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DOMINO-DFU: A study looking at optimising diagnosis of bone infection in people with a diabetic foot ulcer

Submission date
18/06/2021

Recruitment status
Recruiting

Registration date
06/07/2021

Overall study status
Ongoing

Last Edited
12/08/2025

Condition category
Nutritional, Metabolic, Endocrine

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Diabetes affects 4.5 million adults in the UK, a quarter of whom will develop a diabetic foot ulcer (foot wound; DFU). One in five people with a DFU will develop 'high-risk characteristics' of infection in the bone underlying the wound (osteomyelitis; DFO). The treatment for this is usually 6 weeks of antibiotics, but in some cases it needs an operation to remove the infected bone, often with a toe or foot amputation. There is no "gold-standard" diagnostic test and current diagnostic strategies may over-diagnose DFO in up to one-third of people, meaning an unnecessary prolonged course of antibiotics.
This study aims to answer three questions to improve the diagnosis of DFO:
1. What is the current clinical standard for the diagnosis of DFO?
2. Which of the two bone sampling methods gives the best results for the diagnosis of DFO?
3. Can we better diagnose DFO using a combination of wound appearance, blood tests and X-ray?

Who can participate?
All patients with a new DFU attending multidisciplinary (MDT) diabetic foot ulcer service clinics can take part in the full cohort.
Patients who develop high-risk characteristics of osteomyelitis may also take part in a high-risk cohort.

What does the study involve?
Patients who agree to be part of the full cohort will have information collected from their medical notes.
Patients who develop high-risk characteristics of osteomyelitis will have additional information collected from their medical notes, and be asked whether they would like to complete questionnaires (this is optional).
In the future (pending approval) we will ask patients who develop high-risk characteristics of osteomyelitis to have two bone samples taken when they are identified as having high-risk characteristics.

What are the possible benefits and risks of participating?
There are no direct benefits of taking part in the study, participation will help to improve the diagnosis of osteomyelitis in the future.
Patients will be asked to give up some of their time to take part.
In the future (pending approval), patients who have bone samples taken may experience some discomfort or bleeding when the samples are taken.

Where is the study run from?
The Leeds Clinical Trials Research Unit are coordinating the study on behalf of the University of Leeds (UK)

When is the study starting and how long is it expected to run for?
September 2021 to August 2026

Who is funding the study?
The study is funded by the National Institute for Health and Care Research (NIHR) (UK)

Who is the main contact?
Rachael Gilberts or David Russell, domino-dfu@leeds.ac.uk

Study website
https://ctru.leeds.ac.uk/domino-dfu

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

288653

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 49009

Study information

Scientific Title
Diagnosis of osteomyelitis: investigation optimisation in diabetic foot ulcers

Acronym
DOMINO-DFU

Study objectives
Current clinical care may overdiagnose diabetic foot osteomyelitis by up to 30%. The study hypothesis is that the accuracy of diagnosis may be improved by determining the optimal bone sampling technique and combining this with guideline standards of X-ray imaging and blood testing.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 30/07/2021, West London Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, United Kingdom; +44 (0)207 1048 007; westlondon.rec@hra.nhs.uk), ref: 21/PR/0407

Study design
Non-randomized; Both; Design type: Diagnosis, Other, Cohort study

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Diagnostic

Participant information sheet
https://ctru.leeds.ac.uk/domino-dfu/for-patients/

Health condition(s) or problem(s) studied
Osteomyelitis in diabetes with foot ulcer

Interventions

DOMINO-DFU is a multi-centre cohort study of new referrals with a diabetic foot ulcer (DFU) to secondary care MDT diabetic foot ulcer clinics. A sub-cohort with clinical features at high-risk of diabetic foot osteomyelitis (DFO) will be identified for more detailed follow-up in 3 phases.

Registration

All patients who provide consent will be registered into the study. Following registration participants will complete an eligibility assessment. Participants who are deemed as eligible to proceed and agree to continue in the study will proceed to registration into the full clinical cohort. Consent will include inclusion in both the full clinical cohort, and also for inclusion into the high-risk phase 1 and 3 cohorts, should the patient develop high-risk clinical features of diabetic foot osteomyelitis (DFO) at any time during the study period. The patient will also be asked to provide a preference for participation in quality of life and health resource questionnaires in the high-risk cohorts, and the preferred method of receiving these, at the outset. Participants registered in the full clinical cohort will be continuously monitored for development of high-risk characteristics for DFO and eligibility to take part in a high-risk cohort. Participants will be eligible for the high-risk phase that is recruiting at the time of identification of high-risk features. Participants who are registered but found to be ineligible after registration (and were actually ineligible at the time of registration) are not withdrawn from the study and continue with the protocol follow-up schedule. Continuation with the Phase 2 investigation strategy will be at the discretion of the treating clinician and participants may be withdrawn from the investigation strategy but continue in the study.

Baseline assessments for full clinical cohort.

Participants who are eligible to proceed and agree to continue in the study will complete a baseline assessment involving a brief clinical DFU assessment and clinical history in line with details collected from routine clinical data for the National Diabetes Foot Care Audit. Baseline assessments are completed on the same day as registration and may be completed from the clinical records if required.

Assessments

Full clinical cohort

All baseline and outcome assessments will take place either during routine clinical visits to clinics providing a multidisciplinary diabetic foot ulcer service, or through the MDT-DFU clinic records whenever possible, although a small number of patients may need to return for a research specific visit.

Participants will receive routine care by the treating clinician on the day of registration and will be seen again at the clinician's discretion. Participants will be followed up by a research practitioner/registered healthcare professional at routine clinic appointments at 12, 24 and 52 weeks after registration or until ulcer healing. Assessments at these time periods will document whether the participant is alive and has been ulcer free. A research specific telephone call or clinic visit may be necessary for those patients who have been discharged from the MDT diabetic foot service, or lost to clinical follow-up, before they have healed all ulcers on the foot of the index ulcer. Visits will be necessary to confirm the status of the index foot where there is any uncertainty with remote assessment.

Routine standard of care for diabetic foot osteomyelitis (DFO)

Routine standard of care for DFO is poorly documented in the literature. Guidelines state that in those with high-risk clinical characteristics for DFO investigations should include: a foot X-ray, which may need to be repeated after an interval of 3-4 weeks if normal initially; a bone sample

for microbiology; consider blood tests. Additional scans e.g. MRI and CT may be helpful if diagnostic uncertainty persists.
During phase 1 clinicians will continue their current standard of care for the diagnosis of osteomyelitis and we will collect this data to describe current standard practice. This is likely to include at least one X-ray and may include a bone sample and/or blood tests.
During phase 2 and 3, sites will change to a guideline standard of clinical care for patients irrespective of involvement in the DOMINO-DFU study - at least one X-ray, blood tests and a trephine needle bone sample for microbiology. During phase 2, patients will be asked to provide second level consent for both remote and through-the-wound bone samples to define the "best" sampling technique.

High-risk clinical cohorts (phases 1 and 3)
Patients participating in the full clinical cohort will be screened for development of high-risk clinical features for DFO. When these are identified the patient will enter the appropriate phase high-risk clinical cohort. Assessments will take place at baseline, 12, 24 and 52 weeks and will be taken from the clinical notes where possible in line with routine clinical appointments. If the patient is identified as high-risk whilst in clinic and has consented to completion of questionnaires, a paper copy of the baseline questionnaires will be available for completion in clinic, or an electronic version will be provided using the patients preferred method of access (text or email links). Questionnaires will be provided at 4, 8, 12, 24 and 52 weeks. Clinical record reviews will take place throughout the study follow-up to identify adverse event occurrence.

High-risk clinical cohort phase 2 – diagnostic concordance study cohort
Patients presenting with high-risk clinical features in phase 2 of the study will be approached to enter the diagnostic concordance study cohort. This is the only sub-cohort of the study where additional procedures are performed and as such a second level consent will be sought at the time of the high-risk identification for 2 bone biopsies to be taken from the high-risk bone, one through the base of the ulcer and one through normal skin away from the ulcer.
Participants will receive an additional information sheet and asked to provide same day consent. For the majority of patients who have significant nerve damage this is a painless procedure, but all patients will be offered local anaesthesia. The biopsies need to be taken on the day prior to starting urgent antibiotics and will take approximately 20 minutes to perform by a clinician trained in the procedure. All other assessments and follow-up schedules will be as per the phase 1 and 3 high-risk clinical cohorts, including optional participant questionnaires.

High-risk clinical cohort phase 1-3 additional research visits
A research specific telephone call or clinic visit may be necessary for those patients who have been discharged from the MDT diabetic foot service, or lost to clinical follow-up, if data is not available from the clinical notes. Telephone calls can be used to confirm that an ulcer remains healed and that the patient has not had any further episodes of infection in the foot. Visits will be necessary to confirm the status of the index foot where there is any uncertainty with remote assessment, in particular ulcer healing.

Intervention Type
Other

Primary outcome measure
1. Clinical diagnosis of diabetic foot osteomyelitis (DFO) over 52 weeks from baseline collected from clinical notes (full cohort)
2. Standard care for DFO over 12 months collected from clinical notes (Phase 1)
3. Antibiotic use over 12 months collected from clinical notes (Phase 1)

4. Presence and subtype of histological evidence of DFO from bone sample taken at baseline (Phase 2)
5. Presence and number of pathogens per bone sample collected at baseline (Phase 2)
6. Clinical diagnosis of DFO over 52 weeks from baseline collected from clinical notes (Phase 3)

Secondary outcome measures
1. Healing status at 12, 24, and 52 weeks measured as complete re-epithelisation without discharge, maintained for 2 weeks
2. Mortality over 52 weeks from baseline from clinical notes
3. Ulcer recurrence over 52 weeks from baseline from clinical notes
4. Recurrence of DFO over 52 weeks from baseline from clinical notes
5. Outcome of DFO at 12, 24, and 52 weeks (resolution, relapse, remission, need for surgery) from clinical notes
6. Adverse events over 52 weeks from baseline (new infection, hospitalisation, amputation) from clinical notes
7. Health-related quality of life using the Diabetic Foot Scale –Short Form (DFS-SF) and EQ-5D-5L at baseline, 4, 12, 24, and 52 weeks
8. Cost effectiveness using Health resource utilisation using questionnaires at baseline, 4, 8, 12, 24, and 52 weeks
9. Therapeutic yield for current DFO diagnostic practice (Phase 1) from clinical notes
10. Diagnostic yield for bone samples taken at baseline (Phase 2)
11. Patient-reported pain scores (none, mild, moderate, severe) for bone sampling at baseline (Phase 2)
12. Bone sample complications (bleeding, infection, fracture, Charcot) over 52 weeks from baseline (Phase 2 and 3)
13. Diagnostic and therapeutic yield of optimal diagnostic prediction model (Phase 3)

Overall study start date
01/09/2020

Completion date
30/08/2026

Eligibility

Key inclusion criteria
Full clinical cohort:
1. Aged 18 years or over
2. Diagnosed with diabetes mellitus (according to WHO criteria)
3. New active diabetic foot ulcer, as defined by a wound below the malleoli in a person with diabetes
4. Consent to participate (written/witnessed verbal informed consent)

High-risk clinical cohorts:
1. Exhibit one of the following high-risk features for DFO:
1.1. Clinical infection (IDSA criteria) + positive Probe to Bone (PTB); or
1.2. Ulcer with area ≥2 cm^2; or
1.3. Ulcer PTB or
1.4. Ulcer depth ≥3 mm; or
1.5. Dactylitis; or
1.6. “Hard-to-heal” as defined by failure to heal by >50% in the previous 4 weeks

High-risk phase 2 diagnostic concordance study cohort:
1. Provide second-level consent for both ‘through-the-ulcer’ and ‘remote’ bone biopsies

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 4,500; UK Sample Size: 4,500

Key exclusion criteria
No exclusion criteria for full clinical cohort or phase 1 and 3 high-risk cohorts (as advised by PPI members).

High-risk phase 2 diagnostic concordance study cohort:
1. Unable to undergo both ‘through-the-ulcer’ and ‘remote’ bone biopsies
2. Would not be ethically appropriate to approach the patient e.g. on end of life care

Date of first enrolment
01/08/2021

Date of final enrolment
31/08/2025

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Leeds General Infirmary
The Leeds Teaching Hospitals NHS Trust
Great George Street
Leeds
United Kingdom
LS1 3EX

Study participating centre
St George's Hospital
Blackshaw Road
London
United Kingdom
SW17 0QT

Study participating centre
Sandwell and West Birmingham Hospitals NHS Trust
City Hospital
Dudley Road
Birmingham
United Kingdom
B18 7QH

Study participating centre
University Hospital of North Durham
Dryburn Hospital
North Road
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DH1 5TW

Study participating centre
Lancashire and South Cumbria NHS Foundation Trust
Sceptre Point
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Bamber Bridge
Preston
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PR5 6AW

Study participating centre
Great Western Hospitals NHS Foundation Trust
Great Western Hospital
Marlborough Road
Swindon
United Kingdom
SN3 6BB

Study participating centre
Stepping Hill Hospital
Stockport NHS Foundation Trust
Poplar Grove
Hazel Grove
Stockport
United Kingdom
SK2 7JE

Study participating centre
James Cook University Hospital
Marton Road
Middlesbrough
United Kingdom
TS4 3BW

Study participating centre
The Royal Oldham Hospital
Northern Care Alliance NHS Foundation Trust
Rochdale Road
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OL1 2JH

Study participating centre
Derbyshire Community Health Services NHS Foundation Trust
Trust Hq, Ash Green Disability Ctr
Ashgate Road
Ashgate
Chesterfield
United Kingdom
S42 7JE

Study participating centre
North Manchester General Hospital
Delaunays Road
Crumpsall
Manchester
United Kingdom
M8 5RB

Study participating centre
Princess Royal Hospital
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Study participating centre
Barking, Havering and Redbridge University Hospitals NHS Trust
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Study participating centre
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Sponsor type
University/education

Website

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ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Government

Funder Name
NIHR Academy; Grant Codes: NIHR300633

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal.

Intention to publish date
31/12/2025

Individual participant data (IPD) sharing plan
Current IPD sharing statement as of 02/08/2022:
De-identified individual participant data datasets generated and/or analysed during the current study will be available upon request from the Clinical Trials Research Unit, University of Leeds (contact CTRU-DataAccess@leeds.ac.uk in the first instance). Data will be made available at the end of the trial, i.e. usually when all primary and secondary endpoints have been met and all key analyses are complete. Data will remain available from then on for as long as CTRU retains the data.

CTRU makes data available by a 'controlled access' approach. Data will only be released for legitimate secondary research purposes, where the Chief Investigator, Sponsor and CTRU agree that the proposed use has scientific value and will be carried out to a high standard (in terms of scientific rigour and information governance and security), and that there are resources available to satisfy the request. Data will only be released in line with participants' consent, all applicable laws relating to data protection and confidentiality, and any contractual obligations to which the CTRU is subject. No individual participant data will be released before an appropriate agreement is in place setting out the conditions of release. The agreement will govern data retention, usually stipulating that data recipients must delete their copy of the released data at the end of the planned project.

The CTRU encourages a collaborative approach to data sharing and believes it is best practice for researchers who generated datasets to be involved in subsequent uses of those datasets. Recipients of trial data for secondary research will also receive data dictionaries, copies of key trial documents and any other information required to understand and reuse the released datasets.

The conditions of release for aggregate data may differ from those applying to individual participant data. Requests for aggregate data should also be sent to the above email address to discuss and agree suitable requirements for release

Previous IPD sharing statement:
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request - domino-dfu@leeds.ac.uk

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No