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Randomised controlled trial of swab versus tissue sampling for infected diabetic foot ulcers, and comparison of culture versus molecular processing techniques

Submission date
08/01/2019

Recruitment status
No longer recruiting

Registration date
05/03/2019

Overall study status
Completed

Last Edited
20/01/2025

Condition category
Infections and Infestations

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims

When infection is suspected in a diabetic foot ulcer, the clinician will collect a specimen from the wound to send to a laboratory to identify the bacteria causing the infection. There are two ways to collect a wound sample: collecting wound fluid using a cotton swab (wound swab), or taking a small piece of wound tissue (tissue sample). Swabs are easier and this is the most common method used, but some experts and guidelines recommend tissue sampling as it is better at collecting harmful bacteria. The aim of this study is to test whether the information from tissue samples helps clinicians better match the antibiotics to the infection, and so cure the infection and help the ulcer heal more quickly.

Who can participate?

Patients at least 18 years of age with a diabetic foot ulcer in which the clinician suspects either a new or chronic mild to moderate soft tissue infection (as per IDSA guidelines) may be screened. The ulcer must have been present for less than 2 years and there must be no suspicion of osteomyelitis. Patients must be able and willing to provide informed consent for participating in the study and for foot photography and be anticipated to comply with the sampling strategies and follow-up schedule.

What does the study involve?

Participants are randomly allocated to undergo either swab or tissue sampling. Participants have two samples taken at the start of the study, one for standard culture and sensitivity (C&S) and one for molecular processing for central batching and processing using molecular techniques. Study visits align with standard clinic visits and occur at 4, 12 and 26 weeks. It is anticipated that the initial visit (including the approach and consent process) will be extended between 1-2 hours and all subsequent visits by 30-60 mins. There will also be further data extracted from the healthcare records at weeks 4, 12, 26, 39 and 52 (and 104 weeks for participants recruited within a timeline that allows this) e.g. incidence of osteomyelitis, antibiotic prescriptions and duration.

What are the possible benefits and risks of participating?
Participation in this study should show which laboratory test (wound swab or tissue sample) provides the most useful information for doctors and if a bacterial DNA test would help. This will help to improve the treatment of diabetic foot ulcers in the future and benefit other patients. The method used to obtain the tissue sample requires collecting some of the ulcer with a medical blade. A small number of people have a little bleeding and some discomfort after this. This will be managed by the clinical team. Participants are also asked to give up some of their time to take part. Wherever possible the research appointments will be at the same time as the standard clinic appointment. The first visit will be about 1 hour or so longer, and visits at 1, 3 and 6 months may be 30-60 minutes longer. Participants may also be invited to an extra visit after their wound has healed. Travel expenses will be paid if participants need to come to the clinic for any extra visits.

Where is the study run from?
CODIFI2 is being organised by the Clinical Trials Research Unit (CTRU) at the University of Leeds. It is managed by a group of researchers based at universities and hospitals around the UK and a researcher in the USA.

When is the study starting and how long is it expected to run for?
August 2018 to April 2023

Who is funding the study?
National Institute for Health Research Health Technologies Assessment Programme (UK)

Who is the main contact?
Rachael Gilberts, R.M.Gilberts@leeds.ac.uk

Contact information

Type(s)
Public

Contact name
Ms Rachael Gilberts

ORCID ID
https://orcid.org/0000-0003-3326-7900

Contact details
Head of Trial Management
Surgical Interventions, Diagnostics and Devices Division
Leeds
United Kingdom
LS2 9JT
+44 (0)113 343 1724
R.M.Gilberts@leeds.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)

Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 40662

Study information

Scientific Title
CODIFI2: Randomised controlled trial of swab versus tissue sampling for infected diabetic foot ulcers, and comparison of culture versus molecular processing techniques

Acronym
CODIFI2: COncordance in DIabetic Foot Infection 2

Study objectives
To determine the clinical effectiveness of tissue sampling compared to swab sampling, both processed using culture and susceptibility (C&S) methods, in terms of time to healing in patients with a suspected DFU infection.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 17/01/2019 by West of Scotland REC 3, Research Ethics, Clinical Research and Development, West Glasgow Ambulatory Care Hospital, Dalnair Street, Glasgow, G3 8SJ, Tel: +44 (0)141 232 1807, Email: WoSREC3@ggc.scot.nhs.uk, ref: 18/WS/0235

Study design
Randomized; Interventional; Design type: Process of Care, Management of Care

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Diabetic foot ulcer infection

Interventions
The trial is a multi-centre, Phase III, open, prospective, parallel group, randomised controlled trial (RCT) comparing two sample collection techniques (swab and tissue sampling) in clinically infected diabetic foot ulcer (DFU) patients, with blinded outcome assessment, with 3 embedded Sub-studies.

Sub-study 1: The embedded sampling processing sub-study is a cross-sectional study comparing the agreement in detection of the presence of pathogens using molecular or culture techniques.

Sub-Study 2: The value of information analysis will inform the potential value of future research about the choice of sample processing method (culture and molecular processing methods).

Sub-study 3: The embedded cover letter, is a 2-arm parallel group randomised controlled trial comparing the response rates to postal questionnaires when accompanied by either a short standard cover letter requesting response to those accompanied by an “enhanced” cover letter, designed with reference to behavioural change theory.

A total of 730 eligible and consenting participants will be randomised in a 1:1 allocation ratio to either swab or tissue sampling from randomisation to the end of the interventional period (defined as randomisation to a minimum of week 52 post randomisation for all participants or up to week 104 post randomisation where the participant has been recruited more than 104 weeks before the end of the planned recruitment period).

Participants presenting with an infected DFU will have two samples taken at baseline, one for standard culture and sensitivity (C&S) and one for molecular processing for central batching and processing using molecular techniques (sub-study 1). Study visits will align with standard clinic visits and will occur at 4, 12 and 26 weeks. It is anticipated that the initial visit (including the approach and consent process) will be extended between 1-2 hours and all subsequent visits by 30-60 mins for the participant.

There will also be further data extracted from the healthcare records at weeks 4, 12, 26, 39 and 52 (and 104 weeks for participants recruited within a timeline that allows this) e.g. incidence of osteomyelitis, antibiotic prescriptions and duration. Any additional incidence of infection during participation in the trial where a sample would normally be taken as standard of care, the method of sampling will be the randomised sampling strategy.

Assessments/data collection as follows:

Baseline Assessments- Demographics, clinical history, index wound characteristics, current therapies, antibiotics, wound area tracing & photography. Patient reported outcomes; DFS-SF, EQ-5D-3L.

Week 4 - Wound area and tracing photography of ulcer, patient completed questionnaires (DFS-SF, EQ-5D-3L, Health Resource Utilisation Questionnaire, Antibiotics Diary). Record review: Change in treatment following baseline sample, reported index ulcer healing, compliance with randomisation, antibiotic prescriptions & duration, osteomyelitis, adverse events and hospitalisations

Week 12 - Clinical check for healing, patient completed questionnaires (DFS-SF, EQ-5D-3L, Health Resource Utilisation Questionnaire, Antibiotics Diary). Record Review: Reported index ulcer healing, compliance with randomisation, antibiotic prescriptions & duration, osteomyelitis, health resource utilisation, adverse events and hospitalisations

Week 26 - Clinical check for healing, patient completed questionnaires (DFS-SF, EQ-5D-3L, Health Resource Utilisation Questionnaire, Antibiotics Diary), photography of ulcer (random sample). Record Review: Reported index ulcer healing, compliance with randomisation, antibiotic prescriptions & duration, osteomyelitis, health resource utilisation, adverse events and hospitalisations.

Week 39 - postal questionnaires (DFS-SF, EQ-5D-3L, Health Resource Utilisation Questionnaire, Antibiotics Diary). Record review: Reported index ulcer healing, compliance with randomisation, antibiotic prescriptions & duration, osteomyelitis, health resource utilisation, adverse events and hospitalisations

Week 52- postal questionnaires (DFS-SF, EQ-5D-3L, Health Resource Utilisation Questionnaire, Antibiotics Diary). Record review: Reported index ulcer healing, compliance with randomisation, antibiotic prescriptions & duration, osteomyelitis, health resource utilisation, adverse events and hospitalisations

Week 104 - postal questionnaires (DFS-SF, EQ-5D-3L, Health Resource Utilisation Questionnaire, Antibiotics Diary). Record review: Reported index ulcer healing, compliance with randomisation, antibiotic prescriptions & duration, osteomyelitis, health resource utilisation, adverse events and hospitalisations

Outcome Assessment (Healing):

Following notification to the research team by the attending clinical team or the patient, that the index DFU has healed a blinded assessment visit will be arranged for assessment and photography of the index ulcer by the blinded assessor. The visit will be undertaken within 3 days of healing being reported and may be at the participant's routine clinic assessment or at home. The photograph will undergo blinded central review by the clinical members of the Trial Management Group, who will not be aware of the participant's identity or the randomised sampling strategy.

Blinding:

As both swab and tissue sample methods are distinct, requiring different equipment and approaches, it is not possible to blind a participant or the treating clinician to sampling strategy. Therefore the outcome assessment (healing) will be conducted by an independent clinical research nurse/assessor, who will have no previous involvement with, or knowledge of the sampling methods used, and as such will be blind to the randomised sampling strategy. The blinded assessor can be a clinician, research nurse or registered healthcare professional who is suitably trained in the assessment of wound healing. To mitigate the risk of assessment bias the blinded assessor will not be informed as to the randomised group and have no access to the trial Case Report Forms (CRFs) prior to or during the blinded assessment visit. In order to minimise bias, tracings and photographs at baseline and week 4, and confirmation of the index ulcer healing assessments will be returned to the CTRU separate to the main trial CRFs.

In order to assess the risk of under-reporting of healing, a random sample of participants will have their index ulcer photographed by the local principal investigator (or delegate) at their week 26 visit. These photographs will be included with the photographs of healed ulcers and will be reviewed by the panel in a blinded fashion to ensure they are unaware of whether the photo is for confirmation of healing or an assessment of under-reporting.

All photographs will be submitted to CTRU. Photographs taken at first follow-up visit and confirmation of healing visits, and of unhealed index ulcers for randomly selected participants at baseline and week 26 visits will be centrally reviewed at the CTRU by blinded Trial Management Group clinical members.

Sub-Study 1:
The samples taken at baseline for molecular testing will be processed in batches and the results

will be compared to the results from the samples taken for routine microbiology culture to assess the extent of agreement between these two methods. In addition, the appropriateness of empirical antibiotic therapy will be judged against both swab and tissue findings by a 'virtual clinic' study. This 'virtual clinic will comprise of a central panel of clinicians from study sites, including both medical and non-medical prescribers. Results from the molecular and culture method will be presented to the panel, and members will be asked to determine if no change to therapy is required, possible change of therapy following review of participant, or a definite change of therapy required. Panel members will be blind to source of sample (tissue or swab) and samples will be unpaired and presented in a randomised order for judging purposes to eliminate bias. The data presented will be anonymised and the results are not fed back to the participant or their clinician as the virtual clinic is not conducted in real time.

Sub-Study 2:
The trialists will develop a Markov model with Value of Information Analysis (VOIA) from the perspective of the UK NHS and Personal Social Services to assess the cost-effectiveness of culture and sensitivity techniques and molecular techniques. The variables of the model include transition probabilities, costs and quality of life associated with each state. At development stage, literature reviews will identify existing decision analytic models in this area and evidence on transition probabilities, economic costs and quality of life associated with each health state, all of which will enable us to populate the proposed model. This model will then be then re-visited and updated at the end of the study when it will be populated with the trial's data. Finally, the model will be constructed and described in line with best practice in decision economic modelling

Sub-Study 3:
Immediately after randomisation to the main CODIFI2 study is complete, randomisation to the "cover letter" sub-study will occur. Participants will be allocated to receive either the standard or the "Enhanced" cover letter with their postal questionnaire (at week 39, 52 and 104). The PIS informs participants that the trialists are investigating the effect of different communication methods on data completion. They will not explicitly inform participants as to the exact nature of the intervention so that this does not change their behaviour and the response rates observed will be a true reflection of the intervention. The trialists have also consulted Patient Representatives about both the contents of the letters and our intention of running such a study, and have received no objections or concerns to date.

Intervention Type
Other

Primary outcome(s)
Time to Healing of Index Ulcer: Time from randomisation to healing of index ulcer (up to maximum follow-up of 104 weeks). Healing defined as complete epithelialisation, confirmed by a blinded assessor within 3 days after first report of healing; Timepoint(s): End of follow up.

Key secondary outcome(s))
1. Baseline sampling compliance: Binary (Compliant / Not compliant, according to whether sampling at baseline was as randomised), Timepoints: Randomisation
2. Full sampling compliance: Binary (Compliant / Not compliant, according to whether sampling at baseline and all subsequent sampling was as randomised)
Timepoints: from randomisation to 52 weeks (to 104 weeks for patients randomised in the first year) or until healing/amputation/withdrawal/death, if observed first
3. Healing status: Binary (Healed / Not healed, according to primary outcome measure

definition) at the timepoint. Timepoints: 12 weeks, 26 weeks, 39 weeks, 52 weeks. (and 104 weeks for those randomised in the first year)
4. Antibiotic prescribing over 52/104 weeks: number of days during follow-up where at least one antibiotic agent was prescribed for the foot of the index ulcer.
Timepoint: From randomisation to end of follow-up: either date of death/withdrawal/loss to follow-up, or 52 weeks (for later-randomised participants) or 104 weeks (for participants randomised in the first year)
5. Ulcer area (cm-squared) at 4 weeks post randomisation
6. Quality of life, measured using the 6 subscales of the DFS-SF questionnaire derived from the 29 questions of the full questionnaire. Timepoints: 4 weeks, 12 weeks, 26 weeks, 39 weeks, 52 weeks, 104 weeks
7. Quality of life, measured using the Utility score obtained from the 5 3-level questions of the EQ5D-3L questionnaire tool. Timepoints: 4 weeks, 12 weeks, 26 weeks, 39 weeks, 52 weeks, 104 weeks.
8. Adverse events: counts of number of adverse events relating to diabetic foot ulcer, the sampling technique and antibiotic use. Timepoints: From randomisation to 52 weeks (104 weeks for those randomised in first year)
9. Number of days in hospital: count of number of days admitted related to diabetic foot ulcer over the time at risk (i.e. up to death/withdrawal/loss to follow-up or maximum of 52/104 weeks). Timepoints: From randomisation to either death/withdrawal/loss to followup or 52 weeks (104 weeks for those randomised in the first year)
10. Number of amputations: time to amputation of the limb of the index ulcer, and categorical event/censoring, competing risk indicator. Timepoints: from randomisation to 52 weeks (104 for those randomised in the first year)
11. Osteomyelitis: binary occurrence of osteomyelitis from randomisation to timepoint. Date of osteomyelitis taken from date of diagnosis.
Timepoints: 52 weeks. (104 weeks for those randomised in the first year)
12. Death: binary occurrence of death between randomisation and timepoint. Timepoints: 52 weeks. (104 weeks for those randomised in the first year)
13. Cost-effectiveness at 52 weeks Post-Randomisation: EQ-5D-3L and Health Resource Use Questionnaire; Timepoints: 4 weeks, 12 weeks, 26 weeks, 39 weeks, 52 weeks (104 weeks for those randomised in the first year)

Substudy 1 – Agreement substudy
1. Agreement: presence or absence of key organisms, including class of pathogen, or 1 or more pathogens for a sample assessed by either C&S or molecular method. Timepoint: Randomisation
2. Appropriateness of antimicrobial therapy: decision to change or not to change a participant's current antimicrobial therapy, based on the sampling results in a virtual clinic provided with a vignette describing a pts current antimicrobial therapy, ulcer history and microbiology results. Timepoint: Randomisation

Substudy 2 – Value of Information Analysis
The value of information analysis, i.e. the expected gain from reducing the uncertainty around a decision problem by collecting additional evidence/data, will be conducted following the cost-effectiveness analysis. It will allow assessment of the value of undertaking further research to reduce any decision uncertainty.

Substudy 3 – Postal Questionnaire covering letter substudy
1. Return of questionnaire: binary questionnaire returned / not returned variable indicating if the questionnaire is returned, regardless of the state of completion. Timepoints: 39 weeks, 52 weeks, 104 weeks (for those randomised in the first year)
2. Time to return of questionnaire (exploratory): days from questionnaire mailing to return of

questionnaire, and binary returned / not returned indicator. Timepoints: week 39, week 52, week 104 (for those randomised in the first year)

Completion date
30/04/2023

Eligibility

Key inclusion criteria
1. 18 years of age or older at the time of signing the consent form
2. Diagnosis of diabetes mellitus (according to WHO criteria)
3. Presence of a DFU that is suspected as a mild or moderate soft tissue infection (as per IDSA guidelines)
4. Able and willing to provide informed consent for participation in the study
5. Consent for foot photography

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
149

Key exclusion criteria
1. Index ulcer present for > 2 years
2. Presence of suspected osteomyelitis of the index limb
3. Previous participation in the trial
4. Not expected to comply with the sampling strategies (i.e. has a preference)
5. Not expected to comply with the follow-up schedule
6. In the opinion of the local investigator the participant’s foot infection is too severe to include them in the study

Date of first enrolment
01/04/2019

Date of final enrolment
09/05/2022

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
City Hospital
Hucknall Road
Nottingham
United Kingdom
NG5 1PB

Sponsor information

Organisation
University of Leeds

ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Government

Funder Name
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC); Grant Codes: 16/163/04

Results and Publications

Individual participant data (IPD) sharing plan
Current Individual participant data (IPD) sharing statement as of 27/06/2022:

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 believe 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 Individual participant data (IPD) sharing statement:

Individual participant data (with any relevant supporting material, e.g. data dictionary, protocol, statistical analysis plan) for all trial participants (excluding any trial-specific participant opt-outs) will be made available for secondary research purposes 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 be shared according to a controlled access approach, based on the following principles:
1. The value of the proposal will be considered in terms of the strategic priorities of the CTRU, Chief Investigator and Sponsor, the scientific value of the proposed project, and the resources necessary and available to satisfy any data release request.
2. We encourage a collaborative approach to data sharing, and believe it is best practice for researchers who generated datasets to be involved in subsequent uses of those datasets.
3. The timing and nature of any data release must not adversely interfere with the integrity of the trial or research project objectives, including any associated secondary and exploratory research objectives detailed in the ethically approved original research protocol. On an individual trial or research project basis, a reasonable period of exclusivity will be agreed with the trial or research project team.
4. Any data release must be lawful, in line with participants' rights and must not compromise patient confidentiality. Where the purposes of the project can be achieved by using anonymised or aggregate data this will always be used. We will release individual patient data only in a form adjusted so that recipients of the data cannot identify individual participants by any reasonably likely means. We will also only share data when there is a binding agreement in place stating that data recipients will not attempt to re-identify any individual participants.
5. Any data release must be in line with any contractual obligations to which the CTRU is subject.
6. The research must be carried out by a bone fide researcher with the necessary skills and resources to conduct the research project.
7. The research project must have clear objectives and use appropriate research methods.
8. The research must be carried out on behalf of a reputable organisation that can demonstrate appropriate IT security standards to ensure the data is protected and to minimise the risk of unauthorised disclosure.

Data will only be shared for participants who have given consent to use of their data for secondary research.

Requests to access trial data should be made to CTRU-DataAccess@leeds.ac.uk in the first instance. Requests will be reviewed (based on the above principles) by relevant stakeholders. No data will be released before an appropriate agreement is in place setting out the conditions of release. The agreement will govern data retention requirements, which will usually stipulate that data recipients must delete their copy of the data at the end of the planned project.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		14/11/2024	15/11/2024	Yes	No
Basic results	version 1.0		26/06/2024	No	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol (other)	Diabetic foot ulcer photography study: a study within a trial to assess the reliability of two-dimensional (2D) photography for the assessment of ulcer healing in patients with diabetes-related foot ulcers-protocol paper	09/01/2025	20/01/2025	No	No
Protocol file	version 2.0	10/11/2022	13/02/2023	No	No