CADOM

A randomised feasibility study to assess the use of serial magnetic resonance imaging to reduce treatment times in Charcot neuroarthropathy in people with diabetes

Version	1.4
Date	11th June 2020
Sponsor	Norfolk and Norwich University Hospitals NHS Foundation Trust
Trial registration	ISCRTN 74101606
NRES #	[insert MREC number]

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IRAS 222668

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1 Administrative information

This document was constructed using the Norwich Clinical Trials Unit (NCTU) Protocol template Version 3. It describes the CADOM trial, sponsored by Norfolk and Norwich University Hospitals NHS Foundation Trust and co-ordinated by the CI with support from NCTU.

It provides information about procedures for entering participants into the trial, and provides sufficient detail to enable: an understanding of the background, rationale, objectives, trial population, intervention, methods, statistical analyses, ethical considerations, dissemination plans and administration of the trial; replication of key aspects of trial methods and conduct; and appraisal of the trial's scientific and ethical rigour from the time of ethics approval through to dissemination of the results. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to registered investigators in the trial. Sites entering participants for the first time should confirm they have the correct version through a member of the trial team at NCTU.

NCTU supports the commitment that its trials adhere to the SPIRIT guidelines. As such, the protocol template is based on the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2012 Statement for protocols of clinical trials [1]. The SPIRIT Statement Explanation and Elaboration document [2] can be referred to, or a member of NCTU Protocol Review Committee can be contacted for further detail about specific items.

1.1 Compliance

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) the UK Data Protection Act, and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF). Agreements that include detailed roles and responsibilities will be in place between participating sites and NCTU.

Participating sites will inform NCTU as soon as they are aware of a possible serious breach of compliance, so that NCTU can fulfil its requirement to report the breach if necessary within the timelines specified in the UK Clinical Trials Regulations (currently 7 days). For the purposes of this regulation a 'serious breach' is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects in the trial, or
- The scientific value of the trial.

1.2 Sponsor

The Norfolk and Norwich University Hospitals NHS Foundation Trust is the trial sponsor and has delegated responsibility for the overall management of the CADOM trial to the Chief Investigator and NCTU. Queries relating to sponsorship of this trial should be addressed to the CI

1.3 Structured trial summary

Primary Registry and Trial Identifying Number	ISRCTN – No to be confirmed
Date of Registration in Primary Registry	Date when trial was officially registered in the primary registry.
Secondary Identifying Numbers	IRAS: 222668 NNUH R&D Number: UEA Reference: R202374
Source of Monetary or Material Support	NHIR Clinical Doctoral Fellowship ICA-CDRF-2015-01-050
Sponsor	Norfolk and Norwich University Hospitals NHS Foundation Trust,
Contact for Public Queries	Miss Catherine Gooday c.gooday@uea.ac.uk 01603 591019 NIHR Clinical Doctoral Fellow School of Health Sciences University of East Anglia
Contact for Scientific Queries	Miss Catherine Gooday c.gooday@uea.ac.uk 01603 591019 NIHR Clinical Doctoral Fellow School of Health Sciences University of East Anglia
Short Title/Acronym	CADOM
Scientific Title	A randomised feasibility study to assess the use of serial magnetic resonance imaging to reduce treatment times in Charcot neuroarthropathy in people with diabetes
Countries of Recruitment	United Kingdom
Health Condition(s) or Problem(s) Studied	The assessment of Charcot neuroarthropathy in people with diabetes
Intervention(s)	**Intervention** Serial use of MRI at 3, 6, 9 and 12 months to identify disease resolution and thus discontinue immobilisation in addition to standard care

	Standard Care Immobilisation discontinued on the basis of clinical remission determined by skin temperature measurement (Standard Care)
Key Inclusion and Exclusion Criteria	Target population: NHS patients with type 1 or type 2 diabetes and a diagnosis of new or suspected acute Charcot neuroarthropathy **Inclusion Criteria:** • Participants who are willing and have capacity to give informed consent. • People with diabetes as diagnosed by the WHO criteria (Appendix 1) http://www.who.int/diabetes/publications/diagnosis_diabetes2011/en/ • Age 18 years or over • New or suspected new diagnosis of acute CN (no previous incidence of acute CN within the last 6 months on the same foot) treated with off-loading • Understand written and verbal instructions in English **Exclusion Criteria:** • 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 doses of oral glucocorticoids (<10mgs for ≤7 days) are eligible to participate in the study. • Participation in another intervention study on active CN • Contra-indication for MRI • Treatment for previous suspected CN on the same foot in the last 6 months • Suspected or confirmed bilateral active CN at presentation • Active osteomyelitis • Previous contralateral major amputation • Inability to have an MRI scan • Patients receiving palliative care
Study Type	A multicentre, open labelled, two arm randomised controlled feasibility trial
Date of First Enrolment	September 2017
Target Sample Size	60
Feasibility Outcomes	• The proportion of patients who meet the eligibility criteria • The number of eligible patients recruited • The number of participants in which an alternative diagnosis is made during the active phase of the trial • 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 death • Statistical parameters of the key outcome measures to inform a sample size calculation for a definitive trial (estimate of effect size) • Ability to collect quality of life and resource use data
Exploratory Analysis of	Efficacy Outcomes • Preliminary data on days with immobilisation

Clinical and Patient Reported Outcomes	• Progression of foot deformity • Number of new ulcerations on the index foot • Number of new ulcerations on the contralateral foot • Number of new infections on the index foot • Number of new infections on the contralateral foot • Number and severity of falls (Hopkins Fall Grading System)[1] • Number of minor and major amputations on the index foot at the end of the follow up phase of the study • Number of minor and major amputations on the contralateral foot at the end of the follow up phase of the study • The number of participants in each arm requiring further intervention for CN (e.g. further immobilisation) within 6 months of remission? Patient Reported Outcome Measures • Level of pain (Numeric Pain Rating Scale) • Health related quality of life (EQ-5D-5L and SF12) • Hospital Anxiety and Depression Scale (HADS) Economic Evaluation • Resource use (Collected through a patient diary)
Qualitative Study (up to 14 participants)	The qualitative study will explore: • The patient's experience of being treated for CN • The patient's views on the different approaches to monitoring Charcot neuroarthropathy used in this study

1.4 Roles and responsibilities

These membership lists are correct at the time of writing; please see terms of reference documentation in the TMF for current lists.

1.4.1 Protocol contributors

Name	Affiliation	Role
Catherine Gooday	UEA	Chief Investigator
Dr Wendy Hardeman	UEA	Supervisor
Professor Fiona Poland	UEA	Supervisor
Professor Fran Game	Derby Teaching Hospitals NHS FT.	Supervisor & PI
Professor Jim Woodburn	Glasgow Caledonian University	Supervisor
Dr Erika Sims	UEA	Senior Clinical Trial Operations Manager
Debbie Graver	UEA	Clinical Trials Project Manager
Professor Lee Shepstone	UEA	Professor of Medical Statistics
Professor Garry Barton	UEA	Professor of Health Economics
Dr Ketan Dhatariya	NNUH	Consultant Lead, Diabetic Foot Clinic
Mrs Rachel Murchison	NNUH	Lead Podiatrist

1.4.2 Role of trial sponsor and funders

Name	Affiliation	Role
Julie Dawson	NNUH	Sponsor Representative
Thom Marshall Programme Officer NIHR Trainees Coordinating Centre	NIHR	Funder Representative

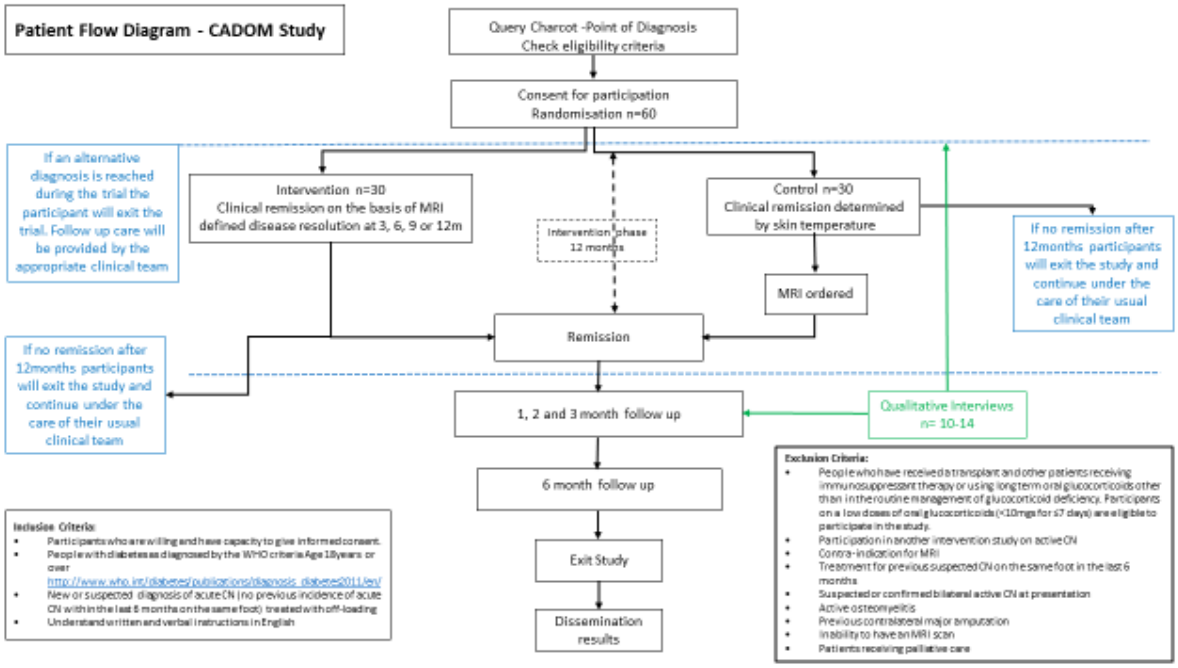
1.4.3 Trial Team

Name	Affiliation	Role and responsibilities
Catherine Gooday	UEA	Overall responsibility for day to day management of the trial. Other responsibilities will include: recruiting patients, obtaining consent, collecting quantitative and qualitative data and facilitating practice development meetings.
Dr Erika Sims	UEA	Responsible for providing operational oversight
Martin Pond	UEA	Head of Data Management
CTU Data Programmer	UEA	Programmer responsible for setting up trial database
Professor Lee Shepstone	UEA	Statistical Advice
Professor Fran Game	Derby Teaching Hospitals NHS FT.	Supervisor & PI at Derby
Dr Ketan Dhatariya	NNUH	Consultant Lead, Diabetic Foot Clinic

1.4.5 Trial Management Group

Name	Affiliation	Role and responsibilities
Catherine Gooday	UEA/NNUH	CI
Dr Wendy Hardeman	UEA	Supervisor
Professor Fiona Poland	UEA	Supervisor
Professor Fran Game	Derby Teaching Hospitals NHS FT.	Supervisor and PI
Professor Jim Woodburn	Glasgow Caledonian University	Supervisor
Dr Erika Sims	UEA	Senior Clinical Trial Operations Manager
TBC	PPRIEs	PPI
TBC	Patient Representative	PPI
TBC	NNUH	Radiologist
Dr Ketan Dhatariya	NNUH	Consultant Lead, Diabetic Foot Clinic
Professor Lee Shepstone	UEA	Statistical Advice
Martin Pond	UEA	Head of Data Management

2 Trial Diagram



3 Abbreviations

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CN	Charcot neuroarthropathy
CRF	Case Report Form
EQ5D	Euroqol 5D
EU	European Union
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
HbA1c	glycated haemoglobin
HRQoL	Health Related Quality of Life
ITT	Intention to Treat
MRI	Magnetic Resonance Imaging
NNUH	Norfolk and Norwich University Hospitals Foundation Trust
NCTU	Norwich Clinical Trials Unit
NICE	National Institute for Health and Care Excellence
PI	Principal Investigator
PPI	Patient and Public Involvement
PIS	Participant Information Sheet
PSS	Personal Social Services
QA	Quality Assurance
QALY	Quality Adjusted Life Year
QC	Quality Control
QMMP	Quality Management and Monitoring Plan
QoL	Quality of Life
RCT	Randomised Controlled Trial
R&D	Research and Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SF-12	Medical Outcomes Short-Form Health Questionnaire
SF-36	Medical Outcomes Short-Form Health Questionnaire
WPD	Working Practice Document
TCC	Total Contact Cast
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team
ToR	Terms of Reference
UK	United Kingdom
USA	United States of America
VAS	Visual Analogue Score

4 Glossary

Charcot Neuroarthropathy commonly referred to as the Charcot foot, is a condition affecting the bones, joints, and soft tissues of the foot and ankle, characterized by inflammation in the earliest phase

Major amputation is an amputation above the ankle

Minor amputations is an amputation below the ankle

5 Introduction

5.1 Background and Rationale

Worldwide the incidence of diabetes is rising. In 2013 the estimated number of people with diabetes worldwide was 382 million people[2]. The number of people with diabetes in the UK has risen from 1.4 million in 1996, to 3.6 million in 2016. By 2035 the estimated prevalence of diabetes in the UK will be 7.4%[2] which equates to 4.9 million people living with diabetes.

Longstanding poorly controlled diabetes can lead to complications. Macro-vascular disease causes strokes and heart attacks. People with diabetes are at twice the risk of developing strokes and heart attacks compared to people who do not have diabetes. Diabetes can also cause peripheral arterial disease. Microvascular disease is associated with kidney disease, eye disease, and peripheral neuropathy. Both peripheral neuropathy and peripheral arterial disease can lead to diabetes related foot complications[3].

Diabetic foot complications are common. They have also been shown to be potentially life shortening or even life-threatening[4]. They place an enormous financial burden on people with diabetes, their families, and the healthcare sector[5]. Management of the diabetic foot disease represent 0.6-0.7% of total NHS expenditure which equates to £1 in every £140[5] . People with diabetes are 23 times more likely to undergo an amputation compared to those without diabetes[6].

CN is a devastating complication of diabetes which primarily affects the foot and ankle. It is a relatively painless and progressive inflammatory destructive arthropathy in a single or in multiple joints due to underlying neuropathy[7]. The pathogenesis is multifactorial but it is often precipitated by minor trauma in the foot, inflammation secondary to foot ulceration, infection or surgery, which goes unrecognised by the patient due to loss of usual sensation[8,9]. It was first described 140 years ago however it still remains a poorly understood and frequently overlooked complication of diabetes[10]. Population based studies have estimated a life time cumulative incidence of CN of 0.4% to 1.3% in people with diabetes rising to as much as 13% in high risk patients[11].

The clinical manifestation of CN is unexplained unilateral inflammation of the foot and/or ankle with or without pain. If there has been a delay in the patient seeking medical advice deformity may already be present[12]. The aim of treatment is to stop the inflammatory process, relieve pain and maintain foot architecture[13]. The international consensus is that the foot should be immobilised in a non-removable device with weekly or fortnightly review [14]. This immobilises the foot, minimising the potential for any further damage. Immobilisation is continued until resolution/remission, this is when there are no longer clinical signs of inflammation, and x-rays are stable with signs of consolidation[15].

Late diagnosis or inadequate off-loading can lead to significant foot deformity, which is the precursor of foot ulceration. An observational study from the USA showed that delayed referral by primary care practitioners to secondary care was associated with a higher chance of CN progressing and subsequent complications developing[16]. Another observational study reported ulceration rates of 37%. 6% of patients developed ulceration during the acute phase of CN, and 31% when the CN

was chronic as a result of footwear design issues, delayed delivery of footwear or patient compliance with wearing the footwear[17]. Ulceration on a CN foot is extremely difficult to heal, the situation is further complicated when infection develops increasing the risk of amputation. Annual major amputation rates for CN vary between centres from 2.7%- 6.6% [18,19]. In many cases, people can no longer provide for themselves or their families. Only 50% of patients who have had a major amputation survive for a further two years [20]. Mortality is increased; average life expectancy is reduced by 14.4 years compared to the general UK population[21]

Studies from the UK have demonstrated a median time to remission of between 9-12 months[9,22,23]. However studies from the USA demonstrate considerably shorter immobilisation times between 3-5 months[24–27]. Results from Brazil and Germany show remission times of 3-12 months and 3-6 months respectively[28,29]. Such a prolonged period of immobilisation is a source of enormous social limitation and consequent reduction in quality of life for the patient[30]. The literature suggests the duration of immobilisation may be influenced by the anatomical location of the CN and the stage of CN when immobilisation is initiated[31].

Intervention and outcome studies, based in a few centres of excellence in CN, are limited by retrospective design, case note review methods, and small participant numbers (typically in the range of 9-55) [9,22–27]. In many studies the lack of standardisation of treatment approaches and outcomes further limits advances in the prevention and care of CN[9].

Inconsistencies exist with respect to level of activity prescribed during treatment and the use of adjunct treatments such as walking aids and supports.

As the disease process of CN progresses signs of inflammation resolve however, the clinician faces the challenge of determining when complete remission has occurred. The presence of neuropathy means that subjective symptoms are often absent and the signs of inflammation can be subtle and are sometimes difficult to grade. Pre-treatment temperature differences between the feet have been shown to vary at presentation ranging from 5.1 to 14.7 °C [24,32].

The management guidelines from the most recent systematic review are that immobilisation should be 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 – case series[15]. Clinical and radiographic diagnosis of CN is difficult [33], normal radiographs at presentation do not exclude CN[34]. Temperature differences have been shown to correlate with radiological changes[32].

There is variability in how different teams have measured the temperature difference between the feet. The most detailed protocol for measuring temperature discrepancy is described by Armstrong et al (1997). It requires a 15 minute acclimatisation period, controlled ambient air temperature, and readings collected from nine different anatomical sites on each foot[32]. This protocol is not easily achievable in a busy clinical environment, with time constraints and an inability to control room temperatures. These factors may have prevented its wide spread adoption, as many case series audits from clinical teams show that they have simplified the approach. One observational study

which did use this protocol achieved disease resolution/remission in 25 of 28 patients referred with acute CN, with a re-exacerbation rate of zero after one year follow up[28]. Other researchers have used different protocols to assess temperature, one study used eight sites on each foot, with three readings taken at each site and an average calculated[35]. Another study used the highest reading in each foot[36]. In a number of studies disease resolution/remission has been defined as a temperature difference of ≤2^{o}C on just one occasion. Other studies have required a temperature difference of ≤2^{o}C to be maintained for two[37] or more consecutive appointments[23]. These differences could extend treatment times by 2-6 weeks as patients need to attend two or more clinic appointments before the foot is judged to be in resolution/remission.

The complications of the diabetic foot, osteomyelitis and CN, have well described appearances on MRI. The use of MRI in determining a diagnosis of CN in the early stages of disease when no signs are evident on plain radiology is well recognised[38]. However serial MRI as a tool to monitor for signs of disease remission is not widely used in routine clinical practice and was not recommended in the systematic review published in 2015[15]. Recently it been suggested that the findings on MRI should be adopted as the criterion standard for establishing disease activity and remission[39]. MRI has the greatest potential to monitor the effect of treatment since the findings are a more direct reflection of the degree of tissue and bone inflammation. The literature suggests that MRI maybe superior to clinical techniques in determining the timing of termination of immobilisation. A small study demonstrated that mean healing time was significantly related to the baseline contrast medium uptake[40]. A significant correlation of intensity of bone marrow oedema in MRI and clinical measures of soft tissue oedema and pain was found in another study[41]. Another small study suggested that semi-quantitative scoring for bone marrow oedema and fracture on MRI might be useful in monitoring treatment of CN[42].

There are no existing qualitative studies that have been undertaken exploring the patients experience and perspectives on the management of CN. It is difficult to make direct comparisons from the published literature on the impact of a diagnosis of CN on the patient. There is evidence that CN has a negative effect on quality of life (QoL) [43], compared to those with uncomplicated diabetes but also in comparison to those with chronic heart failure and Parkinson's disease[44]. In one small study it was suggested that the health status in CN patients was comparable to that following minor lower extremity amputation[30]. Assessing the impact of CN on QoL is important to help establish the optimal methods of treatment and timing of intervention. There are currently no validated disease specific patient reported outcome measures (PROMs) for CN. A systematic review on measures of health related quality of life (HRQoL) could not recommend a specific tool for use in diabetes related foot disease[45]. The most widely used tool was the SF-36, although current research into diabetic foot disease favours the use of SF-12 as it is shorter yet valid alternative to the SF-36 which is considered by many researchers as too long to administer to studies with large samples such as a future definitive RCT. A recent study comparing the outcomes of SF-12 and SF-36 in patients with diabetic foot disease found substantial agreement when comparing the component score for each tool[46]. In England the National Institute for Health and Care Excellence (NICE) favours the EQ-5D. However the use of this particular measure in the treatment of CN may be limited as the actual treatment of immobilisation and rest reduces mobility one of the 5 key components of the

EQ-5D. The systematic review specifically recommended a more detailed analysis of QoL measures in CN[45].

The aim of this study is to explore the use of serial MRI in an attempt to reduce the duration of immobilisation of the foot and thereby reduce the morbidity associated with its routine management and reduce costs. The project will have two components: a feasibility study and embedded within this a qualitative study of the patient's perspective of the experience of being diagnosed with CN and undergoing treatment.

5.1.1 Explanation for choice of comparators

Participants will be randomised to one of two arms;

(a) Serial use of MRI at 3, 6, 9 and 12 months to identify disease resolution and thus discontinuation of immobilisation plus standard care **(intervention)**

(b) Immobilisation discontinued on the basis of clinical remission determined by skin temperature measurement, which triggers an MRI **(standard care)**

The complications of the diabetic foot, osteomyelitis and CN, have well described appearances on MRI. The use of MRI in determining a diagnosis of CN in the early stages of disease when no signs are evident on plain radiology is well recognised[47]. It has recently been suggested that the findings on MRI should be adopted as the criterion standard for establishing disease activity and remission in CN[38]. This is because MRI has the greatest potential to allow monitoring the effect of treatment since it shows bone marrow oedema (inflammation). The majority of clinicians use the measurement of temperature described earlier, despite the increasing availability of MRI.

The literature suggests that MRI maybe superior to clinical techniques in determining the timing of termination of immobilisation. A small study demonstrated that mean healing time was significantly related to the baseline contrast medium uptake. A significant correlation between intensity of bone marrow oedema in MRI and clinical measures of soft tissue oedema and pain was found in another study[41]. A further small study suggested that semi quantitative scoring for bone marrow oedema and fracture on MRI might be useful in monitoring treatment of CN[42].

There is a need for the use of MRI to be formally evaluated in a trial. This trial aims to explore the feasibility of using serial MRI in an attempt to reduce the duration of immobilisation of the foot.

5.2 Objectives

The primary objective of this feasibility study is to determine the feasibility of conducting a large trial to investigate the use of serial MRI scanning in the management of CN. Data will be gathered regarding clinical efficacy during this trial, though it will not be powered for these outcomes – an exploratory analysis of these clinical outcomes will be performed.

5.3 Trial Design

This study will be a 2-arm open labelled randomised controlled study. It will investigate the feasibility of using serial MRI to monitor CN. The study will last for 3 years. There will be an 18-

month recruitment period with a further 12 month intervention and 6 month follow up period (18 months)

6 Methods

6.1 Site Selection

The trial sponsor has overall responsibility for site and investigator selection and has delegated this role to the Chief Investigator.

6.1.1 Study Setting

Participants will be identified at the point of a suspected diagnosis of CN from two diabetic foot clinics based in secondary care in the UK. Initially the collaborating centres identified will be the Norfolk and Norwich University Hospitals NHS Foundation Trust and Derby Hospitals NHS Foundation Trust. As the study progresses the involvement of other centres will be considered, as necessary to meet the recruitment target.

6.1.2 Site/Investigator Eligibility Criteria

Once a site has been assessed as being suitable to participate in the trial, the trial team will provide them with a copy of this protocol.

To participate in the CADOM trial, investigators and trial sites must fulfil a set of criteria that have been agreed by the CADOM Trial Management Group (TMG) and that are defined below.

Eligibility criteria:

- A named clinician who is willing and appropriate to take Principal Investigator responsibility
- Suitably trained staff available to recruit participants, and enter data
- The centre is able to recruit suitable number of patients (20 per annum)
- Timely access to MRI scanning

Trial sites meeting eligibility criteria and that are accepted by the TMG as being suitable to recruit to the trial, will be issued with the CADOM Trial Master File (TMF) documentation to use when considering whether they have the capacity and capability to participate

6.1.2.1 Principal Investigator's (PI) Qualifications and Agreements

The investigator(s) must be willing to sign a compliance statement to comply with the trial protocol (confirming their specific roles and responsibilities relating to the trial, and that their site is willing and able to comply with the requirements of the trial). This includes confirmation of appropriate qualifications, agreement to comply with the principles of GCP, to permit monitoring and audit as necessary at the site, and to maintain documented evidence of all staff at the site who have been delegated significant trial related duties.

6.1.2.2 Resourcing at site

The investigator(s) should be able to demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period (i.e. the investigator(s) regularly treat(s) the target population). They should also have an adequate number of qualified staff and facilities available for the foreseen duration of the trial to enable them to conduct the trial properly and safely.

Sites will be expected to complete a delegation of responsibilities log and provide staff contact details.

The site should have sufficient data management resources to allow prompt data return to NCTU.

6.2 Site approval and activation

On receipt of the signed Clinical Trial Agreement, approved delegation of responsibilities log and staff contact details, written confirmation will be sent to the site PI. The CI will notify the PI in writing of the plans for site initiation. Sites will not be permitted to recruit any patients until a letter for activation has been issued. The CI will be responsible for issuing this after an NCTU green light to recruit process has been completed.

The site must conduct the trial in compliance with the protocol as agreed by the Sponsor and, by the regulatory authority(ies) (as appropriate), and which was given favourable opinion by the Research Ethics Committee (REC). The PI or delegate must document and explain any deviation from the approved protocol, and communicate this to the trial team at NCTU.

A list of activated sites may be obtained from the research fellow.

6.3 Participants

6.3.1 Eligibility Criteria

Patients with previous major amputation or active osteomyelitis have been excluded. This is because it prevents the comparison of temperature differences between the feet (standard care). This is either due to the possibility of bilateral inflammation confounding the results or the absence of a comparator limb.

6.3.1.1 Participant selection

There will be **NO EXCEPTIONS** (waivers) to eligibility requirements at the time of randomisation. Questions about eligibility criteria should be addressed PRIOR to attempting to randomise the participant.

The eligibility criteria for this trial have been carefully considered and are the standards used to ensure that only medically appropriate participants are entered. Participants not meeting the criteria should not be entered into the trial for their safety and to ensure that the trial results can be appropriately used to make future treatment decisions for other people with similar diseases or conditions. It is therefore vital that exceptions are not made to these eligibility criteria.

Participants will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below.

6.3.1.2 Participant Inclusion Criteria

- Participants who are willing and have capacity to give informed consent.
- People with diabetes as diagnosed by the WHO criteria http://www.who.int/diabetes/publications/diagnosis_diabetes2011/en/
- Age 18 years or over
- 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
- Understand written and verbal instructions in English

6.3.1.3 Participant Exclusion Criteria

- 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 doses of oral glucocorticoids (<10mgs for ≤7 days) are eligible to participate in the study.
- Participation in another intervention study on active CN
- Contra-indication for MRI
- Treatment for previous suspected CN on the same foot in the last 6 months
- Suspected or confirmed bilateral active CN at presentation
- Active osteomyelitis at randomisation
- Previous contralateral major amputation
- Inability to have an MRI scan
- Patients receiving palliative care

6.3.1.4 Eligibility Criteria for Individuals Performing the Interventions

The clinicians working in the diabetic foot clinic will be asked to become members of the research team and as such will be carrying out the trial. They will be identified on the delegation log and must have received study specific training to ensure consistency in the way the monitoring is completed.

6.3.1.5 Co-enrolment Guidance

Participants who are involved in other studies where there is a known effect or contraindication to investigation of CN will also be excluded. The CI should be contacted to discuss any concerns over eligibility prior to recruitment. If participants are already involved in trials with exposure to radiation then their eligibility for inclusion in this trial will need to be raised with the CI and discussed by the TMG.

6.3.1.6 Screening Procedures and Pre-randomisation Investigations

Written informed consent to enter and be randomised into the trial must be obtained from participants, after explanation of the aims, methods, benefits and potential hazards of the trial and **BEFORE** any trial-specific procedures are performed or any blood is taken for the trial. The only

procedures that may be performed in advance of written informed consent being obtained are those that would be performed on all patients as part of standard care.

6.4 Interventions - Arm A and Arm B

All patients will attend the secondary care clinic for fortnightly visits or as per current standard care, outlined in 6.4.5. Additional visits maybe arranged depending on clinical need. Procedures which are part of standard care will be completed according to trial specific WPD.

In this trial a standardised assessment of serial temperature measurements will be carried out. This will be completed according to trial WPD. The temperature of both feet will be recorded at intervals of 5 minutes starting at the initial removal of the off-loading device for up to 15 minutes. This will assess acclimatisation and the period of equilibration needed for stabilisation of temperature.

1) Following initial removal of the off-loading device
2) Following a 5 minute resting period
3) Following a 10 minutes resting period
4) Following a 15 minutes resting period

The sites where the temperature will be recorded reflect the current classification tool developed by Sanders and Frykberg[48];

1. distal and proximal interphalangeal joints, metatarsophalangeal, tarsometatarsal joints
2. naviculo-cunieform joints, talo-navicular joint
3. calcaneocuboid joint
4. ankle joint, subtalar joint
5. calcaneus

One X-ray will be additional to standard care this will be taken 6 months post remission. Participants who do not reach this time point within the 18 month intervention and follow-up period will not have this X-ray. This will enable the progression of foot deformity to be assessed. If a participant becomes pregnant during the study they will not have the additional X-ray and will be excluded from the analysis of the progression of foot deformity. Two members of the research team will independently evaluate the images to assess the progression of foot deformity. Inter-rater reliability will be assessed. The X-rays will be anonymised prior to evaluation to ensure the researcher is blinded to participant number and site. The anonymised scans will also be randomly sequenced to avoid bias.

To allow comparison all X-ray and MRI images will be taken as per trial WPD.

The participants will also be asked to complete the following questionnaire/assessments. These will be completed at randomisation, 3 monthly until remission (3, 6, 9 and 12 months), 1 month after remission, and at 6 months post remission;

1) Pain in the foot and/or leg measured using a numerical 0-10 visual analogue scale
2) Health related quality of life assessed by the Medical Outcomes Short-Form Health Questionnaire (SF12)

3) Psychological health status measured using the Hospital Anxiety and Depression Scale (HADs)
4) EQ-5D-5L

Patients will be issued with a patient diary at every visit and ask to complete it over the next fortnight. At each visit the old patient diary will be collected and a new one provided until the next visit.

6.4.1 Arm A (Intervention – Standard Care and Serial MRIs)

Immobilisation discontinued on the basis of MRI defined disease resolution at 3, 6, 9 or 12 months

In the intervention arm participants will receive additional MRIs at 3, 6, 9 and 12 months. Patients randomised to serial MRI will not undergo further MRI once remission has been diagnosed i.e. if remission is diagnosed at 6 months the MRI at 9 and 12 months will not occur.

6.4.2 Arm B (Control – Standard Care and one additional MRI)

Immobilisation discontinued on the basis of clinical remission determined by skin temperature measurement and MRI. In the standard care arm participants will receive one additional MRI when the temperature measurements, X-ray and/or signs and symptoms indicate to the clinical team that the foot is in remission.

A temperature difference of ≤ 2ºC which is maintained or improves on two separate consecutive occasions for a period of ≥4weeks will be the indicator to arrange the second MRI, to confirm the diagnosis of remission.

If participants in either arm of the trial have not reached remission at the end of the 12 month active phase of the study they will exit the study. Ongoing standard care will be provided by their clinical team.

6.4.3 Qualitative Study

There are no existing qualitative studies exploring participant's experiences and perspectives on the management of CN.

The purpose of this qualitative study is to understand the personal experiences of being treated for CN and the participant's experience of being involved in this trial.

The objectives are twofold;

1. To describe the impact of being treated for CN on participants

The domains of the questions will include:

- The personal experience of being treated for CN (e.g. impact on day to day functional activities, employment, leisure pursuits, ability to conduct physical activity, sense of self and self-worth)
- The impact this has had on family members and relationships

- The impact on social participation.

2. Identify ways of refining the trial protocol to improve participant's experience of being involved in any future research; increasing recruitment and retention.

The domains of the questions will include:

- The perceived accuracy of the different approaches to disease monitoring used in the study
- The perceived burden (or otherwise) of the different approaches to disease monitoring
- The participants willingness to be randomised
- The participant's ideas for improvements that could be made to the study to enhance recruitment and retention

In collaboration with PPI representatives these domains will be developed into an indicative topic guide.

As part of the consent form for the main trial participants will be asked whether they would be happy to be approached during the course of the trial to participate in an interview.

The interview will take the format of an interpretative descriptive approach.

A purposive sample of 10-14 participants across both sites will be selected. Diversity across the sample will be ensured by taking into account randomisation arm, treatment times, employment status, gender and age.

Participants approached for the Qualitative study will receive a further information sheet explaining the purpose of the interview and would be consented prior to the interview taking place.

Interviews will last approximately 30-40 minutes in a place of the participants choosing. The interviews will be audiotaped (with participants' permission) and transcribed in full.

6.4.4 Compliance and Adherence

6.4.5 Concomitant Care

All patients will receive treatment as standard for their CN regardless of randomisation into this trial. This will be recorded on the eCRf and form part of the data for this study;

6.4.6 Protocol Treatment Discontinuation

In consenting to the trial, participants are consenting to trial treatments, trial follow-up and data collection. However, an individual participant may stop treatment early or be stopped early for any of the following reasons:

- Adverse event which in the opinion of the treating clinician makes them unsuitable for continued participation in the study
- Inter-current illness that prevents further treatment

- Any change in the participant's condition that in the clinician's opinion justifies the discontinuation of treatment
- Participants who become pregnant during the trial can continue in the trial. They will be excluded from the final X-ray at 6 months post remission.
- Withdrawal of consent for treatment by the participant
- Participant who moves away from the area or decides to transfer to a different hospital for the management of their CN.

As participation in the trial is entirely voluntary, the participant may choose to discontinue trial treatment at any time without penalty or loss of benefits to which they would otherwise be entitled. Although not obliged to give a reason for discontinuing their trial treatment, a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participant's rights.

Participants who discontinue protocol treatment, for any of the above reasons, should remain in the trial for the purpose of follow up and data analysis.

6.5 Outcomes

6.5.1 Feasibility Outcomes

- The proportion of patients who meet eligibility criteria
- The number of eligible patients recruited
- The number of participants in which an alternative diagnosis of the foot disease is made during the intervention phase of the trial
- 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 death
- Statistical estimation for key outcome measures to inform a sample size calculation for a definitive trial
- Feasibility of quality of life and resource data collection

6.5.2 Exploratory Clinical Outcomes

- Days with immobilisation, measured at the end study
- Progression of foot deformity as documented by measuring radiological foot alignment angles. All x-rays will be taken in a weight bearing position with standard views as per WPD. Comparison from baseline, diagnosis of remission, and six months after remission. The angles that will be assessed are:
    - Calcaneal Inclination – the angle formed by the horizontal and a line from the base of the heel and inferior cortex of the calcaneus
    - Talar Declination –the angle between the line originating from the centre of the talus bisecting the talar neck and head and the weight bearing plantar surface from the calcaneus to the 5th metatarsal
    - Talo-first metatarsal angle – the angle between the line originating from the centre of the talus bisecting the talar neck and head, and the line through the longitudinal axis of the first metatarsal.

- Hindfoot-forefoot angle - the angle between the talocalcaneal bisector and the second metatarsal shaft
- Cuboid height (mm) - the distance from the plantar aspect of the cuboid to a horizontal line drawn from the plantar calcaneal tuberosity to the fifth metatarsal head.

Patients who have undergone previous minor amputation and/or previous orthopaedic surgical fixation of the foot altering/removing the anatomical landmarks of the foot will be excluded from this analysis due to the absence of bony landmarks.

At each study visits the following will be measured and recorded on the eCRF:

- Number of new ulcerations on the index foot
- Number of new ulcerations on the contralateral foot
- Number of new infections on the index foot
- Number of new infections on the contralateral foot
- Number and severity of falls (Hopkins Fall Grading System)[1]
- Number of minor and major amputations on the index foot at the end of the follow up phase of the study
- Number of minor and major amputations on the contralateral foot at the end of the follow up phase of the study
- The number of participants in each arm requiring further intervention for CN (e.g. further immobilisation) within 6 months of remission

6.5.3 Patient Reported Outcome Measures

The following outcomes will be collected at randomisation, and three monthly until patient is in remission. They will also be collected 1 month and 6 months post remission:

- Pain in the foot, ankle or leg measured, using the Numeric Pain Rating Scale.
- Health related quality of life assessed by the Medical Outcomes Short-Form Health Questionnaire (SF12)
- Psychological health status measured using the Hospital Anxiety and Depression Scale (HADs)
- EQ-5D-5L
- Economic Evaluation – Reported through a patient diary

6.5.4 Qualitative Study

The following will be explored in a patient interview with up to 14 participants which will take place one month after remission has been diagnosed.

- The participants' experience of being treated for CN measured
- The participants' views of the different interventions used in the study measured

6.6 Participant Timeline

			Active Phase (fortnightly visits throughout active phase of trial)								Remission	Follow Up after remission diagnosed			
Visit Number		1		6		11		18		25		FUV1	FUV2	FUV3	FUV4
month				3m		6m		9m		12m		1month	2months	3months	6months
Week **		0	2 weekly	W12	2 weeky	26	2 weekly	40	2 weekly	52					
Check In/exclusion criteria	*														
Hand out PIS	*														
Consent		*													
Randomisation		*													
Medical History		*													
Foot Surgical history		*													
Medication		*	*	*	*	*	*	*	*	*	*	*	*	*	*
Record any amputation/s		*	*	*	*	*	*	*	*	*	*	*	*	*	*
Record any infection/s		*	*	*	*	*	*	*	*	*	*	*	*	*	*
Record any ulceration/s		*	*	*	*	*	*	*	*	*	*	*	*	*	*
Record any falls		*	*	*	*	*	*	*	*	*	*	*	*	*	*
Hand out patient diary		*	*	*	*	*	*	*	*	*	*				
Collect & upload diary			*	*	*	*	*	*	*	*	*				
Foot temperatures		*	*	*	*	*	*	*	*	*	*	*	*	*	*
MRI (usual care) **		*									*				
MRI (Intervention arm) **		*		*		*		*		*					
Classification		*													
Neuropathy Assess		*													
Vascular Assess		*													
BMI		*		*		*		*		*	*				*
HbA1c (use existing if <3months)		*													
Pain VAS		*		*		*		*		*		*			*
HADS		*		*		*		*		*		*			*
SF-12		*		*		*		*		*		*			*
EQ5D		*		*		*		*		*		*			*
Study specific X-ray															*
			← Duration of active phase of treatment will be variable →												
Patient Interviews			←											→	

6.7 Patient Assessments

Written informed consent to enter the trial must be obtained from participants after explanation of the aims, methods, benefits, and potential hazards of the trial and BEFORE any trial specific procedures are performed. The only procedures that may be performed in advance of written consent being obtained are those that would be performed on all patients in the same situation as standard care.

If the clinical team consider that a patient may be eligible, the patient information sheet should be handed to the patient and they should be given adequate time to consider if they wish to consent.

The tests and investigation as per the study protocol will be in addition to all the other treatment as standard, offered to patients with CN.

6.7.1 *Randomisation Visit*

These visits will take place in secondary care clinics.

Standard Care

- The off-loading device will be provided, if one has already been provided it will be removed and the foot/leg checked for any problems
- Assessment of neuropathy using the 10g monofilament and neurotheisometer

- Palpation of foot pulses
- Measurement of ABPI
- BMI recorded
- Measurement of HbA1c if not previously tested in the last 3 month
- Skin and nail care treatment given as necessary
- Treatment of any underlying wounds, ulceration and/or infection
- The off-loading device will be re-applied

Standard Care (Plus) – these tests and investigations are part of standard care but will be carried our according to trial WPDs. This will ensure standardisation across the site.

- X-ray of the affected foot
- MRI of the affected foot
- Foot temperature assessment

Study Specific Procedures

- The following questionnaires will be administered;
    - Health related quality of life assessed by the Medical Outcomes Short-Form Health Questionnaire (SF12)
    - Psychological health status measured using the Hospital Anxiety and Depression Scale (HADs)
    - EQ-5D-5L
- Participants will also be asked to complete a VAS to assess the pain they have experienced in their foot, ankle or leg over the last two weeks
- At each visit a patient diary will be issued and participants asked to complete it recording other visits to health care professionals. It will then be collected at the next visit and another one issued.

6.7.2 The "active phase" – up to 12 months

These visits will take place in the participant's usual place of care (secondary care). Participants will attend for fortnightly visits. Standard care and study specific procedures will be carried out and recorded on the eCRF.

Study Specific Procedures

- The temperature assessment as per the WPD
- The participant diary will be collected and another issued for participants to complete over the next 2 weeks, until their next study visit.

In both arms remission will be defined as an absence of sub-chondral bone marrow oedema on MRI, as reported by a specialist musculoskeletal radiologist and/or the absence of clinical signs and symptoms of CN. The clinical team will interpret the results of the MRI report to determine remission. As per standard care at this point patients will have a foot and ankle X-ray.

Participants who develop bilateral CN during the study can continue in the trial. The trigger to arrange the MRI in the standard care arm will be based on the absence of signs and symptoms of active CN as assessed by the clinical team.

Patients randomised to A (Intervention – Serial MRI)

Patients randomised to the intervention group will have an MRI of their foot and ankle three monthly (at 3, 6, 9 and 12 months) until the CN has settled. Where possible the scan should be scheduled to coincide with study visits to minimise the number of additional hospital visits.

For participants in the intervention arm if the MRI report indicates to the clinical team that the CN is not in remission participants will continue in the active phase of the study, up to a maximum of 12 months.

Patients randomised to B (Standard Care)

Patients randomised to the standard care will undergo an MRI once the temperature difference between their feet is ≤ 2ºC on two separate occasions at least four weeks apart.

For participants in the standard care arm if the MRI report indicates to the clinical team that the CN is not in remission participants off-loading will be recommenced. Participants will continue in the follow up phase as per the trial protocol.

6.7.3 At three, six, nine and 12 months

In addition to standard care the following questionnaires will be administered to participants in both trial arms. Health related quality of life assessed by the SF-12, Psychological health status measured using the HADs and the EQ-5D-5L. Participants will also be asked to complete a VAS to assess the pain they have experienced in their foot, ankle or leg over the last 3 months. The three monthly assessments will only continue until the patient is in remission. Once the patient is in remission they will move to the follow up phase of the study.

6.7.4 Follow up phase

In both arms once remission is confirmed by the MRI patients will then enter a rehabilitation/weaning phase. They will be transferred into a less restrictive off-loading device and then finally into footwear as per standard care. Participants will continue to attend for monthly trial visits for 3 months to monitor for any sign of relapse. The final visits will be at 6 months post remission. Standard care will continue to be provided.

At each visit study specific procedures will be carried out:

- The temperature will be assessed as per the WPD
- The participant diary will be collected and another issued for participants to complete until their next study visit. (This is only for the first three follow-up visits)

In addition to standard care and study specific procedures the participant will be asked to complete the following questionnaires and additional tests/investigations:

Follow Up - Month 1: VAS, SF-12, HADS and EQ-5D-5Lwill be completed.

Follow UP Month 6: VAS, SF-12, HADS and EQ-5D-5Lcompleted. BMI will be recorded and an X-ray of the foot and/or ankle will be taken.

Relapse will be defined as a temperature difference of >2°C compared to the contralateral foot maintained for two or more occasions or further changes on imaging[15]. As per standard care the final decision as to whether the participant has relapsed will be at the discretion of the clinic team. If this occurs, then the participant will then recommence off-loading with a non-removable device. They will continue to be followed up as per the study protocol.

6.7.5 Alternate Diagnosis

The diagnosis of CN can sometimes be difficult, and a confirmed diagnosis may take several weeks to reach. As per standard care all participants will be treated for CN until it is proven otherwise. If during the course of the trial the clinical team treating the participant decide on an alternative diagnosis then the participant will exit the study. Follow-up care will be provided by the appropriate clinical team.

6.7.6 Early Stopping of Follow-up

If a participant chooses to discontinue their trial treatment, they should continue to be followed up as per current standard care. This will be as close as possible to the follow-up schedule defined in the protocol, providing they are willing. They should be encouraged and facilitated not to leave the whole trial, even though they no longer continue with the trial treatment. If, however, the participant exercises the view that they no longer wish to be followed up either, this view must be respected and the participant withdrawn entirely from the trial. NCTU should be informed of the withdrawal in writing using the appropriate CADOM trial documentation. Data already collected will be kept and included in analyses according to the intention-to-treat principle for all participants who stop follow up early.

Participants who stop trial follow-up early will not be replaced.

6.7.7 Participant Transfers

If a participant moves from the geographical area, making continued follow up at their consenting centre inappropriate, then it will not be appropriate for the patient to continue in the trial.

6.7.8 Loss to Follow-up

Contact details will be stored in the patient records and usual hospital procedures will be used to contact the patient about follow up visits. If this is without success, the patient will be recorded as lost to follow up. Number of patients where this has occurred will be monitored by the TMG. CN patients are normally seen at least fortnightly during the treatment period and monthly during the first 3 months remission period as part of routine care. Six month follow-up visit will be scheduled with participants during a three month visit. The trial has been designed in line with clinical practice to reduce the burden on participants and therefore the number of participants lost to follow-up

6.7.9 Trial Closure

The end of the trial is defined as 18 months after the final patient consents to take part in the study

6.8 Sample Size

As this is a preliminary, feasibility study a power calculation is not required. The sample size will be limited to 60 patients with 30 participants per arm. This number has been chosen based on guidelines from the NIHR and Research for Patient Benefit guidance.

6.9 Recruitment and Retention

6.9.1 Recruitment

Recruitment will be across two sites Norfolk & Norwich Hospital and Derby Hospital. It is anticipated the identified trial centres will be able to recruit 60 patients over an 18-month trial period. If recruitment is below the level anticipated, recruitment may be extended to additional sites.

Clinicians working in the diabetic foot clinics identified for the trial will be asked to identify potential patients. They will make an assessment of the patient's eligibility to join the trial and provide the patient information to prospective patients.

One of the outcomes of the feasibility trial is to assess recruitment and retention, to inform a full scale RCT if warranted.

6.9.2 Retention

Discussion with patients and other PPI representatives, prior to the development of this proposal showed a willingness to participate in the trial. They did not feel the visit schedule was overly burdensome as the majority of visits would be carried out at the same time as their routine clinical appointments. A regular six monthly newsletter will be sent out to all participants.

6.10 Assignment of Intervention

6.10.1 Allocation

Randomisation will take place after the patient has consented to participate in the trial

6.10.1.1 Sequence generation

Eligible consented participants will be randomised on a 1:1 basis to one of the two trial arms using a web based randomisation process. The randomisation scheme will be generated by the NCTU data manager and notified by email to the study team. Allocation will be stratified by centre.

6.10.1.2 Allocation concealment mechanism

The allocation is computer generated so will not be known prior to the participant being randomised. The patient will be allocated a participant number at time of consent. When confirmation of the diagnosis of CN has been entered, and all other pre-designated questions completed in the CRF, the research staff will then have access to the randomisation process for that participant. The treatment allocation will be revealed and linked to that participant number. Allocation is concealed prior to randomisation to prevent treatment bias.

6.10.2 Blinding

It is not possible to blind this study due to the nature of reporting the MRIs, whereby comparison is made with the previous images, which indicates the trial arm the participant has been randomised to.

6.11 Data Collection, Management and Analysis

6.11.1 Data Collection Methods

Each participant will be given a unique trial Participant Identification Number (PIN), this will consist of the centre number and participant number (sequential). Data will be collected at the time-points indicated in the Trial Schedule (section 6.6).

The method of data collection is direct online entry of data onto the central database, stored on servers based at NCTU. This will be carried out by members of the trial team working within each research site. Data may be entered onto paper Case Record Forms (CRFs) prior to entry onto the database (but this is not an essential step). Staff will receive training on data collection and use of the online system.

X-ray images taken at baseline, remission and six month follow up will be transferred from site to the sponsor for analysis using the NHS Image Exchange Portal (IEP) or discs. All images will be anonymised by the site prior to transfer.

Data collection, data entry and queries raised by a member of the CADOM trial team will be conducted in line with the NCTU and trial specific Data Management Standard Operating Procedure.

Identification logs, screening logs, enrolment logs and tapes of qualitative interviews will be kept at the trial site in a locked cabinet within a secured room.

Clinical trial team members will receive trial protocol training. All data will be handled in accordance with the Data Protection Act 1998.

6.11.2 Data Management

Data will be entered in the approved CADOM database by a members of the trial team at each site and protected using established NCTU procedures.

Data will be entered under the participants PIN number onto the central database stored on the servers based at NCTU. Access to the database will be via unique, individually assigned (i.e. not generic) usernames and passwords, and only accessible to members of the CADOM trial team at NCTU, and external regulators if requested. The servers are protected by firewalls and are patched and maintained according to best practice. The physical location of the servers is protected physically and environmentally in accordance with University of East Anglia's General Information Security Policy 3 (GISP3: Physical and environmental security).

The database will be developed by NCTU Data Management, in conjunction with the CADOM trial team. The database software provides a number of features to help maintain data quality, including;

maintaining an audit trail, allowing custom validations on all data, allowing users to raise data query requests, and search facilities to identify validation failure/ missing data.

After completion of the trial the database will be retained on the servers of NCTU and the sponsor servers for the X-ray images for on-going analysis of secondary outcomes.

The identification, screening and enrolment logs, linking participant identifiable data to the pseudoanonymised Participant Identification Number, will be held locally by the trial site. This will either be held in written form in a locked filing cabinet or electronically in password protected form on hospital computers. After completion of the trial the identification, screening and enrolment logs will be stored securely by the sites for 15 years

6.11.3 Non-Adherence and Non-Retention

The consent form will explain that if a participant wishes to withdraw from the study, the data acquired prior to that point will be retained, unless the patient requests otherwise. Reason for withdrawal will be recorded, if given, as will loss to follow up.

6.11.4 Statistical Methods

6.11.4.1 Statistical Analysis Plan

A full Statistical Analysis Plan (SAP) will be developed between the trial statistician and Chief Investigator and agreed with the trial's management group prior to analysis

The feasibility measures will be presented as point estimates with 95% confidence intervals. There is no intention, at this stage, for any formal comparative analyses regarding these measures, though levels of missing data will be explored with respect to certain baseline characteristics, e.g. age, measures of disease severity.

Estimates of outcome variability (e.g. the standard deviation) will be made with 95% confidence intervals to help inform future sample size calculations. Any between group efficacy analyses are exploratory only. The suggested primary efficacy outcome measure, days with immobilisation, will be analysed using a Cox regression model. Regression models with appropriate error terms (e.g. Normal or Poisson distributions) will be applied to the secondary outcomes.

6.11.4.2 Study Outcomes

Feasibility measures

- Number of eligible patients recruited, recruitment and retention levels, willingness of clinicians to participate in the study, and dropout rates.

Efficacy outcomes

- Days with immobilisation, for the intervention versus standard care will be measured
- Number of foot ulcers, infections, falls, minor and major amputations from randomisation to the end of the study
- Progression of foot deformity from randomisation – remission, and at the end of the study.
- Changes in psychological health status assessed by the Hospital Anxiety and Depression Scale (HADS) from baseline at, 3, 6, 9 and 12 months, remission and at the end of the study period.
- Changes in health related quality of life assessed by the Medical Outcomes Short-Form Health Questionnaire (SF12) from baseline at, 3, 6, 9 and 12 months, remission and at the end of the study period.
- Changes in reported pain experienced in the foot, ankle or leg as reported on a Visual Analogue Scale (VAS) from baseline at, 3, 6, 9 and 12 months, remission and at the end of the study period.

Economic Evaluation of resource use

- Collected through a patient diary

6.11.4.4 Additional Analyses

No subgroup analysis is planned and any proposed subgroup analyses will be agreed with the appropriate governance committees.

6.11.5 Analysis Population and Missing Data

The exploratory efficacy analyses will be on the 'Intention-to-treat' population, i.e. as per randomisation rather than intervention actually received. There are no plans to impute missing data, i.e. these analyses will be on a 'complete case' basis.

6.11.5.1 Economic evaluations

This 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.

Estimation of cost-effectiveness, within a health-technology assessment, is an iterative process[49]. In this trial we aim to monitor levels of resource-use and quality of life (QoL), to inform the decision as to how costs and benefits should be measured as part of a future, more definitive study.

NICE guidance [50]recommends that costs are calculated from the perspective of the NHS and personal social services (PSS). However, it is acknowledged that not all cost data can be collected, and it is suggested that the focus be on large cost drivers and those costs that are likely to differ between arms[51]. We will thereby seek to monitor levels of resource-use associated with the intervention and standard care arm of the study.

Intervention - Serial use of MRI at 3, 6, 9 and 12 months to identify disease resolution and thus discontinue immobilisation

Standard Care - Immobilisation discontinued on the basis of clinical remission determined by skin temperature measurement

Data on other primary, and secondary care visits and admission to hospital will be collected. This information will be extracted using a patient diary and secondary care notes. Time off work and levels of informal care will also be monitored. Appropriate unit costs will subsequently be attached to all items of resource-use[52].

In line with guidance [50] the EQ-5D-5L [53]will be used to measure quality of life (QALY (Quality Adjusted Life Year) scores can be calculated from the EQ-5D[54]. Participants will be asked to complete the EQ-5D-5L at 3 months, at 6 months, 9 months, 12 months, 1 month after remission, and at 6 months post remission

6.11.5.2 Health Economic Analysis Plan

The main purpose of the analysis is to inform how the above data on costs and effects would be collected within a more definitive study. Thus, we will estimate completion rates and seek to identify big cost drivers, in order to inform this decision. Additionally, though the results of this will need to be treated with caution, a preliminary cost-effectiveness analysis will also be performed. As such, we will estimate the mean incremental cost and mean QALY gain associated with the intervention compared to standard care.

6.12 Data Monitoring

6.12.1 Data Monitoring Committee

This has been assessed as a low risk trial.

6.12.2 Interim Analyses

No interim analyses is planned

6.12.3 Data Monitoring for Harm

The TMG will be provided with safety data from each treatment arm about any adverse event related to the monitoring carried out as part of the trial. The TMG will make recommendations to the Trial Sponsor on the continuation or early stoppage of the trial in the unlikely event that there are concerns over harm to participants.

6.12.3.1 Safety reporting

The intervention in the trial is increased frequency of MRI scanning which is compared with standard care of MRI scanning to confirm resolution of following temperature assessment of the affected limb. Contrast is not used for MRI scans in this study. Thus a pragmatic approach to safety reporting will be used. MRI scans are being performed in NHS trusts under routine clinical protocols. Adverse incidents resulting from MRI scans will be reported by the research site in line with the trusts clinical incident reporting policy. A copy of the incident form will be forwarded to the CI of the trial as soon as practicable. They will be forwarded to the Trial Sponsor on receipt by CI and will be reviewed by the TMG.

The following anticipated events are recorded as secondary outcomes. They will be reported as clinical events and reviewed by the TMG.

CN -RELATED SAFETY OUTCOMES

- Worsening of existing ulceration
- Infection of an ulcer
- Secondary ulceration on either limb
- Major and minor amputation
- Increase in pain

Off-loading – RELATED SAFETY OUTCOMES

- Falls as a consequence of wearing the off-loading device
- Iatrogenic skin irritation or lesions from off-loading device

6.12.3.2 Procedures to follow in the event of female participants becoming pregnant

In the event of a female participant becoming pregnant they have the option to withdraw from the trial. All participants who become pregnant will be excluded from the X-ray at 6 months post remission.

6.12.4 Quality Assurance and Control

6.12.4.1 Risk Assessment

The Quality Assurance (QA) and Quality Control (QC) considerations for the CADOM are based on the standard NCTU Quality Management Policy that includes a formal Risk Assessment, and that acknowledges the risks associated with the conduct of the trial and proposals of how to mitigate them through appropriate QA and QC processes. Risks are defined in terms of their impact on: the rights and safety of participants; project concept including trial design, reliability of results and institutional risk; project management; and other considerations.

QA is defined as all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP and applicable regulatory requirements. QC is defined as the operational techniques and activities performed within the QA system to verify that the requirements for quality of the trial related activities are fulfilled.

6.12.4.2 Central Monitoring at NCTU

NCTU staff will review Case Report Form (CRF) data for errors and missing key data points. The trial database will also be programmed to generate reports on errors and error rates. Essential trial issues, events and outputs, including defined key data points, will be detailed in the CADOM trial Data Management Plan.

6.12.4.3 On-site Monitoring

The frequency, type and intensity of routine and triggered on-site monitoring will be detailed in the CADOM Quality Management and Monitoring Plan (QMMP). The QMMP will also detail the

procedures for review and sign-off of monitoring reports. In the event of a request for a trial site inspection by any regulatory authority, NCTU must be notified as soon as possible.

6.12.4.3.1 Direct access to participant records

Participating investigators must agree to allow trial related monitoring, including audits, REC review and regulatory inspections, by providing access to source data and other trial related documentation as required. Participant consent for this must be obtained as part of the informed consent process for the trial.

6.12.4.4 Trial Oversight

Trial oversight is intended to preserve the integrity of the trial by independently verifying a variety of processes and prompting corrective action where necessary. The processes reviewed relate to participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect participants, including reporting of harms; completeness, accuracy and timeliness of data collection; and will verify adherence to applicable policies detailed in the Compliance section of the protocol. Independent trial oversight complies with the NCTU trial oversight policy.

In multi-centre trials this oversight is considered and described both overall and for each recruiting centre by exploring the trial dataset or performing site visits as described in the CADOM Management and Monitoring Plan.

6.12.4.4.1 Trial Management Team

The Trial Management Team (TMT) will be set up to assist with developing the design, co-ordination and day to day operational issues in the management of the trial, including budget management. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TMT terms of reference.

6.12.4.4.2 Trial Management Group

A Trial Management Group (TMG) will be set up to assist with developing the design, co-ordination and strategic management of the trial. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TMG terms of reference.

The TMG will review serious clinical incidents associated with MRI scanning and adverse events described in 6.13.3.1 to

- Detect any trends, such as increases in un/expected events, and take appropriate action
- Provide advice to the CI to when to seek information from investigators where required
- Provide advice to Sponsors on the risk of the trial continuing and take appropriate action where necessary

6.12.4.4.3 Independent Data Monitoring Committee

CADOM is a feasibility trial with no planned interim analyses. The intervention is low risk thus no DMC is required.

6.12.4.4.4 Trial Sponsor

The role of the sponsor is to take on responsibility for securing the arrangements to initiate, manage and finance the trial. When an institution is the trial sponsor and has delegated some and/or the totality of Sponsor's responsibilities to the NCTU, the Sponsor's form for delegated responsibilities should be completed and signed by all parties before the start of the trial.

7 Ethics and Dissemination

7.1 Research Ethics Approval

Before initiation of the trial at any clinical site, the protocol, all informed consent forms and any material to be given to the prospective participant will be submitted to the relevant REC for approval. Any subsequent amendments to these documents will be submitted for further approval. Before initiation of the trial at each additional clinical site, the same/amended documents will be submitted for local Research and Development (R&D) confirmation of capacity and capability.

The rights of the participant to refuse to participate in the trial without giving a reason must be respected. After the participant has entered the trial, the clinician remains free to give alternative treatment to that specified in the protocol, at any stage, if s/he feels it to be in the best interest of the participant. The reasons for doing so must be recorded. After randomisation the participant must remain within the trial for the purpose of follow up and data analysis according to the treatment option to which they have been allocated. However, the participant remains free to change their mind at any time about the protocol treatment and follow-up without giving a reason and without prejudicing their further treatment.

7.2 Competent Authority Approvals

This is not a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC. Therefore, a CTA is not required in the UK.

7.3 Other Approvals

The protocol will be submitted by those delegated to do so to the relevant R&D department of each participating site for confirmation of capacity and capability. A copy of the confirmation, site agreement and of the Participant Information Sheet (PIS) and consent form on local headed paper must be forwarded to the co-ordinating centre before participants are randomised to the trial.

The protocol has received formal approval and methodological, statistical, clinical and operational input from the NCTU Protocol Review Committee.

7.4 Protocol Amendments

Substantial protocol amendments (e.g. changes to eligibility criteria, outcomes, sample size calculations, analyses) will be decided by the Chief Investigator. Each site-PI will be informed of the potential changes. Such amendments will be submitted to HRA for approval. Once approved, the protocol amendments will be circulated to trial personnel and implement within the appropriate timescale dependent upon the HRA categorisation

7.5 Consent

Patients will be provided with a Patient Information Sheet (PIS) and given time to read it fully. Following a discussion with a medical qualified investigator or suitable trained and authorised delegate, any questions will be satisfactorily answered and if the participant is willing to participate, written informed consent will be obtained. During the consent process it will be made completely

and unambiguously clear that the participant is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting their treatment.

Consent will be re-sought if new information becomes available that affects the participant's consent in any way. This will be documented in a revision to the patient information sheet and the participant will be asked to sign an updated consent form. These will be approved by the ethics committee prior to their use.

A copy of the approved consent form is available from the NCTU trial team.

7.5.1 Consent to Qualitative Interviews

As part of the consent form for the main trial participants will be asked whether they would be happy to be approached to participate in an interview. The interview will explore their experiences of being treated for CN, and views about participating in the trial.

A purposive sample of 10-14 participants across both sites will be selected. Diversity across the sample will be ensured by taking into account treatment times, employment, gender and age.

Selected participants will receive a further information sheet explaining the purpose of the interview and will be consented prior to the interview taking place.

Once informed consent has been obtained, the researcher will seek the participant's permission to audio record the interview, explaining the reasons for doing so. If a participant does not wish the interview to be recorded, the researcher will make written notes of the interview. Participants will be reassured that neither the transcription nor the handwritten notes will contain any personal identifying information and that nobody will listen to the tape or read the notes of the interview, except for members of the research team and a transcriber who will be asked to sign a confidentiality agreement.

7.6 Confidentiality

Any paper copies of personal trial data will be kept at the participating site in a secure location with restricted access. Identifiable data (limited to consent forms for monitoring purposes), will be kept at the NCTU office with only authorised NCTU staff members having access. Only staff working on the trial will have password access to this information.

Confidentiality of patient's personal data is ensured by not collecting patient names on CRFs and storing the data in a pseudonymised fashion at NCTU. At trial enrolment the patient will be issued a participant identification number and this will be the primary identifier for the patient, with secondary identifiers of month and year of birth and initials.

The patient's consent form will carry their name and signature. These will be kept at the trial site, and a copy sent to NCTU for monitoring purposes. They will not be kept with any additional patient data.

7.7 Declaration of 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.

7.8 Indemnity

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.

7.9 Finance

CADOM is fully funded by an NIHR Clinical Doctoral Fellowship grant number ICA-CDRF-2015-01-050. It is not expected that any further external funding will be sought.

7.10 Archiving

The investigators agree to archive and/or arrange for secure storage of Journey trial materials and records for a minimum of 15 years after the close of the trial unless otherwise advised by the NCTU.

7.11 Access to Data

Requests for access to trial data will be considered, and approved in writing where appropriate, after formal application to the TMG and TSC. Considerations for approving access are documented in the TMG and TSC Terms of Reference. The CI and trial statistician at NCTU will have access to the full trial dataset

7.12 Ancillary and Post-trial Care

The sponsor does not intend to provide any interventions or other care to patients after trial completion.

7.13 Publication Policy

7.13.1 Trial Results

The results of the trial will be disseminated regardless of the direction of effect. Ownership of the data arising from the study resides with the trial team. The publication policy will be in line with rules of the International Committee of Medical Journal Editors. The TMG will decide on the dissemination strategy including presentations, publications and authorship with any difficulties being resolved by the TSC.

7.13.2 Authorship

For main publications, the TMG will nominate a writing group, which will consist of members of the TMG supplemented by site PIs and others who have made major contributions, who will be responsible for drafting the main manuscripts for publication. These individuals will be named on the final publication.

7.13.3 Reproducible Research

The CADOM Trial Protocol will be published and made available for public access throughout the trial period.

8 Ancillary Studies

9 Protocol Amendments

[A brief summary of areas of the protocol that have undergone major amendment along with details of the ethics and MHRA approval dates. Full details of old and new wording (tracked and cleaned versions) should be kept according to the NCTU procedures in relation with filing amendments.]

2nd August 2019

6.4.3 and 7.5.1 Changed to allow qualitative interviews to be completed during the whole course of the trial. Also updated on 6.6 Patient timeline.

11th June 2020

6.4 and 6.5.2 Changed to clarify the analysis of X-rays to monitoring the progression of foot deformity

6.11 and 6.11.2 Updated to confirm the process and storage arrangements for the electronic transfer of X-ray images to the sponsor for analysis

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11 Appendix 1

Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus. Abbreviated Report of a WHO Consultation.
(Downloaded 22nd June 2017)

hba1c_diagnosis.11
11 (downloaded 22r