot. If the clinical team decides on an alternative diagnosis during the trial, then the participant will exit the study. We anticipate that alternative diagnosis will include infection, gout, arthritis, soft tissue injuries or deep vein thrombosis. Follow-up care will be provided by the appropriate clinical team.

For the qualitative study, we have identified five participant characteristics which will purposively inform the sampling framework and will seek to maximise variation in sex, age, history of previous foot complications, duration of treatment for the current episode of CN and employment status. In addition to these factors, we will also ensure that participants equally represent both study arms.

Outcomes

We will measure a range of feasibility, clinical efficacy and patient centred outcomes (Table 2). We will record time to MRI confirmed remission of CN with off-loading treatment (days), and its variance will be used to inform the sample size for a full-scale trial.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Participants who are willing and have capacity to give informed consent.	People who have received a transplant and others receiving immunosuppressant therapy or using long-term oral glucocorticoids other than in the routine management of glucocorticoid deficiency. Participants on a low dose of oral glucocorticoids (< 10 mg for ≤ 7 days) are eligible to participate in the study.
People with diabetes as diagnosed by the WHO criteria http://www.who.int/diabetes/publications/diagnosis_diabetes2011/en/	Participation in another intervention study on active CN.
Age 18 years or over.	Contra-indication for MRI.
New or suspected diagnosis of acute CN (no previous incidence of acute CN within the last 6 months on the same foot) treated with off-loading.	Treatment for previous suspected CN on the same foot in the last 6 months.
Understand written and verbal instructions in English.	Suspected or confirmed bilateral active CN at presentation.
	Active osteomyelitis at randomisation.
	Previous contralateral major amputation.
	Inability to have an MRI scan.
	People receiving palliative care.

For participants in the standard care plus arm, remission is defined as a temperature difference of ≤ 2 °C which is maintained or improves on two separate consecutive occasions for a period of at least four weeks [8] or at the discretion of the clinical team when temperature difference is not valid; for example in the presence of bilateral foot disease. In the standard care plus arm, this will then trigger an MRI. In the intervention arm remission is defined as an absence of subchondral bone marrow oedema on MRI, as reported by a radiologist and the absence of clinical signs and symptoms of CN. The clinical team will interpret the results of the MRI report to determine remission.

The final visit will be six months after remission. During these six months, we will continue to monitor the foot using the standardised assessment of foot temperature for any clinical signs that the CN has relapsed. We have defined relapse as a temperature difference of > 2 °C compared to the contralateral foot maintained for two or more occasions or further changes on imaging. The final decision as to whether the CN has relapsed will be at the discretion of the clinical team.

Table 2 Feasibility, clinical efficacy and patient centred outcomes

Feasibility outcomes	Clinical efficacy outcomes (collected at all study visit)	Patient centred outcomes (collected at baseline, 3 monthly until remission, then at 1 and 6 months post remission)
The proportion of patients who meet the eligibility criteria	Number of new ulcerations on the index or contralateral foot	Health-related quality of life measured: Short Form 12 questionnaire (SF-12) [40] EuroQol-5D-5 L questionnaire (EQ-5D-5 L) [41]
The number of eligible patients recruited	Number of new infections on the index or contralateral foot	Hospital Anxiety and Depression Scale (HADS) [42]
The number of participants in which an alternative diagnosis is made during the active phase of the trial	Number of minor and major amputations on the index or contralateral foot at the end of the follow-up phase of the study	Pain as assessed by Visual Analogue Scale (VAS)
The proportion of patients that withdraw or are lost to follow-up. The term 'withdrawal' encompasses two potential scenarios: withdrawal due to loss of consent or withdrawal due to deaths	Number and severity of falls (Hopkins Fall Grading System) [43]	Patient diary
Statistical parameters of the key outcome measures, duration in off-loading to inform a sample size calculation for a definitive trial	The number of participants in each arm requiring further intervention for CN (e.g. further immobilisation) within 6 months of remission	
Ability to collect quality of life and resource use data		

We will explore the feasibility of collecting resource use and quality of life data, to inform the design of the health economics component of a future definitive trial. Data on all primary care and secondary care visits and admissions to hospital will be collected. Time off work and levels of informal care will also be assessed. We will use the qualitative interviews to gain a deeper, more detailed and rounded contextualised understanding of participants' lived experience of CN and of taking part in this study.

Planned interventions

Standard care plus participants will receive standard care for the assessment and management of CN and any other foot problems; alongside this, we will collect study measures (Fig. 2). If participants have not had a recent diagnostic X-ray or MRI (within the last 3 weeks, prior to randomisation), this will be requested. In this study, we have standardised the assessment of foot temperature to monitor CN by using the same device, the Thermofocus 01500A3*. Every 14 days, the temperature of both feet will be recorded at intervals of 5 min, starting at the removal of the off-loading device and up to 15 min. The sites where the temperature will be measured are based on the classification tool developed by Sanders and Frykberg [44]. We will classify the stage using the modified [45] Eichenholtz classification tool [46] and location of the CN [44] at baseline using anterior/posterior, oblique and lateral weight bearing X-rays.

Intervention in addition to standard care plus, participants in the intervention arm will receive serial MRIs at 3, 6, 9 and 12 months. Intervention participants will not undergo further MRIs once remission has been diagnosed, i.e. if remission is

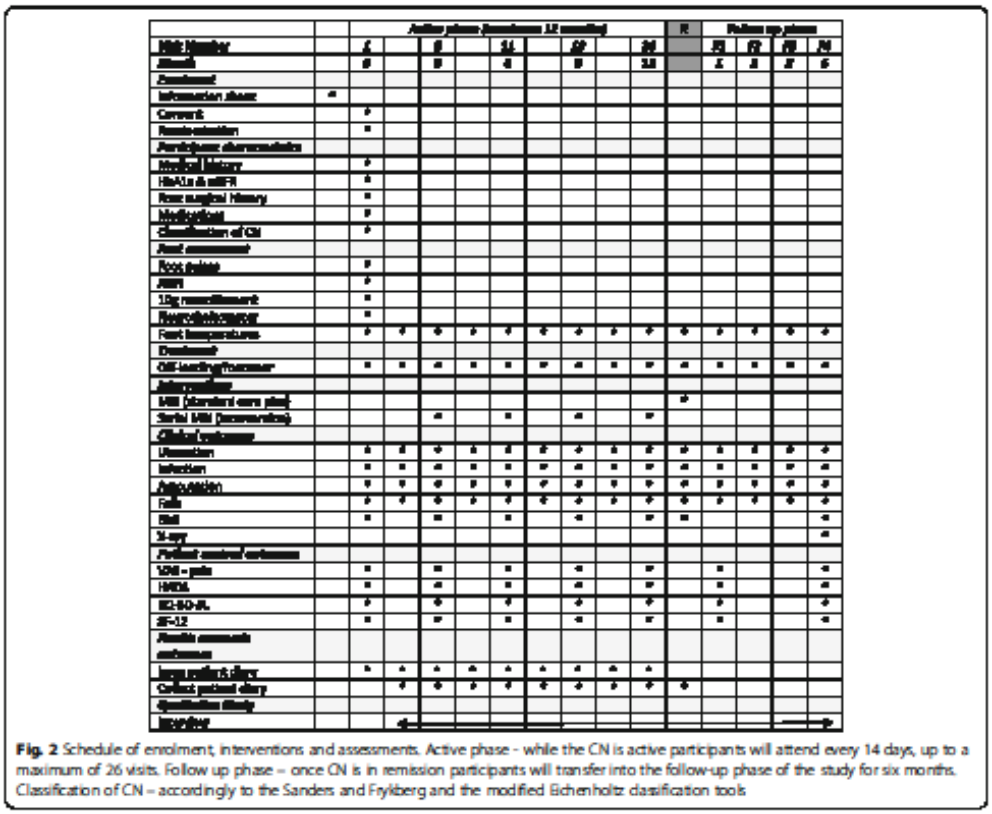

Fig. 2 Schedule of enrolment, interventions and assessments. Active phase - while the CN is active participants will attend every 14 days, up to a maximum of 26 visits. Follow up phase – once CN is in remission participants will transfer into the follow-up phase of the study for six months. Classification of CN – accordingly to the Sanders and Frykberg and the modified Eichenholtz classification tools

diagnosed at 6 months, the MRIs at 9 and 12 months will not occur.

Study procedures (Fig. 2)

The schedule of enrolment, interventions and assessments is shown in Fig. 2. After giving written informed consent (see Additional file 2), participants will attend for visits every 14 days until remission. All visits will take place in multidisciplinary foot clinics. Wherever possible, study measurements and trial interventions will coincide with the participant's existing clinic appointments. This will reduce study burden which is likely to help increase recruitment and retention rates. The study protocol (v1.3, dated 22 July 2019) is based on the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Statement for protocols of clinical trials (see Additional file 1).

Prior to participating in the interviews about the lived experience of CN, participants will receive a further patient information sheet explaining the purpose of the interview and will be asked to complete another consent form (see Additional file 3). All the qualitative interviews will be carried out by the first author (CG), using a semi-structured approach. The topic guide will include a number of probes designed to prompt the participant to increase the level of detail and depth of the information provided from the participants' own viewpoint. Interviews will last approximately 30–40 min in a place of the participant's choosing. The interviews will be audiotaped (with the participant's permission) and transcribed in full to capture language and their own expressions.

Analyses

Quantitative analysis

The feasibility measures including eligibility, recruitment, retention and withdrawals will be reported as point estimates with 95% confidence intervals. There is no intention to conduct any formal comparative analyses for these measures, though levels of missing data will be explored with respect to certain baseline characteristics, e.g. age and measures of disease severity. Variability in outcomes (e.g. standard deviation) will be estimated with 95% confidence intervals to inform the sample size calculations for a full-scale trial. Any between-group efficacy analyses will only be exploratory. There are no plans for any interim analyses.

We will assess progression of foot deformity by comparing X-rays at baseline, remission and six months post remission. We will measure the change in the calcaneal inclination, talar declination and talo-first metatarsal angle between the X-rays. People who have undergone previous minor amputation and/or previous orthopaedic surgical fixation of the foot which alters or removes the anatomical landmarks of the foot will be excluded from this analysis due to the absence of bony landmarks.

The main purpose of the economic analysis is to inform how the data on costs and effects would be collected within a definitive study. Thus, we will estimate completion rates and seek to identify big cost drivers, in order to inform this decision. A preliminary cost-effectiveness analysis will also be performed, although the findings will be treated with caution. As such, we will estimate the mean incremental cost and mean QALY gain associated with the intervention compared to standard care plus.

Qualitative analysis

The qualitative interviews will be analysed using inductive thematic analysis using the six-step model [47]. The first author (CG) will read all the transcribed interviews to record emerging ideas. The interviews will then be subjected to line-by-line coding using the NVivo data management package. The coding framework will be refined by a second researcher, who will cross-check it against a small sample of transcripts. A modified framework approach will be used to organise the analysis. The coded data will be subjected to a thematic analysis, identifying key categories and themes from the data, ensuring that all participants' responses are adequately captured and their meaning authentically interpreted. This approach will provide rich descriptions of the data representing accounts of the diverse and personal experiences of people who have taken part in the study and been treated for acute CN.

Data management and quality assurance

We will set up a Trial Management Group to assist with co-ordination and strategic management of the feasibility study. An initial on-site initiation visit will be completed by CG prior to the sites opening. The primary method of data collection by the research teams will be direct online entry of data onto a purpose-designed secure password-protected electronic case record form. The database complies with data protection requirements [48] on confidentiality and anonymity. Quality management and monitoring procedures have been discussed and agreed with the sponsor. Central monitoring has been considered appropriate for this study with the option to escalate findings and conduct 'for-cause' on-site triggered monitoring visit if indicated. We will review completed consent forms and selected data points for quality assurance at each site within a week after randomisation of the first participant. Subsequent monitoring will be completed at six monthly intervals to coincide with the Trial Management Group meetings and at the end of data collection.

Safety reporting

Safety monitoring and reporting of adverse events has been discussed and agreed with the sponsor. The study has been assessed as low risk; therefore, there will not be a data monitoring committee. The intervention consists of increased frequency of MRI scans without contrast, so a pragmatic approach to safety reporting will be used. MRI scans will be performed in NHS hospitals under routine clinical protocols. Adverse events resulting from MRI scans will be reported by the research teams in line with the Hospital Trust's clinical incident reporting policy. A copy of the anonymised incident form will be forwarded to the Chief Investigator (CG) and reviewed by the Trial Management Group. All other anticipated events, e.g. ulceration, infection, amputation, pain, falls and death will be recorded as secondary outcomes.

Discussion

CN is a poorly understood and under researched complication of diabetes, associated with increased morbidity and mortality compared to people with diabetes without peripheral neuropathy. Evidence is lacking about the factors that influence the unexplained variation in treatment times, relapse rates and complications such as ulceration and amputation. We have also identified a lack of evidence to support the efficacy of current monitoring techniques in CN. There is evidence from small studies that MRI may be superior to current methods of monitoring for remission in CN, but this has not been formally evaluated using robust designs. The results of this feasibility study will inform the decision about progressing to a full-sized pragmatic randomised controlled trial: the number of sites required, trial design, the frequency of MRI monitoring and the choice of process and outcome measures. The embedded qualitative study will provide contextual and meaningful insight into people's experiences of living with CN and what factors they see as contributing to their engagement with the prescribed treatment. Secondly, the qualitative study will advance our understanding of how the condition impacts on participants' quality of life and may contribute to future work on patient reported outcomes measures in this area [49]. Finally, the findings from the qualitative study will provide additional insights into aspects of the trial design and processes that could be improved, in terms of engagement of, and acceptability to participants, based on the participants' experience of involvement in the feasibility study. These aspects could include feedback on the frequency of trial visits, the length of the active and follow-up phases of the trial and the choice and frequency of completing validated questionnaires. The results of this study will be disseminated to researchers, clinicians, people with diabetes and relevant stakeholders through presentations, publications and social media press releases.

Trial status

The CADOM trial originally opened for recruitment in December 2017 and is currently recruiting participants. Recruitment will continue until the end of November 2019.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s40814-020-00611-3.

Additional file 1. SPIRIT Checklist.
Additional file 2. Informed consent form—feasibility trial.
Additional file 3. Informed consent form—qualitative interviews.

Abbreviations

ABPI: Ankle brachial pressure Index; BMI: Body mass Index; CN: Charcot neuroarthropathy; eGFR: Estimated Glomerular filtration rate, ml/min; EQ-5D-5 L: Euroqol 5D; F: Follow-up visit; HADS: Hospital Anxiety and Depression Scale; HbA1c: Glycated haemoglobin (A1c), mmol/mol; MRI: Magnetic resonance Imaging; NHS: National Health Service; R: Remission; SF-12: Medical Outcomes Short-Form Health Questionnaire; VAS: Visual Analogue Scale

Acknowledgements

This trial is sponsored by the Norfolk & Norwich University Hospitals NHS Foundation Trust, rd.office@nnuh.nhs.uk. We are very grateful to all the staff at the Norwich Clinical Trials Unit, all the staff and participants at the trial centres, and Ms Sarah Doyle, Research Administrator.

Authors' contributions

CG is the NIHR Clinical Doctoral Fellow and Chief Investigator. CG and FG developed the initial idea for the research. WH, FP, FG, JW, ES and KD all made substantial contributions to the conception and design of the trial. CG drafted the manuscript. All authors critically reviewed and revised the manuscript for important intellectual content. LS provides statistical support. All authors read, amended and approved the final manuscript.

Funding

Catherine Gooday is funded by a National Institute for Health Research (NIHR), Clinical Doctoral Fellowship for this research project. This paper presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Availbility of data and materials

The datasets generated and/or analysed during the current trial will be available from the corresponding author on reasonable request, provided appropriate credit is attributed to the original authors and the data source.

Ethics approval and consent to participate

The trial has been reviewed by East Midlands-Derby Research Ethics Committee, April 10, 2017, ref 17/EM/0288. The trial is registered on the ISRCTN registry: reference number ISRCTN74101606. All participants will provide written consent to take part in the feasibility trial and will be re-consented by a member of the research team prior to participating in the qualitative interviews. In the future, if amendments to the protocol are required, the Chief Investigator (CG) will work with the sponsor to apply for approval from Research Ethics Committee and the Health Research Association. Following approval of the amendments this will be cascaded to the research sites. The NHS Indemnity scheme will apply to the potential liability of the sponsor for harm to participants arising from the management and conduct of the research.

Consent for publication
Not applicable

Competing interests
The investigators named on the protocol have no financial or other competing interests that impact on their responsibilities towards the scientific value or potential publishing activities associated with the trial.

Author details
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Publisher's Note

D) Ethical approval for feasibility and qualitative studies

NHS
Health Research Authority

East Midlands - Derby Research Ethics Committee
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

04 October 2017

Miss Catherine Gooday
School of Health Sciences
Univeristy of East Anglia
Norwich
NR4 7TJ

Dear Miss Gooday

Study title:	**A randomised feasibility trial to define outcome measures for acute Charcot neuroarthropathy in Diabetes and their use in assessing clinical management.**
REC reference:	**17/EM/0288**
Protocol number:	**R202374**
IRAS project ID:	**222668**

Thank you for your letter, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact hra.studyregistration@nhs.net outlining the reasons for your request.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet completed any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering letter on headed paper [Covering Letter]		11 July 2017
Interview schedules or topic guides for participants [Interview Topic Guide]	V1.0	27 June 2017
IRAS Application Form [IRAS_Form_11072017]		11 July 2017
Letter from funder [NIHR Contract]		
Non-validated questionnaire [VAS Pain Scale]	1	23 June 2017
Other [Lone Worker Policy]	1.6	31 October 2015
Other [Response to ethics meeting queries]		01 September 2017
Participant consent form [Consent form CADOM V1.1 25th August 2017 Clean copy]	1.1	25 August 2017
Participant consent form [Tracked changes Consent form CADOM V1.1 25th August 2017]	1.1	25 August 2017
Participant consent form [Consent form CADOM Qualitative Interviews V1.1 25th August 2017 Clean copy]	1.1	25 August 2017
Participant consent form [Tracked changes Consent form CADOM Qualitative Interviews V1.1 25th August 2017]	1.1	25 August 2017
Participant information sheet (PIS) [PIS Qualitative Study V1.1 25th August Clean copy]	1.1	25 August 2017
Participant information sheet (PIS) [Tracked changes PIS Qualtative Study V1.1 25th August]	1.1	25 August 2017
Participant information sheet (PIS) [PIS Feasibility Study V1.1 25th August Clean copy]	1.1	25 August 2017
Participant information sheet (PIS) [Tracked changes PIS Feasibility Study V1.1 25th August]	1.1	25 August 2017
Research protocol or project proposal [Tracked changes CADOM Protocol V1.1]	1.1	01 September 2017
Sample diary card/patient card [Patient Diary Clean copy]	1.1	01 September 2017
Sample diary card/patient card [Tracked changes Patient Diary V1.1 1st September]	1.1	01 September 2017
Summary CV for Chief Investigator (CI) [CV Chief Investigator]		23 June 2017
Summary CV for student [Student CV]		23 June 2017
Summary CV for supervisor (student research) [Dr Hardeman CV]		27 June 2017
Summary CV for supervisor (student research) [Professor Woodburn CV]		27 June 2017
Summary CV for supervisor (student research) [Professor Game CV]		03 July 2017
Summary CV for supervisor (student research) [Professor Polands CV]		05 July 2017
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Patient Flow Diagram]	V1.0	27 June 2017
Validated questionnaire [EQ-5D-5L]	n/a	23 June 2017
Validated questionnaire [SF-12 Questionnaire]		23 June 2017
Validated questionnaire [HADS Questionnaire changes from REC review]	1.1	

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

17/EM/0288	**Please quote this number on all correspondence**

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

Yours sincerely

pp. V. Swift

Dr John S Fenlon
Chair

Email: NRESCommittee.EastMidlands-Derby@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Ms Julie Dawson*
Mr Andrew Holmes, Norfolk & Norwich University Hospitals NHS Foundation Trust

E) HRA approval for feasibility and qualitative studies

NHS
Health Research Authority

Miss Catherine Gooday
School of Health Sciences
University of East Anglia
Norwich
NR4 7TJ

Email: hra.approval@nhs.net

04 October 2017

Dear Miss Gooday

Letter of HRA Approval

Study title:	**A randomised feasibility trial to define outcome measures for acute Charcot neuroarthropathy in Diabetes and their use in assessing clinical management.**
IRAS project ID:	**222668**
Protocol number:	**R202374**
REC reference:	**17/EM/0288**
Sponsor	**Norfolk & Norwich University Hospital NHS Foundation Trust**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

IRAS project ID	222668

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document *"After Ethical Review – guidance for sponsors and investigators"*, issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application

IRAS project ID	222668

procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

Your IRAS project ID is **222668**. Please quote this on all correspondence.

Yours sincerely

Michael Pate
Assessor

Email: hra.approval@nhs.net

Copy to: *Ms Julie Dawson – Norfolk & Norwich University Hospitals NHS Foundation Trust – Sponsor contact*
Mr Andrew Holmes - Norfolk & Norwich University Hospitals NHS Foundation Trust – Lead NHS R&D contact.

F) EQ-5D-5L Questionnaire – Feasibility study

Patient ID: _ _ _ _ Trial Number: _ _ _ _ _ _ _ DOB: _ _/_ _ _ _/_ _ _ _ _

Date of Completion: _ _/_ _ _ _/_ _ _ _ _

Health Questionnaire

English version for the UK

153566_KFORT Version 1.0 19 Jan 2016

Patient's Trial Number: __ __ __ __ __ __

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

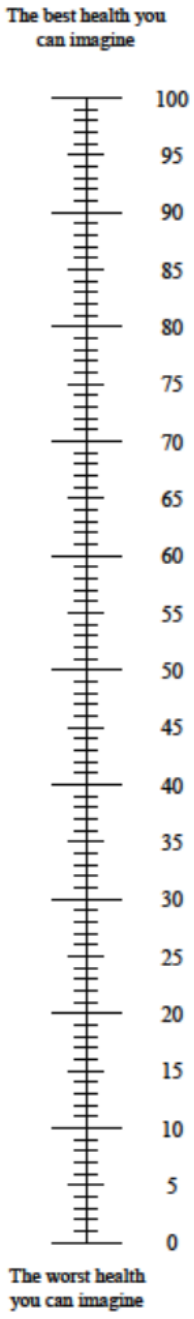
I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

KFORT Version 1.0 19 Jan 2016

Patient's Trial Number: _ _ _ _ _ _

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



3

KFORT Version 1.0 19 Jan 2016

G) SF-12 Questionnaire – Feasibility study

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please tick the one box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?**

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
b Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3

3. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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6. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt downhearted and low?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Page 3

H) Hospital Anxiety and Depression Scale (HADS) Questionnaire – Feasibility study

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week. Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all

		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

I) Participant Information Sheet - Feasibility study

University of East Anglia

Insert local header

A study to assess the use of serial MRI to reduce treatment times in Charcot in people with diabetes.

(Short title: CADOM)

Charcot neuroArthropathy Diagnostic Outcome Measures

Patient Consent Form

Principal Investigator:.....

Patient Study ID: ..... Initials: .....

Please initial each box

1. I confirm that I have read and understand the information sheet Version 1.2 10th January 2019 for the above study. I have had the opportunity to ask questions and been given satisfactory answers. ☐
2. I have been given a full explanation of the purpose of the study and what I will be expected to do. ☐
3. I understand that my medical notes and data collected during the study may be looked at by individuals from the Clinical Trials Unit at the University of East Anglia, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research I give permission for these individuals to have access to my records. ☐ YES ☐ NO
4. I understand that my participation is voluntary and that I am free to withdraw at any time without my medical care or legal rights being affected ☐
5. I consent to the storage including electronic, of personal information for the purposes of this study. I understand that any information that could identify me will be kept strictly confidential and that no personal information will be included in the study report or other publication. ☐

Small research studies have shown that repeatedly assessing the foot with magnetic resonance imaging (MRI) could be more accurate than current methods used to monitor the condition (e.g., X-rays and measuring the temperature of the feet). MRI is a scan that uses strong magnetic fields and radio waves to produce detailed images of the inside of the body. MRI may help your doctor or podiatrist decide when to stop treatment, and for patients it may decrease the time that they have to wear a cast or walking boot. The current study will investigate this in more detail than previous studies have done.

The aim of this study is to assess whether regularly repeating MRI scans of your foot ("serial"MRI) reduces treatment times for Charcot in people who live with diabetes.

Some participants will be invited to participate in an interview at the end of the study, to gain information into their experiences of living with Charcot and their involvement in this study.

Why have I been invited?
You are being invited because you have diabetes and have been diagnosed with a suspected Charcot foot.

Do I have to take part?
No. It is entirely up to you to decide if you would like to participate. If you do not wish to take part that's OK. Your decision will not affect the quality of care you receive.

If you decide NOT to take part you and your Diabetic Foot Team will agree on which treatment you receive. This may be the same as the treatment you would have received by taking part in this research study.

If you do decide to take part you are free to withdraw at any time, without giving a reason. Information collected up to your withdrawal may still be used.

What will I need to do if I take part?
If you agree to take part in this research you will either receive standard care for Charcot (according to the best way we know at the moment) or serial MRI.

For participants who receive standard care this will include an MRI at the beginning of the study, and another one when the clinical team think the Charcot has healed.

Participants in the other group (the intervention group) will receive the same standard care plus up to four additional MRI scans to monitor the progression of Charcot. At the end of the study we will compare the results in the two groups.

The study has two phases: the "active phase" (up to 12 months) and the "follow up phase" (6 months). If you chose to take part in the study your involvement will last for a maximum of 18 months. The entire research project will last for three years.

The table below shows what will happen during each of the study visits. The yellow highlight indicates normal care which would be carried out routinely as part of clinical care.

Task	1st visit	Active Phase 2 weekly	Remission	Follow Up Visit	Final Visit
Testing foot sensation	✓				
Testing blood supply to the foot	✓				
Weight and height measurement	✓	✓ 3monthly	✓		✓
Removing and applying cast/boot	✓	✓		✓	
Skin, nail and wound care	✓	✓	✓	✓	✓
Measuring foot temperatures	✓	✓	✓	✓	✓
X-ray of foot and ankle	✓				✓
MRI of foot and ankle (standard care)	✓		✓		
MRI of foot and ankle (intervention)	✓	✓ 3 monthly			
Complete patient diary		✓	✓	✓	✓
Questionnaires and pain scale	✓	✓ 3 monthly		Only at first one	✓

Most visits will be arranged at the same time as your attendance at your regular clinic visit. You may need to attend extra visits to have the additional MRI scan (s) although we will try and arrange this for the same time as your clinic visits. If we need to ask you to attend an additional visit over and above usual care we will be able to reimburse reasonable travel expenses.

In additional to the standard care every two weeks we will ask you to complete a diary recording the number of times you have attended hospital, doctors or other appointments related to your health. This will help us understand the cost of managing Charcot.

Every three months we will ask you to complete questionnaires about how you feel and whether the Charcot is impacting on your everyday activities such as washing yourself. We will also ask you to record whether your foot has been painful or not. This will take approximately 20-30 minutes to do. In total you will be asked to do this up to six times during the study.

Will I benefit from taking part?

Although you would not receive any extra benefit from taking part, you may like to know that research like this helps in continually improving the treatments and care provided to patients with similar conditions now and in the future.

Are there any disadvantages/risks to me in taking part?

Your appointment time will increase if you take part in the study from around 45minutes to nearer one hour and occasionally slightly longer. There are only minimal disadvantages and risks involved in taking part in this research, and these are described below.

It is possible that during a research study new information becomes available about the treatment under investigation. If this happens, your research team will tell you and discuss whether you want to or should continue with the study. If you decide not to continue, your research team will make sure that you receive your usual care. If you decide to continue in the study you will be asked to sign an updated consent form.

It is possible that the new information means it is in your best interests to withdraw from the study. If that happens your research team will explain those reasons and arrange for your care to continue.

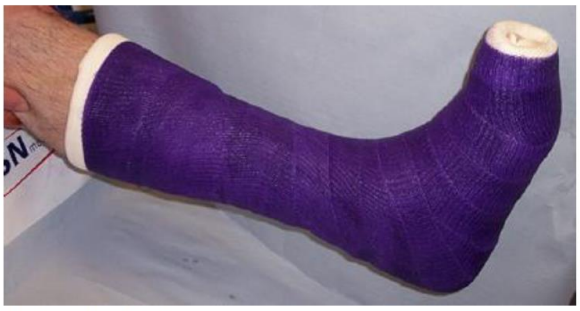
If the study is stopped for any other reason, your research team will tell you why and make sure that you receive your usual care.

Temperature Measurement

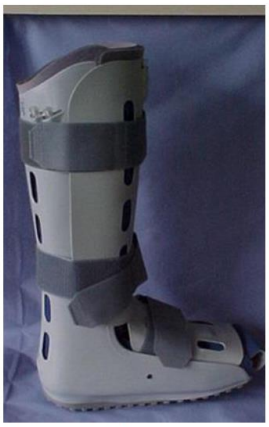
As part of usual care the clinical team would normally measure and record the skin temperature of your feet. In this study we are going to ask them to do this in a specific way. After removing the cast or boot and shoe/sock they will check the temperature on each foot in five places; the temperature will be checked immediately and again five, ten and 15 minutes later. Doing the test in this way takes slightly longer than normal and will extend the time you need to spend in clinic by around ten minutes

The cast/ boot (Picture 1 Cast and Picture 2 Boot)

Issuing you with a cast/boot is part of standard care for people who have a suspected or confirmed Charcot. The cast/boot that you wear may rub and cause skin irritation or ulcerations on your foot or leg, although these normally heal quickly. Wearing the cast/boot may affect your balance and this might make you more likely to trip or fall. If you feel unsteady then the research nurse or podiatrist can provide you with walking aids such as crutches to improve your balance.



Picture 1 – Cast

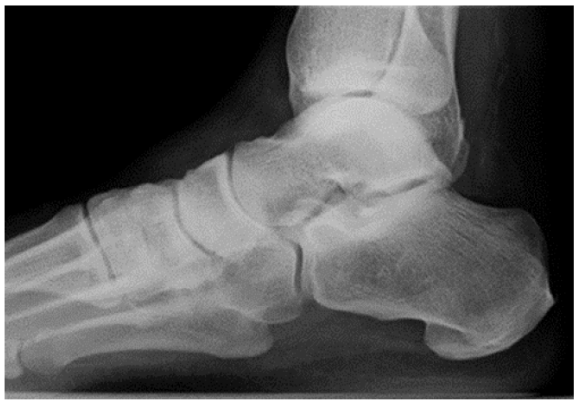


Picture 2 - Boot

X-ray (Picture 3)

If you take part in this study you will undergo a number of x-ray examinations of your foot and/or ankle. You would have received most of these as part of you standard care, even if you don't participate in the trial, however you will receive one additional examination if you do take part.

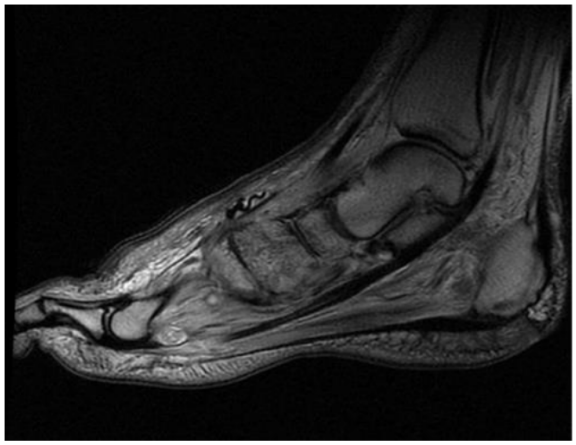
X-rays use ionising radiation to form images of your body and provide your doctor with clinical information. The radiation dose from one of these examinations is equivalent to around four hours of natural background radiation. Exposure to radiation can cause cell damage that may after many years or decades turn cancerous. We are all at a risk of developing cancer in our lifetime and the additional risk from the radiation exposure you may receive in this study may be described as negligible.



Picture 3 - X-ray of a normal ankle

MRI (Picture 4)

If you are in the intervention group you will have up to four MRIs in addition to your usual treatment. Having an MRI is entirely painless. You should not feel any discomfort during the scan and experience no after effects. Some people find the confined space of an MRI scanner upsetting. This should not be the case in this study as only your legs and feet will need to go into the scanner. You will need to lie flat and still for about 30 minutes while the scan is done.



Picture 4 – MRI of a normal ankle

There is a very small possibility that either the X-Ray or MRI will show an abnormality that you or your clinical team are unaware of. If this occurs than the clinical team looking after your Charcot will discuss this with you. If it is appropriate and with your agreement they will refer you on to the relevant team within the hospital for further assessment and management as necessary. They will also inform your GP.

What will happen to the information collected about me during the study?
Your medical information will be kept strictly confidential by the researcher and the clinical teams taking part in the trial. The people carrying out the research will only be given as much information from your medical records as is needed for this research and that information will be anonymised. They will not be given your name, where you live or anything that could identify you.

A copy of your consent form will be sent by encrypted email to the Clinical Trials Unit. This is to check that the researchers have completed the form correctly. Once the form has been checked the paper copy will be destroyed via secure waste disposal.

Because it is so important that we are able to continue following up people who are already in the study, we would like to ask you to consent to your identifiable details being registered with the NHS Information Centre. These may be used to help us keep in touch with you and follow up your health status. We will have confidentiality and security agreements in place to ensure your details are dealt with in the strictest confidence. You do not have to agree to this, and you can continue to take part in the trial even if you do not want to agree to this.

What will happen to the results of the study?
When we have completed all the study, we will write up the findings and publish it in journals that are read by health professionals, and researchers . The results of the research will also be published in publications that are accessible to people with diabetes for example 'Balance' the Diabetes UK publication. As this research is being carried out as part of a PhD the results will be written up in a thesis. We would also like to contact you at the end of the study to share the results with you.

Who is organising and funding the research?
The study has been designed by a researcher Miss Catherine Gooday, NIHR Clinical Doctoral Fellow and Principal Podiatrist. It is sponsored by the Norfolk & Norwich University Hospitals NHS Foundation Trust. It is funded by a National Institute for Health Research, Clinical Doctoral Fellowship Grant ICA-CDRF-2015-01-050.

If you would like to read more about the study visits, tests and investigations, or general conduct of the study the researcher, members of the supervisory team and the clinical teams taking part in the trial can provide you with more information. If you would prefer you can go on-line to the study website at https://www.uea.ac.uk/cadom

What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions. The researchers can be contacted on *(insert number)* If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure or the local NHS Patient Advice and Liaison Service (PALS) on *(Insert local details.)*

Who has reviewed the study?
To protect your interests and make sure that all research in the NHS is ethical, an independent group called a Research Ethics Committee has to approve the study. This study has been reviewed and given favourable opinion by the NRES - Derby Research Ethics Committee.

Catherine is being supervised by an academic and clinical team comprising of experts in Charcot and in managing clinical trials. The supervisory team consists of;

- Dr Wendy Hardeman; School of Health Sciences, University of East Anglia
- Professor Fiona Poland; School of Health Sciences, University of East Anglia
- Professor Frances Game; Department of Diabetes and Endocrinology Derby Hospitals NHS Foundation Trust
- Professor Jim Woodburn; Institute for Applied Health Research, Glasgow Caledonian University

Further information contact:
Insert local details here

UK Clinical Research Collaboration (UKCRC) published a leaflet entitled 'Understanding Clinical Trials'. This leaflet gives you more information about medical research and looks at some questions you may want to ask. A copy may be viewed online at www.ukcrc.org or may be obtained by writing to UKCRC, 20 Park Crescent, London, W1B 1AL.

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

J) Informed Consent Form - Feasibility study

University of East Anglia

Insert local header

A study to assess the use of serial MRI to reduce treatment times in Charcot in people with diabetes.

(Short title: CADOM)

Charcot neuroArthropathy Diagnostic Outcome Measures

Patient Consent Form

Principal Investigator:.....

Patient Study ID: ..... Initials: .....

Please initial each box

1. I confirm that I have read and understand the information sheet Version 1.2 10th January 2019 for the above study. I have had the opportunity to ask questions and been given satisfactory answers. ☐
2. I have been given a full explanation of the purpose of the study and what I will be expected to do. ☐
3. I understand that my medical notes and data collected during the study may be looked at by individuals from the Clinical Trials Unit at the University of East Anglia, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research I give permission for these individuals to have access to my records. ☐ YES ☐ NO
4. I understand that my participation is voluntary and that I am free to withdraw at any time without my medical care or legal rights being affected ☐
5. I consent to the storage including electronic, of personal information for the purposes of this study. I understand that any information that could identify me will be kept strictly confidential and that no personal information will be included in the study report or other publication. ☐

ICF CADOM study Version 1.3 23rd January 2019
IRAS 222668

University of East Anglia

6. I understand that even if I withdraw from the above study, the data collected from me up to that point will be used in analysing the results of the study. ☐

7. In the event that the MRI or X-ray shows a previous unknown condition that might need further medical or surgical intervention I agree to the research team referring me on as necessary and informing my GP. ☐

8. I understand that information held by the NHS and records maintained by the NHS Information Centre may be used to keep in touch with me and my health status. I give my permission to register my identifiable details with the NHS Information Centre. ☐

9. I agree to being contacted by the research team when the Charcot has settled, to ask if I would consider taking part in an interview. The interview would involve discussing the experience of being diagnosed and treated for Charcot, and being involved in this study ☐ YES ☐ NO

10. I give permission for a copy of this consent form to be kept confidentially and securely by the Norwich Clinical Trials Unit. ☐

11. I am happy to be contacted to receive updates on how the study is progressing and to be informed about the results of the study at the end ☐

12. I agree to take part in the study. ☐

…….	…….	…….
Name of the patient (Print)	Date	Patient's signature

…….	…….	…….
Name of person taking consent (Print)	Date	Signature

Original to be retained and filed in the site file. 1 copy to patient, 1 copy to be filed in patient's notes

K) Participant Diary - Feasibility study

University of East Anglia

Insert local header

CADOM – Patient Diary

Participant Diary Number .....

Start Date of Diary | | | | | | | | |

Participant Initials | | | |

Participant ID | | | | | |

Visit 1 only (Randomisation)	
What is your highest formal education	
Do you have home help?	☐ Yes ☐ No
If yes: How many hours per week do you have help?	

CADOM Patient Diary V1.2 8th May 2018

Please complete the rest of this form every fortnight recording whenever there is a visit by or to a doctor, nurse, podiatrist or other professional, whether for the Charcot or any other reason

Are you currently working paid / unpaid?	☐ Yes ☐ No
Over the last two weeks have you had to leave work / change your job? Please explain why you have left work or changed jobs	☐ Yes ☐ No ☐ I have left work due to my Charcot ☐ I have changed my job due to my Charcot ☐ I have left work for reasons not related to my Charcot ☐ I have changed my job for reasons not related to my Charcot
If you are working; are you working the same, more or less hours since being diagnosed with Charcot?	☐ Same ☐ More ☐ Less
If you are working; did you have any days off due to your Charcot in the last fortnight?	/days

Activity	Did you get help since your last visit 1. Yes 2. No	If you had help: How many hours per week did you get?
Getting in and out of bed		
Getting dressed		
Eating		
Going to the toilet		
Bathing		
Shopping		
Cleaning		

CADOM Patient Diary V1.2 8th May 2018

Any other consultation with your doctor, nurse, podiatrist or other health care professional

Date	Who was the conversation with? 1. GP 2. Hospital Doctor 3. District Nurse 4. Practice Nurse 5. Ward Nurse 6. Research nurse/podiatrist 7. Other	Was it wholly or at least partly to do with the foot? 1. Wholly 2. Partly 3. No	Was it a 1. Telephone conversation 2. Face to face meeting	How long did the visit take in minutes (i.e. how long was the interaction)	If seen somewhere other than at home what was the means of transport? 1. Own car 2. Bicycle 3. Taxi 4. Public transport 5. Hospital based transport 6. Other(please describe)	How long did it take in hours and minutes (i.e. the total time out of the house altogether? (Circle correct units)	Roughly how much were the total travel expense (e.g. taxi fare, bus parking, miles in own car)
						Hrs/Mins	
						Hrs/Mins	
						Hrs/Mins	
						Hrs/Mins	
						Hrs/Mins	
						Hrs/Mins	
						Hrs/Mins	
						Hrs/Mins	
						Hrs/Mins	

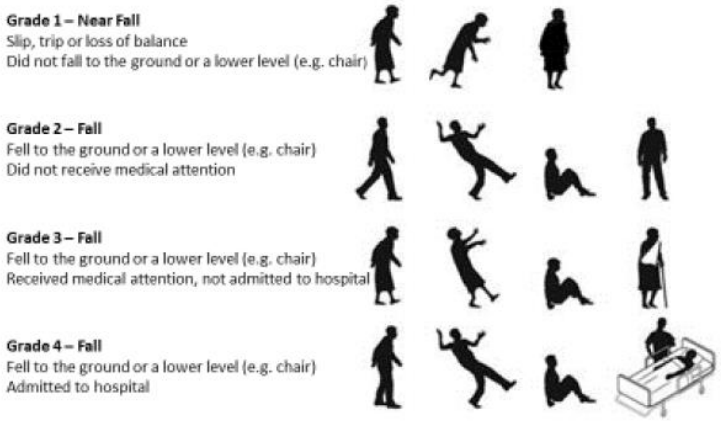
CADOM Patient Diary V1.2 8th May 2018

Please complete the rest of this form every fortnight recording whenever there is a visit by or to a doctor, nurse, podiatrist or other professional, whether for the Charcot or any other reason

Are you currently working paid / unpaid?	☐ Yes ☐ No
Over the last two weeks have you had to leave work / change your job? Please explain why you have left work or changed jobs	☐ Yes ☐ No ☐ I have left work due to my Charcot ☐ I have changed my job due to my Charcot ☐ I have left work for reasons not related to my Charcot ☐ I have changed my job for reasons not related to my Charcot
If you are working; are you working the same, more or less hours since being diagnosed with Charcot?	☐ Same ☐ More ☐ Less
If you are working; did you have any days off due to your Charcot in the last fortnight?	/days

Over the last two weeks has the off-loading cast or boot you are wearing caused you to trip or fall?	☐ Yes	☐ No				
If you have fallen; how many times has this happened in the last 2 weeks?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ more than 5
If you have fallen; using the picture below for guidance please tell what grade the fall was (If you have had multiple falls please grade the one that was the most serious)	☐ 1	☐ 2	☐ 3	☐ 4		

Hopkins Falls Grading System



Hopkins Fall Grading Scale, ©John Hopkins University

L) Visual Analogue Scale Pain - Feasibility study

CADOM

Date ☐☐☐☐☐☐☐☐

Participant Initials ☐☐☐

Participant Number ☐☐☐☐☐

Visual Analogue Scale

Please ask the patient to complete the visual analogue scale. When this has been completed, please measure the distance in millimetres between 0 (the left hand end of the scale) and the mark made, then record the measurement in the worksheet/eCRF.

Local Pain Score (VAS) by the patient

No Pain _____ Worse Pain

0 100

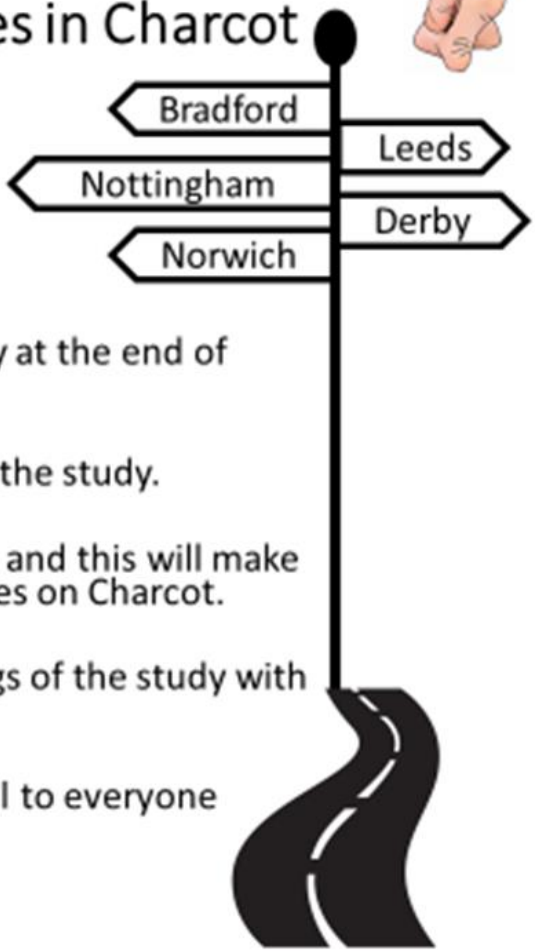
CADOM VAS Version 1.0 23rd June 2017

M) Participant newsletter – Study update

CADOM Newsletter - V1 12/02/2020. IRAS 222668

A study to assess the use of serial MRIs to reduce treatment times in Charcot in people with diabetes

Thank you for taking part in our study



Study Update

- ✓The final participant joined the study at the end of November 2019.
- ✓ In total 43 people are taking part in the study.
- ✓ 43 is an amazing number of people, and this will make this globally, one of the largest studies on Charcot.
- ✓We will be ready to share the findings of the study with you at the end of 2021.
- ✓Thank you, we are extremely grateful to everyone who took part.

Interviews

Over the last six months I have been travelling round the sites. It has been a pleasure to meet some of you. I have spoken to 14 of you who have kindly shared you experiences of what it is like to live with a Charcot.

I am now analysing the information you shared with me and will let you know the results later this year.

Thank you

If you would like to contact me to discuss anything to do with the trial then please email me at:
nnu-tr.cadom@nhs.net

Catherine Gooday

N) Participant newsletter – Returning questionnaires

CADOM Newsletter – 25/02/2021 IRAS 222668

A study to assess the use of serial MRIs to reduce treatment times in Charcot in people with diabetes

Thank you for taking part in our study

All the sites are now in the final stages of data collection. I hope to begin analysing the data after the last participant visit at the end of March 2021.

I realise the Covid-19 pandemic has impacted on some face-to-face study visits, and that you may have been unable to attend some or all of your visits over the last 12 months.

I am aware that your final study visit has just passed or is due in the next few weeks.

To minimise the disruption to the study caused by Covid-19 pandemic, and to try and collect as much information as possible I am writing to ask you if you would kindly consider completing the questionnaires enclosed with this letter.

You would normally be asked to complete these when you attended for your final study visit but I realise you may not be able to attend this visit. These are the same questionnaires you have completed regularly over the course of the study.

The information you provide on these forms is totally anonymous. Once you have completed them I would be grateful if you could post them back to me at the Norfolk and Norwich University Hospital in the enclosed stamped addressed envelope.

I appreciate you taking the time to complete these questionnaires.

I will be back in touch with you once I have analysed the results of the study to let you know what I found, and what I propose to do next.

Thank you

If you would like to contact me to discuss anything to do with the trial then please email me at:
nnu-tr.cadom@nhs.net

Catherine Gooday

O) Log of REC approval for amendments – Feasibility and qualitative studies

No	Type	Date Submitted	Date Approved	Description	Old Version Date	New Version Date
1	Minor	1011/17	17/11/17	*In the protocol* Primary Outcome has been clarified to identify that the term 'withdrawal' encompasses two potential scenarios. Withdrawal due to loss of consent Withdrawal due to death	1.1 01/09/17	1.2 07/11/17
1	Minor	10/11/17	17/11/17	*In the protocol* One of the exclusion criteria has been clarified to provide extra guidance to recruiting sites Old Statement People who have received a transplant and other patients receiving immunosuppressant therapy or using glucocorticoids other than in the routine management of glucocorticoid deficiency New Statement (additional text in blue) People who have received a transplant and other patients receiving immunosuppressant therapy or using long term oral glucocorticoids other than in the routine management of glucocorticoid deficiency. Participants on a low dose of oral glucocorticoids (<10mgs for ≤7 days) are eligible to participate in the study.	1.1 01/09/17	1.2 07/11/17
1	Minor	10/11/17	17/11/17	*In the protocol* The old web link for the definition of diabetes is no longer active a new web link has been added. It has changed from https://www.diabetes.org.uk/Documents/Professionals/hba1c_diagnosis.1111.pdf to the publications page on the WHO website - http://www.who.int/diabetes/publications/diagnosis_diabetes2011/en/	1.1 01/09/17	1.2 07/11/17
2	Minor	01/05/18	11/05/18	*Consent Form for Feasibility Study* In point 1 of the consent form, I have noticed that the date/version for the PIS reference is incorrect and refers to a previous version.	1.1 25/08/17	1.2 01/05/18

				Current text I confirm that I have read and understand the information sheet Version 1.0 dated 3rd July 2017 for the above study. I have had the opportunity to ask questions and been given satisfactory answers. Revised text I confirm that I have read and understand the information sheet Version 1.1 dated 25th August 2017 for the above study. I have had the opportunity to ask questions and been given satisfactory answers.		
2	Minor	01/05/18	11/05/18	*Consent Form for Qualitative Interviews* In point 1 of the consent form, I have noticed that the date/version for the PIS reference is incorrect and refers to a previous version. Current text I confirm that I have read and understand the information sheet Version 1.0 dated 23rd June 2017 for the above study. I have had the opportunity to ask questions and been given satisfactory answers. Revised text I confirm that I have read and understand the information sheet Version 1.1 dated 25th August 2017 for the above study. I have had the opportunity to ask questions and been given satisfactory answers.	1.1 25/08/17	1.2 01/05/18
3	Minor	09/05/18	17/05/18	*Patient Diary for Feasibility Study* Change's page 2 – Questions about employment The ordering of the questions has been updated to flow better. There has been no change to the content	1.1 01/08/17	1.2 08/05/18
3	Minor	09/05/18	17/05/18	*Patient Diary for Feasibility Study* Change's page 3 – Activity Table Early feedback from participants and analysis of the data has shown that these boxes are duplicating data collection and creating some confusion for participants. This is affecting the quality of data collected. I propose to make the following changes to the patient data collection sheet.	1.1 01/08/17	1.2 08/05/18

				Delate column 2 Clarify the wording of column 3 Delate column 4,5 and 6 as this can be calculated from the information in column 3		
4	Minor	25/06/18	24/07/18	*Additional Site - Nottingham*	N/A	N/A
5	Minor	26/06/18	N/A	*Additional Site – Leeds* *NOT SENT DUE TO ERROR ON FORM AND DELAYED OPENING*	N/A	N/A
6	Minor	30/10/18	05/11/18	*Additional Site – Leeds*	N/A	N/A
7	Minor	26/11/18	12/12/18	*Additional Site – Bradford*	N/A	N/A
8	Minor	14/01/19	15/01/18	*Changes to PIS (feasibility study) when it became apparent supplementary info sheets not approved in original application*	1.1 25/08/17	1.2 10/01/19
9	Minor	11/02/19	20/02/19	*Changes to ICF (feasibility study) to update the date and version number of PIS*	1.2 01/05/18	1.3 23/01/19
10	Minor	06/06/19	22/06/19	*Extend recruitment until Nov 19*	N/A	N/A
SA 1	Substantial	06/08/19	06/09/19	*Change to allow interviews to be carried out throughout the study* *IRAS* *Protocol* *PIS feasibility* *ICF feasibility* *New newsletter developed to inform existing participants*	 1.2 07/11/17 1.2 10/01/19 1.3 23/01/19 N/A	 1.3 18/07/19 1.3 18/07/19 1.4 18/07/19 1.0 01/08/19
11	Minor	11/06/20	27/07/20	Transfer of X-rays from site to sponsor for analysis, and clarification of procedure for analysis	1.3 18/07/19	1.4 11/06/20
12	Minor	10/07/20	24/07/20	To allow questionnaire data to be collected from participants where study visits cannot take place due to the COVID-19 pandemic. Site staff will be asked to post study questionnaires to them. Questionnaires completed by participants will be returned directly to the Sponsor using a pre-paid envelope and entered on to the database by a member of the central study team	NA	NA

P) Published qualitative study paper

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DIABETIC Medicine

RESEARCH ARTICLE

A qualitative study to understand people's experiences of living with Charcot neuroarthropathy

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Abstract

Aims: Charcot neuroarthropathy (CN) is a complication of neuropathy, in people with diabetes. Treatment requires the prolonged wearing of an offloading device, which can be challenging. The importance of understanding people's perspectives for promoting their engagement in self management is well known. However, no such studies have been done in CN. This qualitative study aimed to understand people's experiences of CN.

Methods: Semi-structured interviews with a purposive sample of 14 participants with CN, recruited from a randomised controlled trial. We gathered opinions, thoughts and the meanings participants attributed to their experiences of CN and its physical, socio-economic and physiological effects and how this affected their families and relationships. We analysed the interviews using Inductive Thematic Analysis.

Results: Four analytic themes were identified: (1) 'Trapped at home isolated and missing social life and daily life routines'; (2) 'Disruption to people's roles, responsibilities, relationships and mobility, which people adapted to try and address and manage'; (3) 'Pain which participants related to the direct or indirect consequences of wearing the cast or boot'; and (4) 'Blame for developing CN, attributed to themselves and healthcare professionals'. Participants described guilt about needing more support, expressing frustration, low mood and low self-esteem.

Conclusion: This study highlights experiential aspects of the previously unrecognised burden of CN. Its physical, social and emotional impacts on participants and their families are substantial and sustained. There is a need to raise clinical awareness of CN and its wider effects.

Trial registration: ISRCTN74101606. Registered on 6 November 2017, http://www.isrctn.com/ISRCTN74101606?q=CADom&filters=&sort=&offset=1&totalResults=1&page=1&pageSize=10&searchType=basic-search

KEYWORDS

Charcot neuroarthropathy, diabetes complications, guilt, pain, qualitative research, social participation, social support

1 | BACKGROUND

Living with any long-term condition can affect people's lives, and change people's roles and responsibilities, financial situation and housing needs.[1] These changes can affect the individual, their families and their relationships and for all involved they can be difficult to accept and adapt to. It is known that living with diabetes has a negative effect on people's experiences and their emotional well-being, with higher levels of depression and other mental health problems than the general population.[2] Having a diagnosis of diabetes also reduces people's health-related quality of life.[3] In type 2 diabetes, developing diabetes-related complications has been associated with further-reduced health-related quality of life.[2]

Foot and ankle complications including, ulceration, amputation and Charcot neuroarthropathy (CN) represent a major socio-economic challenge because of the affect they have on people's physical and psychological function.[4] Foot complications place a financial burden on people with diabetes,[5] their families and the healthcare system.[6] To date, qualitative research around diabetic foot complications has focused on people's experiences of preventing and managing foot ulceration and amputation. A qualitative meta-synthesis of 42 papers on the patient's perceptions and experiences of diabetic foot care found that foot ulceration had significant and long-term physical, socio-economic, psychological and interpersonal consequences.[4]

CN is a complication of diabetes associated with neuropathy which primarily affects the foot and ankle. It is a progressive condition that affects the bones, joints and soft tissues. There is uncontrolled inflammation and bones become osteopaenic which can lead to fractures, joint dislocation, deformity and ulceration. Treatment aims to stop the inflammatory process, relieve pain and maintain foot architecture by wearing an offloading device, usually a non-removable below knee cast or walker boot.[7] Studies from the UK show a median time to remission of between 9 and 12 months.[8,9] However, international studies report considerably shorter time to remission, in the United States of 3–5 months,[10,11] in Brazil and Germany 3–12 months and 3–6 months, respectively.[12,13] We do not fully understand the impact that wearing an offloading device for this length of time can have on peoples' physical, psychological and social comfort.[14]

We do not know whether the findings from research into experiences of people with foot ulceration are relevant to people with CN. The evidence about the effects on people living with CN comes from quantitative findings about how people experience changes in anxiety, depression and quality of life, and not about peoples' lived experiences.

Novelty Statement

- This study has shown that receiving treatment for Charcot neuroarthropathy has physical, socio-economic and psychological consequences, which extend beyond the burden of wearing an offloading device.
- Participants were frustrated about the impact of living with Charcot neuroarthropathy and experienced low mood and low self-esteem. The physical and emotional effects of living with Charcot neuroarthropathy on participants and their families were substantial and sustained.
- To limit the negative consequences of living with Charcot neuroarthropathy, there is a need to increase awareness of Charcot neuroarthropathy. Health and social care professionals should adopt a more holistic approach to supporting individuals with Charcot neuroarthropathy.

The National Institute for Health and Care Excellence NICE (2015) guidelines 'Diabetic foot problems: prevention and management' recommended more in-depth research into the health-related quality of life of people with CN.[15] A more detailed and nuanced understanding of how people live with CN could encourage more effective and constructive relationships between people with CN and healthcare and social care professionals. Gaining an understanding of the physical and psychosocial experiences of people with diabetes and CN could help develop interventions to improve experiences of people receiving treatment for CN and so reduce personal, healthcare and social care costs.

To address this research gap, this study sought to capture the participants' experiences of living with CN.

2 | AIM AND OBJECTIVES

In this qualitative study, we aimed to further the understanding of people's experiences of CN. The objectives were to explore:

- The perceived effect of CN on day-to-day functional activities.
- The effect of living with CN on social participation.
- How receiving treatment for CN may affect people's relationships with family, friends and colleagues.
- The effect of these experiences on people's sense of self and self-worth.

3 | PARTICIPANTS AND METHODS

We recruited a sample of participants from people with confirmed CN who took part in a feasibility trial on the use of serial MRI in disease monitoring. The inclusion and exclusion criteria for the feasibility trial have previously been reported.[16] The interviews were carried out in secondary care clinics between August 2019 and January 2020.

A sample size of 10–14 was set, based on recommendations for strategic and practical reasons of ensuring adequate information from the widest range of people.[17] Five participant characteristics were chosen to purposively inform the sampling framework to maximise variation: sex, age, history of previous foot complications, duration of treatment for the current episode of CN and employment status. These characteristics were selected to identify shared patterns that cross cases and ensure that unique or diverse experiences of CN were captured.

Face-to-face semi-structured interview data were collected using a topic guide (Data S1). The knowledge and experience of the clinical members of the research team, and the findings from the literature review informed the initial framework for the topic guide. The topic guide was then refined following feedback from patient and public representatives. We sought to collect participants' self-accounts of their opinions, thoughts, feelings and to identify meanings that they attribute to different CN-related areas of experience.

All participants provided written consent to take part in the feasibility trial and were re-consented by a member of the research team prior to participating in the qualitative interviews.

The interviews were recorded and then transcribed. We used Inductive Thematic Analysis and the six-step model to analyse the data.[18] In this process, the data are subjected to a rigorous analysis over six steps: (1) familiarisation gaining familiarity with the data, (2) generating initial codes, (3) searching for themes across codes, (4) reviewing themes, (5) defining and naming themes, and then (6) sharing the findings with healthcare and social care professionals, policymakers and people with diabetes. One researcher (CG) read all the transcribed interviews to record emerging ideas, then coded the transcriptions line-by-line supported by NVivo12. The initial coding framework was refined by a second researcher (FP) and cross-checked against a small sample of transcripts. The coded data were then abductively thematically analysed, identifying key categories and themes (Data S2). To enhance the credibility of the analysis, we produced a newsletter capturing the key themes, with illustrative examples as an engaging means to ask participants, how far these themes capture their own experiences of living with CN.

TABLE 1 Participant characteristics

Baseline participant characteristics	$n = 14$
Study details	
Duration of participation in study median [25th–75th IQR]	161 [103.5–241.75]
Intervention arm *n* [%]	8 [57%]
Sociodemographic	
Men *n* [%]	8 [57%]
Age (years) mean ±SD	61 ± 9.1
Highest education *n* [%]	
Stayed in school until 16	6 [43%]
Stayed in education until 18	3 [21%]
Vocational/occupational, training/qualification	4 [29%]
Degree	1 [7%]
Non-removable knee-high offloading device (cast or boot) *n* [%]	6 [43%]
Working at diagnosis *n* [%]	6 [43%]
Previous minor amputation *n* [%]	4 [29%]
Previous CN *n* [%]	3 [21%]

4 | RESULTS

In all, 42 of the 43 participants in the feasibility study agreed to be contacted about the qualitative study. We interviewed 14 participants whose characteristics are summarised in Table 1. Participants wore a mixture of non-removable and removable below knee casts/boot. Participants were selected in sequence to ensure they would meet the sampling framework criteria and achieved a maximum varying sample. No participants were excluded from the study. We identified four key themes:

- 'Trapped at home isolated and missing social life and daily life routines'.
- 'Disruption to people's roles, responsibilities, relationships and mobility, which people adapted to try and address and manage'.
- 'Pain which participants related to the direct or indirect consequences of wearing the cast or boot'.
- 'Blame for developing CN attributed to themselves and healthcare professionals'.

4.1 | Trapped at home isolated and missing social life and daily life routines

The theme 'trapped at home isolated and missing social life and daily life routines' was voiced by all the

participants. While everyone interviewed expressed these feelings, across the data there were differing nuances, often reflecting individuals' different circumstances before diagnosis.

Expressions of isolation were mainly associated with 'physical isolation' where the offloading device restricted participants' social interactions. Social isolation resulted from a combination of factors: disability caused by wearing the cast making it more difficult to go out, distance as people could not easily access public transport to visit family and friends who did not live locally, and for a few participants a perceived social stigma about wearing the offloading device. They reported on how this affected casual social interactions, such as meeting and talking to people when out shopping and during formal or planned interactions such as going to work, meeting family, friends or attending clubs.

> *I can't do nothing; can't obviously... can't do stairs or anything. Um, I've had to finish my job because it involved all walking. P3 female, aged 50–60*

However, one participant reported experiencing both 'physical and emotional isolation'; they were unable to go out to meet people and their relationship with their partner had broken down as a direct result of their being unable to do the things they used to do. They experienced rejection and being ostracised within their own home. Being isolated led participants to report feelings of low mood. While not all relationships had broken down, participants with spouses, partners and children all described how restrictions in their own mobility also affected their relations with others in various ways.

> *Oh, here's a thing – my wife's on at me because it's limited her social life. The limitations and the future. Um, it's alright saying well, its four months out of your life, but you try telling my wife that. P9 male, aged 60–70*

Realising these limitations contributed to participants' feelings of guilt and being a burden, sometimes leading to friction in relationships, and to further stress and anxiety for the individuals involved. Participants described how not only did their partners and spouses provide physical support, but also provided emotional support, without which they would not have been able to cope.

> *It's just horrible. I'm lucky I had a good one at the side of me, otherwise... [whispers] – I don't know what I'd have done." P5 male, aged 60–70*

Important differences in the experience of participants who had paid employment were associated with whether participants were able to continue working while wearing the offloading device, and how they perceived their current and long-term job security. Participant reported that they missed work and the purpose it gave to the day. They also discussed how work was important for social interaction with colleagues and not being at work, contributed to them feeling isolated.

> *I miss work. I don't miss the job; I miss the colleagues. So, as I say, it's not so much the place, it's the people isn't it. P3 female, aged 50–60*

For those participants who were in paid work before but not after their diagnosis this raised financial implications, which contributed to feelings of stress and anxiety.

> *I'm not earning any sick pay and I've got a financial... it's put me in a serious financial situation. It's caused a lot of stress, sleepless nights, um...not eating. P6 male, aged 60–71*

Participants described trying to find a balance between following the advice from healthcare professionals while managing the impact of living on a reduced income. People explained how they spend less when they did not go to work, not using as much petrol, and not buying newspapers, coffees and lunches but overall, the main expenses of mortgages, rent and household bills did not change. Participants also had long-term concerns over whether they would ever be able to return to the type of work they did before their diagnosis.

Participants identified the things they could no longer do while wearing the offloading device, and then discussed how not being able to do the activities they had previously enjoyed made them feel bored and contributed to feelings of low mood.

> *Some days, an hour feels like a day. It's just the monotony of being within these four walls. You feel like they're closing in. I've gotta get out of here. P6 male, aged 60–71*

Participants went on to discuss how they had adapted and changed the things they used to do to try and fill the time and combat these feelings of low mood, frustration, monotony and boredom. A common activity which participants described replacing work or other leisure activities with was watching the television. Participants did not consider watching the television as a good substitute for the activities they have previously enjoyed, it just filled the time.

4.2 | Charcot neuroarthropathy disrupts people's roles, responsibilities, relationships and mobility. People adapted to try and address and manage'

Thoughts and feelings around 'disruption and adaptation' appeared to play a pivotal role for participants living with CN and was a powerful theme common to all these participants. Participants reported many challenges while wearing the offloading device and ways in which they had adapted to overcome these. They discussed the frustrations that wearing the offloading device had caused them and how this had sometimes negatively affected their mood. The participants reported that their mobility inside and outside the home, family relationships and caring responsibilities had all changed extensively.

> *I've gone from being very outgoing to just being at home; I don't do nothing; I don't get around or anything. P3 female, aged 50–60*

Often the participants self-managed a range of underlying health conditions, some but not all related to their diabetes. Participants' health before the diagnosis of CN influenced what level of disruption and the range of adaptations that they needed to make. Nearly all the participants had made adjustments to cope with immediate restrictions caused by while wearing the offloading device and in anticipation of future foot problems. Participants reported that they could no longer do basic household jobs such as hoovering. These types of tasks had been taken over by their partners or others in their households.

> *Well, sort of housework type thing. I can't do hoovering and that, which was my sort of duty but I don't do that. [Laughs] I don't shopping anymore, I get that delivered by a company P1 male, 60–70.*

Many participants had decided to make adaptations to their house to help them manage while wearing their cast or boot, and to make life easier in the future should they have further foot problems. They commented that the adaptations had made their home safer for them, made daily tasks easier to carry out and ensured they maintained their independence. Participants described purchasing anti-slip mats for bathrooms, buying grabbers to pick up things from the floor, a reclining chair, having bathrooms adapted and fitting a stair lift. One person was in the process of a major house renovation to make their home more accessible for wheelchairs. Participants thoughts about their health in general and foot health were the main factors that influenced the level of adaptations they made.

They also described the importance of friends in helping them maintain their independence, and that they would not have managed without their support. Participants used sticks and crutches to improve stability while wearing the cast or boot, but it made relatively simple tasks such as carrying a drink or saucepans when cooking difficult. While participants expressed gratitude for help from family and friends, they also resented being more reliant on others to help and would have preferred to be able to manage on their own and so maintain their independence.

Wearing the offloading device appeared to reduce peoples' stability in standing and walking and to increase falls risks. Participants talked about how they addressed this risk while trying to minimise it by using walking aids, wheelchairs and mobility scooters.

> *I fell at home and then I fell outside accident and emergency ... I know it's got to be on, and I know it's on for a good reason, but it just alters your life completely. P3 female, aged 50–60*

Many participants had caring responsibilities for relatives and found, that their ability to fulfil their role as a career was now reduced, which caused additional stress. Participants described how the dynamics of family relationships had altered, with some participants reporting how roles within the household had changed with husbands and/or children now taking over the housework. Some struggled and with guilt about not being able to do their fair share of the household chores. Some participants faced conflict in their relationships with spouses or partners over the change in roles and responsibilities and having less money. However, on the whole, the majority of participants described how supportive friends and family had been and how they could not have managed physical or emotionally without this help and support.

4.3 | Pain which participants related to the direct or indirect consequences of wearing the cast or boot

Pain which participants related to the direct or indirect consequences of wearing the cast or boot was a powerful theme that emerged during the interviews and was reported by 13 of the 14 participants. Some participants commented that their current pain medication did not adequately relieve their symptoms and sought to discuss this with their healthcare team. The participants interviewed wore a mixture of devices: non-removable and removable

casts and below knee walkers. Participants had mixed opinions about which device they thought was more comfortable. Regardless of the type of device most of the participants attributed the pain they were experiencing to the offloading device being worn to protect the foot, rather than to the CN itself.

> *hips hurt while I'm walking. Knees hurt when I'm walking, when they didn't before. P1 male, aged 60–70*

Some participants reported that cast or boot intensified their nerve pain, they experience in their foot and leg. Participants acknowledged that it was important to wear the device but explained that they nonetheless wanted more support and advice from healthcare professionals on things that they could do themselves to minimise and manage the pain.

4.4 | Participants attribute blame for developing CN on themselves and healthcare professionals

Participants thought that more understanding and awareness of CN by both healthcare professionals and people living with diabetes was important. This would improve recognition of the signs and symptoms as well as ensure prompt treatment and improve outcomes. In some cases, participants thought that their own actions or inactions had contributed to them developing CN.

> *I wasn't as strict with me insulin and things like that. As I should have been. I know what I've done and yeah; suffering now. I'll lecture anyone now if they tell me that they don't do it themselves. P14 female, aged 50–60*

Participants talked about how a lot of information was given to them by healthcare professionals when they are diagnosed with diabetes which was difficult to absorb and remember. Several participants suggested that if people with diabetes were more aware of the importance of looking after themselves and their diabetes, they may be less likely to develop further problems. Participants who thought that their diagnosis of CN was initially misdiagnosed by non-specialist healthcare professionals reported feelings of anger and resentment.

5 | DISCUSSION

This study identifies the previously unrecognised, distinctive and onerous aspects and life implications of the burden of CN experience. Receiving a diagnosis of CN, often without warning, frequently resulted in denial, shock, fear, anger and resentment. Analysing the semi-structured interview data produced four themes. The first theme, 'trapped at home isolated and missing social life and daily life routines', highlighted the effects of social isolation whereby participants experienced resting the foot and wearing the cast/boot as restricting their interactions with others. The second theme, 'disruption to people's roles, responsibilities, relationships, and mobility, which people adapted to try and address and manage', focused on how participants reported being less mobile and more unsteady, which affected their ability to do household chores, shopping and care for others. The third theme was 'pain which participants related to the direct or indirect consequences of wearing the cast or boot: participants attributed the pain to wearing the offloading device rather than the CN. The final theme 'blame for developing CN attributed to themselves and healthcare professionals' which participants attributed to their own actions or inactions and/or healthcare professionals missing the diagnosis.

Other studies which explored the experiences of people with diabetic foot ulceration showed that the restrictions of resting, wearing an offloading device and pain can leave people socially isolated.[19-22] Our participants described a disconnection from their social networks related to work, family or leisure.

Our study has provided deeper insights and context to the quantitative research which shows that CN decreases participants' physical ability to perform tasks, such as shopping, cleaning and gardening.[23,24] Our results are consistent with the overall theme described for people with diabetic foot ulceration as a 'lifetime of behavioural change', with a life of fear, restrictions and pain[21,22] and social, psychological physical and economic impacts.[20] There is a need to work with patients to balance the need to rest and offload the foot against the substantial physical limitations and emotional stresses.

Being isolated, managing and adapting to the disruption, caused by wearing the offloading device profoundly affected participants' well-being. Our participants described that healthcare professionals focus on the physical (e.g. offloading device) and medical issues (e.g., diabetes) associated with the CN, while attending less to emotional impact. In other studies, people with diabetic foot ulceration and amputation have reported their need for additional psychological support.[22] Our study shows that there is still some way to go to meet this need.

The general advice from healthcare and social care professionals about overall good health and diabetes management is to be physically active and maintain a healthy weight. When people are diagnosed with CN, they are

advised to be less physically active, rest the foot and wear offloading devices which further restrict their mobility. For participants in this study, these recommendations and physical limitations fostered their own concerns for their overall health and was reflected in their emotional distress.

This study has shown consistency between the thoughts and views expressed by participants on impacts on family members and those which were reported by the family members themselves in other studies. These include limitations to social activities, tensions within relationships,[20] impaired mobility, frequent hospital visits and fear of amputation[25]

This study shows that pain has a substantial role in influencing participants overall experience of living with CN. Pain associated with wearing the offloading device was often felt in the more proximal joint sites of the knee, hip and back rather than the foot itself. This confirms the findings from other studies where participants experienced pain when using such devices.[20,21,26,27] Clinical teams need be more aware of and responsive to such pain experiences to ensure that they identify patients who are experiencing pain and where relevant, can then work with participants to look for solutions to effectively manage this pain, which, in turn, would reduce one of the triggers for emotional distress.

Individuals' experiences of blame was the final theme to emerge from analysis. As in studies among participants with foot ulceration or amputation, participants reported that their actions and inactions as regards taking care of their feet: by not inspecting their feet regularly, not wearing their prescribed footwear or seeking help immediately they noticed a problem, and self management of their diabetes had directly led to or slowed down their recovery from foot complications.[28-30] In many instances, participants engaged in what they regarded at the time as reasonable risk-taking, trying to achieve a balance between quality of life and treatment compliance. Healthcare professionals may risk labelling participants as 'non-compliant' if they do not understand the everyday difficulties people face while wearing an offloading device for several months.

In this study, some participants blamed healthcare professionals for missing the diagnosis of CN with resulting anger and frustration. The participants' experiences are consistent with retrospective case series reports showing missed or delayed diagnosed of CN,[31,32] leading to worse outcomes. Our study is also consistent with studies from the United States and Ireland where participants blamed healthcare professionals and healthcare systems for causing foot problems to develop and for delays in receiving treatment for foot complications.[28,30,33] Despite national, and international guidelines for the assessment and management of diabetic foot complications including CN, this study and other studies have found that people are still not being referred on to specialist services soon enough. This results in worse outcomes for people and increased cost to the healthcare providers.

5.1 | STRENGTHS AND LIMITATIONS

The strength of this study is that the sample reflected the known typical characteristics of people who develop CN. However, the role of ethnicity, social and cultural differences was not specifically explored in this study and omitting this may affect issues around generalisation. Although the interviews were carried out when participants still received treatment for CN, the time since initial diagnosis was up to 6 months which could have introduced some recall bias. The interviews only captured the stories participants shared on that day. A longitudinal qualitative study may provide further insight into how peoples' experiences change over time.

5.1.1 | Implications for health and social care professionals and policymakers

The overarching recommendations arising from this study are to increase awareness of CN among healthcare and social care professionals and people with diabetes. Professionals need to adopt a more holistic approach to support individuals living with CN. Healthcare professionals need to develop a therapeutic alliance with people with CN and understand the reasons behind individuals' motivations and choices.

First, multidisciplinary diabetic foot teams should be expanded to include professionals with skills to support the profound emotional effect of CN on well-being. Alongside this, there is an opportunity to upskill existing multidisciplinary team members to support people in a holistic way. Standard measures of depression and/or anxiety could be incorporated into clinical assessment to identify people who would benefit from support or referral to physiological services. Second, healthcare professionals need to work with people to find solutions to manage their pain. Third, multidisciplinary foot teams need to develop more formal links with social care professionals and voluntary organisations, to help participants access additional financial and non-financial support. Fourth, we recommend improved links with physiotherapy departments to provide strategies on how to minimise the pain experienced when walking with offloading devices and make use of home or telehealth physical activity programmes already

developed for people with other long-term conditions. Finally, and importantly, there is a need to expand the role of people with CN who are experts by experience in service re-design, thus improving their overall experience and care provided.

5.1.2 | Recommendations for research

The study findings highlight the need for research to better understand the reasons behind the concept of reasonable risk-taking, balancing treatment adherence with quality of life. There is a need to develop strategies that move beyond education and actively support people to self manage their diabetes and foot complications, using behaviour change techniques such as goal setting and review, self monitoring, and habit formation.

6 | CONCLUSION

Overall participants expressed frustration, experiencing low mood and low self-esteem. These physical and emotional effects of CN on participants, their families and relationships were substantial and sustained. Living with CN has ramifications that extend beyond the physical limitations imposed directly by wearing the offloading device. There are further physical, socio-economic and psychological consequences people prioritise if they are to manage their lives and their health. People with CN need to be able to access a wider range of support beyond their clinical team, to include psychological and social care services.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

The trial has been reviewed by East Midlands—Derby Research Ethics Committee, 04/10/2017, ref: 17/EM/0288, and conforms to the Helsinki Declaration (revised 2013). All participants provided written consent to take part in the feasibility trial and were re-consented by a member of the research team prior to participating in the qualitative interviews.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

The investigators have no financial or other competing interests that impact on their responsibilities towards the scientific value or potential publishing activities associated with this study.

AUTHOR CONTRIBUTIONS

CG is the NIHR Clinical Doctoral Fellow and Chief Investigator. CG and FG developed the initial idea for the study. CG, WH and FP designed the study. CG conducted the interviews. CG and FP completed the analysis. CG drafted the manuscript. All authors contributed to the manuscript for important intellectual content. All authors read, amended and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Gooday C, Hardeman W, Game F, Woodburn J, Poland F. A qualitative study to understand people's experiences of living with Charcot neuroarthropathy. *Diabet Med*. 2022;00:e14784. doi:10.1111/dme.14784

Q) Topic guide for qualitative study

- Is this Charcot your first foot problem?
- How long have you been receiving treatment for the Charcot for?
- What thoughts went through your mind when you were told you had been diagnosed with Charcot?
- What factors influenced your decision to agree to treatment with the cast/boot?
- Tell me about your experience of being treated for Charcot.
- How did you find being in a cast/boot?
    - Please can you tell me about any problems the cast or boot have caused you?
- Please can you describe how receiving treatment for Charcot has impacted on your day-to day life?
    - Are there things that you would like to do that you cannot because of the Charcot? Can you tell me about these?
    - Can you describe the impact of not being able to do the things you would like to do?
- How do you think receiving treatment for Charcot has impacted on your family/friends?
    - Can you explain in more detail what the impact has been?
    - Has anything happened as a result of this, can you tell me about it?
- Please can you tell me about what you think the long-term implications of CN will be for you and/or your family?
- Can I ask you to describe how you think Charcot will affect you in the future?

R) Participant newsletter – advising of amendment to timing of interviews

CADOM Newsletter - V1 01/08/2019. IRAS 222668

A study to assess the use of serial MRIs to reduce treatment times in Charcot in people with diabetes

Thank you for taking part in our study

Study news

- There are now five hospitals inviting people to take part in the study.
- So far 28 people are taking part.
- The first participant interview has taken place as some people are starting to finish the study.
- We will still be inviting people to join the study until the end of November 2019.

Update about interviews

You may remember we asked you if would be willing to taking part in an interview at the end of trial. We would like to learn more about your experiences of living with Charcot and being in this study.

We are now proposing to carry out the interviews while your treatment for Charcot is ongoing rather than only after your treatment had been completed. Your local podiatrist or nurse may ask you if you are still happy to take part in the interview. If so, we will then arrange to meet with you at a time and place convenient for you.

I really look forward to meeting you and hearing about your experiences of living with Charcot. If you would like to contact me to discuss this or any thing to do with the trial then please email me at: nnu-tr.cadom@nhs.net

Thank you

Catherine Gooday

S) Participant Information Sheet - Qualitative study

University of East Anglia

Insert local header

CADOM Interview study

Charcot neuroArthropathy Diagnostic Outcome Measures

Patient Information Sheet

Investigators
The chief investigator is Miss Catherine Gooday, NIHR Clinical Doctoral Research Fellow, Principal Podiatrist.

Local investigator: *(Insert name here)*

This study is being undertaken as part of an NIHR Clinical Doctoral Fellowship, educational project.

Invitation to take part in an interview

You have already kindly agreed to take part in the CADOM study. This study aims to find out whether the use of serial magnetic resonance images (MRI) reduces treatment times in people who live with diabetes and Charcot.

You are now being invited to take part in an interview.

Please take time to read the following information carefully and please talk to others about the study if you wish. Take as much time as you want to decide whether or not you wish to take part. You do not have to take part if you do not want to.

What is the purpose of this study?
Our aim is to better understand the experiences of people who develop Charcot and how treatment affects people's everyday life. At the moment we don't know people's experiences. The information gained from the interviews will help doctors, nurses and podiatrists to better communicate with people with this condition, and take their experiences and needs into account.

Why is it important to know your views about taking part in the CADOM trial?
If this study finds that the use of MRI could be beneficial, then we may conduct a much large study involving several hundred people. By understand people's experiences of this study we can use this information to improve the design of the next study.

Why am I being invited to take part?
We are writing to you because you are taking part in the CADOM study. We want to talk to at least 10 and up to 14 study participants about their experiences of being treated for Charcot and their views about being involved in the study.

Do I have to take part?
No. It is entirely up to you to decide. If you do not want to take part that's OK. Your decision will not affect the quality of care you receive. If you're happy to take part, you will need to give about one hour of your time. The researcher Catherine Gooday will contact you to arrange a date and time to suit you. Catherine will come and meet you in a place that is convenient for you.

There are no right and wrong answers to any questions; we are just interested in hearing your experiences.

With your permission the interviews will be recorded using a digital voice recorder so that we can keep an accurate record of everything you say. If you do not wish to have the interview recorded the researcher will take notes during the interview.

Once the interview has happened the recording or notes will be uploaded immediately onto a secure University computer. If this is not possible they will be transferred or scanned onto a NHS secure encrypted memory stick and then uploaded onto the secure University computer as soon as possible. The recording will then be deleted from the recorder and the notes destroyed.

The recroding and notes from the interview will be kept until the results of the study and PhD thesis have been written up.

The interview will be anonymised before it is transcribed. It will be transcribed by the researcher or a member of the University of East Anglia staff who has signed a confidentiality agreement.

What are the possible disadvantages of taking part?
If you take part in the interviews, you will need to give roughly one hour of your time.

What will happen to the results of the study?
When we have completed all the interviews, we will write up the findings and publish it in journals that are read by health professionals, and researchers . The results of the research will also be published in publications that are accessible to people with diabetes for example 'Balance' the Diabetes UK publication. The results of the interviews will also be looked at together with the results of the main study, to help us understand the results of the main study further. As this research is being carried out as part of a PhD the results will be written up in a thesis. We would also like to contact you at the end of the study to share the results with you.

What will happen to the information collected?
A copy of your consent form will be sent by encrypted email to the Clinical Trials Unit. This is to check that the researchers have completed the form correctly. Once the form has been checked the paper copy will be destroyed via secure waste disposal.

Because it is so important that we are able to continue following up people who are already in the study, we would like to ask you to consent to your identifiable details being registered with the NHS Information Centre. These may be used to help us keep in touch with you and follow up your health status. We will have confidentiality and security agreements in place to ensure your details are dealt with in the strictest confidence. You do not have to agree to this, and you can continue to take part in the trial even if you do not want to agree to this.

Only the research team will know that you have taken part in an interview. Your name will not be written on the interview transcript. You will be anonymised in any written reports of the research.

We may use written quotations from the interviews in presentations and teaching but these will be anonymised. The recording of the interviews will be stored securely until the end of the study then they will be destroyed. The transcriptions will be stored securely for a period of 15 years after the study is finished; then they will be destroyed.

Who is organising and funding the study?
The study has been designed by a research team led by Miss Catherine Gooday, NIHR Clinical Doctoral Fellow and Principal Podiatrist. It is sponsored by the Norfolk & Norwich University Hospitals NHS Foundation Trust. It is funded by a National Institute for Health Research, Clinical Doctoral Fellowship Grant ICA-CDRF-2015-01-050.

If you would like to read more about the study visits, tests and investigations, or general conduct of the study the researcher, members of the supervisory team and the clinical teams taking part in the trial can provide you with more information. If you would prefer you can go on-line to the study website at https://www.uea.ac.uk/cadom

What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions. The researchers can be contacted on *Insert local number*. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure or the local NHS Patient Advice and Liaison Service (PALS) on *Insert local number*.

Who has reviewed the study?
To protect your interests and make sure that all research in the NHS is ethical, an independent group called a Research Ethics Committee has to approve the study. This study has been reviewed and given favourable opinion by the NRES - Derby Research Ethics Committee.

Catherine is being supervised by an academic and clinical team comprising of experts in Charcot and in managing clinical trials. The supervisory team consists of;

- Dr Wendy Hardeman; School of Health Sciences, University of East Anglia
- Professor Fiona Poland; School of Health Sciences, University of East Anglia
- Professor Frances Game; Department of Diabetes and Endocrinology Derby Hospitals NHS Foundation Trust
- Professor Jim Woodburn; Institute for Applied Health Research, Glasgow Caledonian University

Further information and contact:
Insert local details here

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

T) Informed Consent Form - Qualitative study

University of East Anglia

Insert local header

Interviews

Experiences of being treated for Charcot neuroarthropathy and views about taking part in the clinical trial.

(Short title: CADOM)

Charcot neuroArthropathy Diagnostic Outcome Measures

Patient Consent Form

Principal Investigator: .....

Patient Study ID: ..... Initials: .....

Please initial each box

1. I confirm that I have read and understand the information sheet Version 1.1 dated 25th August 2017 for the above study. I have had the opportunity to ask questions and been given satisfactory answers. ☐
2. I have been given a full explanation of the purpose of the study and what I will be expected to do. ☐
3. I understand that my medical notes and data collected during the study may be looked at by individuals from the Clinical Trials Unit at the University of East Anglia, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research I give permission for these individuals to have access to my records. ☐ YES ☐ NO
4. I understand that my participation in the interview is voluntary and that I am free to withdraw from the study at any time, without having to give a reason. ☐
5. I understand that the interview will be recorded on a digital recorder. I give permission for doing this. ☐

Qualitative Interviews CADOM study Version 1.2, 1st May 2018
IRAS 222668 ☐

University of East Anglia

Insert local header

6. I understand that the recordings will be saved on a secure computer at the University of East Anglia. The recordings will be destroyed at the end of the study. The transcripts will be kept for 15 years.

7. I consent to the storage including electronic, of personal information for the purposes of this study. I understand that any information that could identify me will be kept strictly confidential and that no personal information will be included in the study report, my thesis, or other publication. ☐

8. I understand that what I say during the interview is confidential, in accordance with the Data Protection Act. However, you must be aware that if you tell the interviewer something which shows that there is a significant risk to you or someone else, they may need to pass this information on. If this happens, they will discuss it with you first before anyone else is told ☐

9. I am happy to be contacted to receive updates on how the study is progressing and to be informed about the results of the study at the end. ☐ YES ☐ NO

10. I give permission for a copy of this consent form to be kept confidentially and securely by the Norwich Clinical Trials Unit. ☐

11. I agree to take part in an interview for the above study. ☐

.....	.....	.....
Name of the patient (Print)	Date	Patient's signature
.....	.....	.....
Name of person taking consent (Print)	Date	Signature

Original to be retained and filed in the site file. 1 copy to patient, 1 copy to be filed in patient's notes

U) Qualitative study interview codebook

Name	Ref	Illustrative quote
***Blame for developing CN attributed to themselves and healthcare professionals*.**		
Blame	14	I knew after the first Charcot in the left foot that I had to be more careful. And I suppose I blamed myself for not taking more care, when my husband was saying, come on, turn round we can go home. 'No, I can walk another…'
Fears and worries	19	Every time I get pain in this foot now, I'm thinking, oh my god.
Lack of awareness & raising awareness	13	I think the most important thing is education for people nobody knows about it not even people with diabetes on insulin, they don't know, and they should
People's perception what caused CN	24	I was given the boots, but I wasn't given the information that I should ween myself off out of the air cast, so I didn't.
Perceived benefits	3	But I have got my sugar levels down.
Problems following advice to rest	18	I've got to be very careful about the extra walking. If it isn't necessary, I don't do it; there are certain things I've got to do.
Problems getting a diagnosis	52	I think I had a fall and I kept going to the…I went to the hospital; to A&E and they just said it was a sprain, to carry on as normal. So, I kept going to work
Thoughts about diagnosis	31	They decided it was a CHARCOT foot and was told that I would be in plaster for a year. I thought I would kill them [Laughs], but I didn't.
Thought's future	45	Every time I get pain in this foot now, I'm thinking, oh my god.
Disruption to people's roles, responsibilities, relationships, and mobility, which people adapt to try address and manage.		
Adaptions to make life easier	14	I've had to do my main shopping online via computer instead of going out and looking.
Appearance	17	Just how it looks, makes me look like I've got a stigma, I've got a disability and I can't do things normally.
Boredom	9	I'll get fed up with that and I'll read a magazine or something or I'll…then I'll get fed up with that and I'll think, what can I do next?
Name	**Ref**	**Illustrative quote**
Caring responsibilities for others	38	So that was me main worry; not about me, about me mum you see. So, I have got to function so that I can look after her, you know.
Difficulty doing daily household jobs (cleaning etc)	32	It's just not being able to do anything, it's horrible. I mean, I love cooking, but I can't do it; I can't cook standing up and then you've got sticks on – I can't take a hot saucepan off the stove
Emotional impact	52	I said to my husband, I could just sit down and sob me heart out but I'm not going to

Feelings about consequences work	40	I can't do nothing; can't obviously…can't do stairs or anything. Um, I've had to finish my job because it involved all walking and
Guilt	13	You see then I feel under pressure because I'm putting pressure on her as well. So, that makes me feel awkward.
Help and support	30	Everyone is very kind and want to offer to do things when you can't do them; I've had people do my shopping and that's very kind of them.
How fill time	11	I go in the shed and count screws. [Laughs] You know, sort out nuts, screws and bolts. Sometimes I get frustrated.
Impact of CN on personal daily activities (washing etc)	14	Sometimes, she's had to help me out of the shower because me balance isn't very good. I've fell out the bath a couple of times,
Making yourself useful	9	I like it, if she gives me something to do where I need to find this – go on the internet and find this…
Mobility impact and adaptations	85	It made me not want to walk around. I did get some crutches but then I hurt my thumb on the crutches, so I had to stop using those.
Money worries	29	That's another thing you've got to think about. The cost of everything.
Relationships communications with partners and spouses	49	It's just horrible. I'm lucky I had a good one at the side of me, otherwise…[whispers – I don't know what I'd have done.]
Talking about wearing casts & boots	61	It was such a bad experience for me at first, I was offered this heavy wellington boot it's not suitable for me someone in their sixties. It needed pumping up manually it felt like a slab on my foot.
Name	**Ref**	**Illustrative quote**
Transportation issues	30	I come in a taxi; it's the only way I can get here, otherwise it's three buses and I can't do buses because I can't get up the steps.
Unsteadiness falls	46	I have had moments where I have crashed to the floor
Weight issues	13	I've put a stone on in weight after a year, which I'm not happy about. [Laughs] And now I've got back problems, due to all the sitting around.
What other people see and say	21	They talk to X. 'What's she done? Is she alright? Is she in pain?'
Pain which participants related to the direct or indirect consequences of wearing the cast or boot.		
Cast pain	6	When I went back to the clinic, they asked me where the boot was. I told them it crippled me, it was enough to finish me off

Foot pain	12	There's pain with it that…when you're a diabetic you're not supposed to have any pain with it but there is
Nerve pain	6	
No pain	4	So…it's fine, it doesn't hurt so there isn't any discomfort or anything,
Other pain	1	I've got Raynaud's as well and medication for Raynaud's is no longer available.
Pain knees, hips etc	7	The most pain I get is from this foot and my hips, you know, from it being off balance.
Treatment for pain	10	It's just so painful though and it's the medication that needs sorting to get the combination right
Trapped at home isolated and missing social life and daily life routines.		
Bereavement	5	We've just lost mum six-weeks ago, so, she was a big help, want she, she used to do a lot of stuff. I think we'll manage; we've got no choice, we'll have to.
Boredom	9	I'm bored of watching tele until you…[laughs] there's only so much daytime tv you can take.
Christmas	7	Couldn't help her at Christmas but she has, she's been a brick. I've aid it before but if it wasn't for the wife…I don't know. But luckily, I've got the old girl
Comparing their life to others worse off	11	Sitting in that waiting room, it ain't very nice you know
Name	**Ref**	**Illustrative quote**
Doing things with children	1	Yeah, I'm afraid they're a bit like me, they're geeks. So, there's a certain amount of commonality there.
Emotional impact	52	Terrible, terrible, honestly. I wouldn't wish this on me best mate or me worst enemy.
Exercising	12	I'm used to using the exercise to help the sugar. So, when I found that I couldn't exercise as much, I started to think right, well, I won't bother with that then, I'll just trim the diet a bit more and try to balance it that way.
Families and not being able to visit	29	We used to visit family in X, but we can't…we haven't done that for a long time and that really hurts.
Going out and about	54	I'm used to being with people all the time, conversing, but I can't now do that as much. I wish I could go out more
How life has changed - impact	47	Now, if I knew this was what would happen…pfft. It's horrible, but I can see a bit of light at the end of the tunnel, so…
Loneliness	8	For the first seven months, apart from coming here, I was house bound.
Money worries (stops going out)	29	I's the cost; it's the cost of going out anywhere

Relationships communications with partners and spouses	49	It’s not fair on her because if we do go out, she can’t drink because obviously she’s driving and it does put a lot of the pressure on her, so…yeah
Things miss or can't do	53	Really, holidays are out of the question till I’ve been able to…everything’s going well with that. Um
Walking the dog and pets	13	I’ve had problems health wise but not being able to go out, not being able to take me dog for a walk.

V) Participant newsletter - Summary of results qualitative study

CADOM Interviews Newsletter - V1 13/10/2020. IRAS 222668

A study to understand people's experiences of living with Charcot.

Thank you for meeting me to talk about your experiences of living with Charcot. I met and spoke to 14 people who took part in the study. Over the last six months I have been working full time in the NHS, so it has taken me longer than I expected to analyse the interviews. I have now had time to think about the thoughts, feelings, and views you kindly shared with me and I would like to share the emerging findings with you. If you would like to, and have time, please will you read short accounts of what people said to me, on the next pages, then think about how far they capture your own experiences of living with Charcot.

I have divided these findings into four kinds of comments:

"Isolation and missing out"

"Disruption and adaption"

"Pain"

"Blame"

If you have any comments you wish to make please either write alongside the findings or in the comment boxes. Telling me your views about what I heard may help me understand more clearly what they may mean for your own experiences.

I have enclosed two copies of these findings: one for you to keep and one for you to send back if you wish to share any comments with me. You can return the form in the enclosed stamped addressed envelope ; it does not ask you to record your name, so your comments would be anonymous. Alternatively you can email your comments to me at: nnu-tr.cadom@nhs.net

Catherine Gooday

1

Thank you

Isolation and missing out

There were a number of ways that people reported that the Charcot and wearing the cast or boot had affected their lives, leaving them feeling trapped at home, isolated and missing the things they used to do.

Working and volunteering

- Some people described missing both their work and work colleagues and felt this contributed to feelings of isolation.
- Some people reported that the financial worries of not working made them feel stressed.
- A few people were worried about long-term job security.

Taking part in leisure activities

- Not being able to do the things people previously enjoyed made some people feel bored and contributed to feeling low.
- For a few people, financial worries meant that they were not able to enjoy leisure activities as often as they used to.
- Some people talked about how they missed being able to exercise, and how a lack of exercise may affect their diabetes.
- A few people reported that they no longer had the energy to do the things they previously enjoyed.

Meeting people

- Some people reported that they now had to plan outings, and it was more difficult to be spontaneous.
- Many people reported they were unable to visit family and friends.
- Some people also described how wearing the cast or boot also impacted on the social life of their husbands, wives or partners.

Your comments

2

Disruption and adaption

Some people described how receiving treatment for Charcot and wearing the cast or boot had made daily tasks more difficult, and how they now relied on family, friends and paid help. People discussed the changes they had made to allow them to live safely, comfortably and as independently as possible.

Mobility

- Nearly all the people interviewed described how the cast or boot restricted their mobility and that this in turn presented challenges in going out.
- Some people said that they had lost their independence.
- Difficulties around accessing and safely using public transport were reported by some people as reasons for not going out.
- Unsteadiness and concerns over falling both inside and outside the house were reported by nearly everyone.
- Many people said that they had fallen and injured themselves.

Adapting at home

- Some people reported how difficult they found doing even simple tasks such as carrying cups of drinks while using sticks and crutches.
- Some people reported how they could no longer do household chores, and these had been taken over by family or friends.
- Some reported how they were making adaptions to their home to make life easier and safer.

Relationships and caring

- Those people with caring responsibilities said they were frustrated that they now needed to rely on help (either paid or unpaid) to look after your relatives.
- Some people felt that they were putting an extra burden on your family asking for help while wearing the cast or boot.
- Some people felt their family had really supported them both emotionally and physically.
- For other people wearing the cast or boot and the disruption that this caused had sometimes led to friction in relationships.

Your comments

3

Pain

Ongoing pain in one or both feet and legs was a serious problem for some people.

- Some people described experiencing pain in the Charcot foot when walking.
- Many people reported pain in their other foot, leg, hip and back.
- Some people felt pain in the foot and ankle when they were wearing the cast or boot.
- Some people felt their foot was burning and tingling.

Blame

People discussed the reasons they thought the Charcot had developed, and why it might have happened to them. Other people talked about their frustrations at the time it had taken to get a correct diagnosis.

Personal responsibility

- Some people thought if they had taken better care of themselves and their feet, they might not have developed Charcot.
- Some people felt it was important to provide more information to people with diabetes on the possible complications. They felt if people were aware they might take more care of their diabetes to prevent problems and spot them earlier.

Delayed diagnosis

- Some people saw their diagnosis of Charcot as being missed or delayed.
- People viewed this delayed diagnosis as leading to their foot becoming more deformed and taking longer to heal.
- Some people were very frustrated and angry about the delay to diagnosis, this was contributing to their feelings of stress.
- Nearly everyone felt there was a lack of awareness around Charcot for non specialist health care professionals.

Your comments

4

Thank you

W) Permission for the reproductions of figures and tables used in this thesis

Figure	Title	Author	Permission
2-1	Diabetes complications		Not applicable
2-2	Plain X-rays to illustrate the progression of deformity leading to fractures, dislocation, and deformity		Not applicable (Royal College of Radiologists, 2017)
2-3	Pathogenesis of Charcot neuroarthropathy	*Kaynak* et al*., (2013*)	Open-access article distributed under the terms of the Creative Commons Attribution License
2-4	Anatomical location of Charcot neuroarthropathy	Game et al., (2012)	Not applicable
2-5	Plain X-rays demonstrating the different stages of the Eichenholtz classification system		Not applicable (Royal College of Radiologists, 2017)
2-6	Pictorial representation of the anatomical classification systems described by Sanders and Frykberg and Brodsky		Not applicable
2-7	Clinical presentation of CN the left foot is red and swollen compared to the unaffected right foot		Not applicable
2-8	Photography of the assessment of foot temperature using infrared thermography		Not applicable
2-9	Algorithm for the assessment and management of CN		Not applicable
2-10	Imaging in early CN a=X-ray no abnormalities b=MRI showing classic bone marrow oedema not evident on X-ray	Rosskopf et al., (2019)	Open-access article distributed under the terms of the Creative Commons Attribution License
2-11	Rogers classification adapted from	Rogers and Bevilacqua, (2008)	Approved
2-12	Examples of the different types of off-loading devices		Not applicable
2-13	Pictorial representation of the progression of deformity leading to ulceration	Rosskopf et al., (2019)	Open-access article distributed under the terms of the Creative Commons Attribution License

Table	Title	Author	Permission
2-1	Causes of CN		Not applicable
2-2	Modified Eichenholtz classification system a	Wukich and Sung, (2009)	Approved
2-3	Sanders and Frykberg and Brodsky classification systems		Not applicable

Definitions

Relapse of Charcot neuroarthropathy (in the context of this research)**:** a temperature difference of >2°C compared to the contralateral foot maintained for two or more occasions or further changes on imaging.

Remission of Charcot neuroarthropathy (in the context of this research)**:** for participants in the standard care arm remission is defined as a temperature difference of ≤ 2°C which is maintained or improves on two separate consecutive occasions for a period of at least four weeks. In the intervention arm remission is defined as an absence of sub-chondral bone marrow oedema on MRI, as reported by a radiologist and assessed by the clinical team with the absence of clinical signs and symptoms of CN.

Glossary of terms

This glossary consists of terms and phrases that are routinely used and understood by healthcare professionals and researchers who work with people with diabetes and diabetic foot complications. To develop this glossary where appropriate I have used definitions from published guidelines such as the International Working Group on the Diabetic Foot Guidelines - IWGDF Guidelines. In this instance I have included the reference to the source document.

Immobilise/immobilisation: fixation of the foot and ankle joints through the application of a cast or boot to limit movement, in order to promote healing of the Charcot neuroarthropathy.

Major amputation: Resection of a segment of a limb through a bone or through a joint which is proximal to the ankle (Van Netten*et al.*, 2020b).

Non-removable device: an offloading device that cannot be removed by the patient (Bus *et al.*, 2020).

Offloading: the relief of mechanical stress (pressure) from a specific region of the foot (Bus *et al.*, 2020).

Plantar Pressure: The distribution of forces over a given plantar foot surface, mathematically defined as 'force divided over the contact area'. Often expressed as peak pressure or pressure-time integral (Van Netten *et al.*, 2020b).

Removable offloading device: an offloading device that can be removed by the patient (Bus *et al.*, 2020).

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