NHS
Health Research Authority

The **P**ersonalised **A**ntibiotic **D**uration for **C**ellulitis **(PAD-C)** Cohort Study

This protocol has regard for the HRA guidance

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ii. LIST OF ABBREVIATIONS

AMR	Antimicrobial Resistance
ANOVA	Analysis of variance
CSS	Cellulitis severity score
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
HRA	Health Research Authority
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IV	Intravenous
NHS R&D	National Health Service Research & Development
NIHR	National Institute for Health Research
PIS	Participant Information Sheet
QoL	Quality of Life
REC	Research Ethics Committee
SF-12	Medical Outcomes Study Short Form 12-Item Health Survey
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SCR	Summary Care Record
TTO	To Take Out

iii. STUDY SUMMARY

Trial Title	The Personalised Antibiotic Duration for Cellulitis (PAD-C) Cohort Study	
Internal ref. no. (or short title)	PAD-C Cohort	
Study Design	Prospective cohort study with nested technology comparison	
Trial Participants	Patients with lower limb cellulitis receiving antibiotic treatment in a hospital or another service based outside of the hospital, which will conduct ongoing follow-up regardless of location.	
Planned Sample Size	Up to 240	
Follow up duration	90 – 180 days	
Planned Study Period	3 years 3 months	
	Objectives	Outcome Measures
Primary	To understand what features of individual patients predict how likely they are to make a sustained recovery from cellulitis. This information will be used to test and refine a previously developed risk score that predicts clinical outcomes of patients with cellulitis. To investigate whether early response to antibiotic treatment (e.g. reduction in skin temperature and patient-reported symptoms) improves the predictive ability of a previously developed risk score.	Sustained recovery, defined as no initiation of new antibiotic treatment for cellulitis at the same site through to 90 days.
Secondary		Recovery at 28 days, defined as the absence of warmth and tenderness at the site, with improvement in swelling and acute colour change, that did not require new antibiotic treatment. Patient-reported time to resolution of cellulitis and symptoms of pain and swelling, using a numeric and verbal marked scale. Patient-reported time to return to work/normal activities and quality of life at 90 days (+/- 180 days on a subset of patients in whom there is >180 days available before the study ends). Patient-report on whether the cellulitis has exacerbated their other medical conditions collected at day 28. Cellulitis-related readmission and mortality within 90 days (+/- 180 days

		on a subset of patients in whom there is >180 days available before the study ends). Antibiotic usage and antibiotic-related adverse events collected daily until discharge or completion of hospital antibiotic treatment.
Nested technology comparison		
Nested technology comparison	To identify the best technological device for measuring affected skin temperature change (as an objective measure of early response) in patients with cellulitis.	Comparison of: Repeatability coefficient (repeatability of the measurements taken by the temperature measurement devices) Agreement between the methods quantified by estimating the limits of agreement. Mean time taken to measure skin temperature. Failure rates in obtaining a measurement of skin temperature.

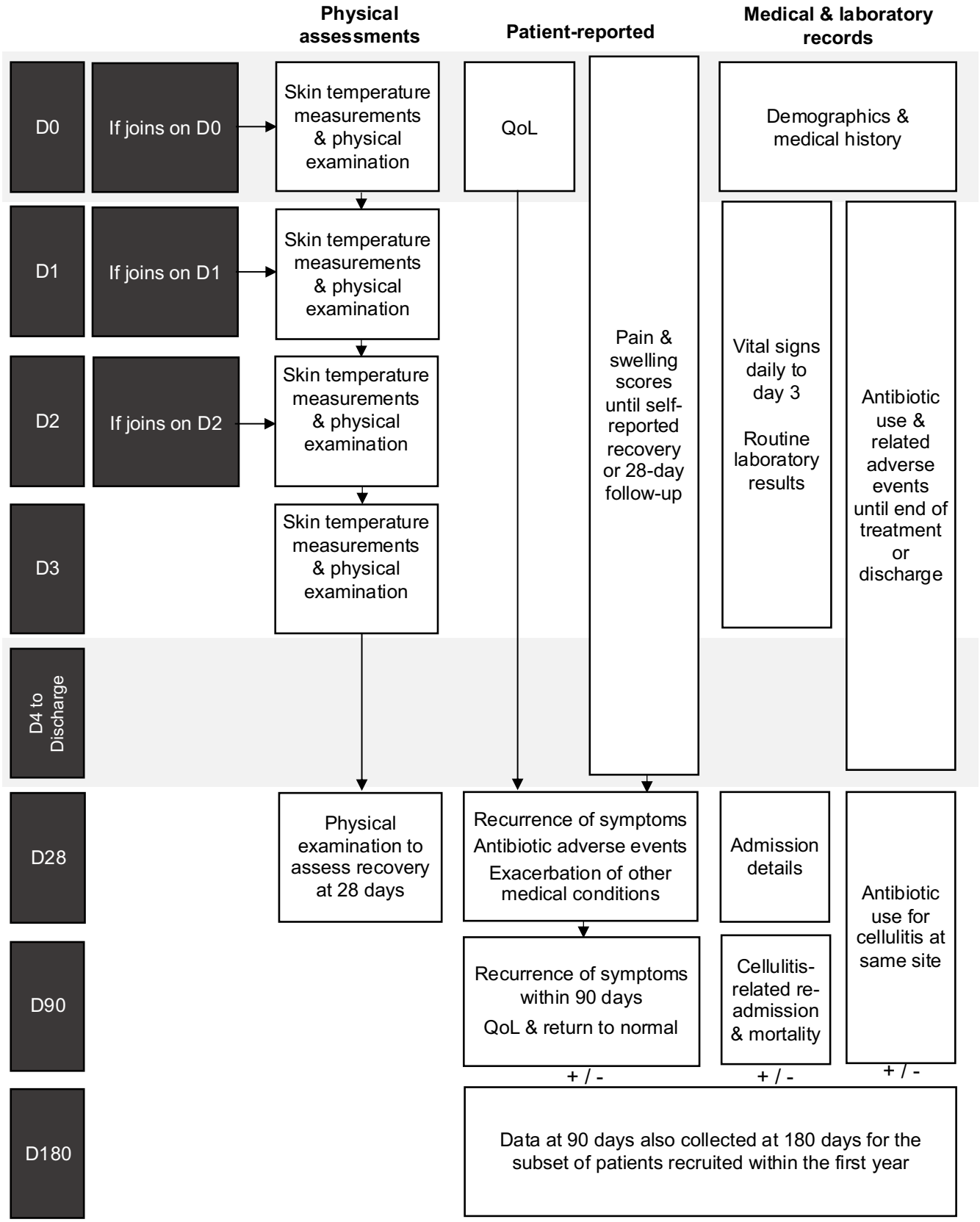
iv. FUNDING

The National Institute for Health Research is the funder of the study.

v. KEYWORDS:

Cellulitis; antibiotics; treatment duration; treatment length

vi. STUDY OVERVIEW



1 BACKGROUND & RATIONALE

Cellulitis is a bacterial infection of the skin characterised by pain, swelling and loss of mobility, usually affecting the legs.[1] Cellulitis is the commonest form of acute skin and soft tissue infection and is one of the commonest infections leading to hospitalisation.[1,2] Treatment is with either oral or intravenous (IV) antibiotics depending on severity and the first-line recommended agent in the UK is flucloxacillin.[3]

It is not known what the optimal duration of antibiotic treatment for cellulitis is. Recommendations vary from 5[1,4] to 10-14[3,5] days but, in practice, patients often receive over 14 days of therapy.[6-12] Clinical evaluation of patients is complicated by the fact that local inflammation can persist for several days even when patients are making a good response.[13] Clinicians often prolong treatment in the hope of ensuring cure, but consequently overtreat many patients.[14] Unnecessary antibiotic use accelerates the development of antimicrobial resistance (AMR), which is an urgent threat to human health.[15,16]

For several common bacterial infections there is now good evidence that shorter courses of antibiotics are as effective as longer courses for most patients.[14,17,18] The benefits of reducing antibiotic exposure include reducing the risks of antibiotic-associated adverse events and subsequent antibiotic-resistant infections.[19,20] However, there is still uncertainty about which patients with cellulitis can be safely treated with a shorter duration of antibiotic therapy.[21]

A recent systematic review and meta-analysis of trials comparing a longer to a shorter duration of antibiotics for cellulitis found no evidence of a difference in clinical response for patients followed up to one month.[22] However, the most recent trial, which compared 6 to 12 days of treatment and followed patients up to 90 days, found more recurrences in the short treatment group (24% versus 6%, P=0.045).[21] The trial failed to show non-inferiority of short-duration treatment but crucially three-quarters of patients treated for 6 days did achieve sustained cure to 90 days. This study sets out to address how to identify these patients so that they can avoid the harms of prolonged antibiotics.

Observational studies have also found no relationship between antibiotic duration and clinical recovery or recurrence in cellulitis.[22] Instead, they demonstrate that important predictors of outcomes are pre-existing patient factors (e.g. prior episodes of cellulitis[23] and other medical conditions[10,24,25]) and illness severity[26] (e.g. sepsis[10,23]). Early response to treatment at 48-72 hours is another potentially important predictor, but the evidence is sparse and inconsistent.[27,28] This study will determine whether early response to treatment predicts how well patients with cellulitis fully recover.

Current methods of measuring early response, such as assessing a reduction in the area of affected skin, are hard to evaluate objectively and consistently by visual observation alone.[29,30] Devices to directly measure skin temperature are now available and a handful of small studies have recently begun to examine their use in cellulitis.[29,31-33] Skin temperature measurement has shown promise as an objective marker of early response in cellulitis and could potentially support personalisation of treatment, but more evidence is needed. This study will also help to identify the best technological device for measuring affected skin temperature change (as a measure of early response) in patients with cellulitis.

2 OBJECTIVES AND OUTCOME MEASURES

2.1 Primary objective

To understand what features of individual patients predict how likely they are to make a sustained recovery from cellulitis. This information will be used to test and refine a previously developed risk score that predicts clinical outcomes of patients with cellulitis.

2.2 Secondary objectives

To investigate whether early response to antibiotic treatment (e.g. reduction in skin temperature and patient-reported symptoms) improves the predictive ability of a previously developed the risk score.

To identify the best technological device for measuring affected skin temperature change in patients with cellulitis.

Occurring separately but parallel to this study, a large-scale retrospective analysis of electronic health records will be undertaken to develop a risk score to predict clinical outcome in patients with cellulitis. Only limited information on early response to antibiotic treatment will be available, a limitation that the current study overcomes. The desired outcome of these two pieces of research is to develop an algorithm based on the risk score and clinical response, which prescribers can use to tailor decisions about antibiotic treatment duration for patients with cellulitis and could be tested in a future trial.

2.3 Outcome measures/endpoints

2.3.1 Primary endpoint/outcome

Sustained recovery, defined as no initiation of new antibiotic treatment for cellulitis at the same site through to 90 days.

While appropriate antibiotic therapy of cellulitis is associated with early cure rates of up to 96%, a recent trial highlighted the major risk of short antibiotic treatment to be recurrence assessed at 90 days (24% in the short-duration arm).[21] It is also the most frequently identified outcome that is important to patients and healthcare professionals,[34,35] and there is a striking lack of data around outcomes beyond 30 days in cellulitis.[22]

2.3.1 Secondary endpoints/outcomes

Cohort study
Recovery at 28 days, defined as the absence of warmth and tenderness at the site, with improvement in swelling and acute colour change, that did not require new antibiotic treatment.

Patient-reported time to resolution of cellulitis and symptoms of pain and swelling, using a numeric and verbal marked scale.

Patient-reported time to return to work / normal activities and quality of life assessed using the Medical Outcomes Study Short Form 12-Item Health Survey (SF-12). This will be collected on all patients at baseline, 90 days +/- 180 days.

Patient-report on whether the cellulitis has exacerbated their other medical conditions collected at day 28.

Cellulitis-related readmission and mortality within 90 days (from electronic healthcare records) +/- 180 days.

Antibiotic usage events (from medical notes daily until discharge or completion of hospital antibiotic treatment) and antibiotic-related adverse events (from medical notes, laboratory records and patient-reported).

Nested technology comparison

Comparison of:

- Repeatability coefficient (repeatability of the measurements taken by the temperature measurement devices).
- Agreement between the methods quantified by estimating the limits of agreement.
- Mean time taken to measure skin temperature.
- Failure rates in obtaining a measurement of skin temperature.

3 STUDY DESIGN AND SETTING

This study is an observational study with a nested technology comparison of three temperature measurement devices. The study is based at University Hospitals Sussex NHS Foundation Trust (a merger between Brighton and Sussex University Hospitals NHS Trust and Western Sussex Hospitals NHS Foundation Trust from 1st April 2021), at up to four hospital sites where participants will be recruited. The expected duration of participant involvement is under 2.5 hours in total: that includes the consent process, in-study assessments, patient-reported outcomes and follow-up appointments.

4 PARTICIPANT ELIGIBILITY CRITERIA

4.1 Inclusion criteria

Adults (age ≥18 years) will be eligible for inclusion if they are identified by their treating clinician as having lower limb cellulitis that requires IV or oral antibiotic treatment either from the hospital or another service based outside of the hospital, which will conduct ongoing follow-up regardless of

location. The clinicians' diagnosis of cellulitis (or change to an alternate diagnosis) will apply from days 0-3.

4.2 Exclusion criteria

The exclusion criteria are patients:

- who have already received 3 or more calendar days of antibiotics from the hospital for cellulitis.
- who have been treated for a previous episode of cellulitis in the preceding 28 days.
- receiving antibiotic therapy for another indication that is anticipated to continue for longer than the antibiotic treatment for cellulitis and that, in the judgement of the investigator, would impact the study assessments.
- for whom a surgical procedure to treat their cellulitis is planned (i.e. debridement of suspected necrotising skin / soft tissue infection).
- who, in the judgement of the investigator, do not have a clear diagnosis of cellulitis (to enable the exclusion of infections, such as severe/deep diabetic foot infection, which may be loosely labelled as cellulitis, but treated with different guideline antibiotic agents and durations)
- lack capacity to give informed consent to participate.
- are receiving end-of-life care.
- are already involved in a CTIMP of relevance to the treatment of their cellulitis.
- are unlikely, in the opinion of the investigator, to comply with study procedures.

5 STUDY PROCEDURES

5.1 Recruitment

5.1.1 Participant identification

Members of the clinical team responsible for the patient's care will contact the research team to notify them of potential participants. The research team will maintain close liaison with the clinical team (e.g. through handover meetings) and refer to Trust systems for managing acute admissions. Eligibility will be confirmed by an appropriately trained member of the research team.

5.2 Consent

Potential participants will be approached by a member of their clinical team and offered the Participant Information Sheet (PIS). The PIS has been designed to fit onto two sides of A4 paper along with the Informed Consent Form (ICF) and should take less than 10 minutes to read. The participant will be given sufficient time to read the PIS (a minimum of 10 minutes) before a member of the research team will approach them. They will be given the opportunity to ask any questions and discuss anything they wish to explore further. The participant does not need to decide at the time they are first approached and will be offered more time as required, up to the point at which they cease to be eligible (i.e. 2 calendar days after the day they received their first dose of antibiotics for cellulitis from the hospital).

An appropriately trained member of the research team will explain to potential participants the rationale for the study, why they have been invited and what it will involve. Participants will be informed:

- that their participation is voluntary
- that they may withdraw consent to participate at any time
- that choosing not to participate will not affect the medical care they receive
- that if they lose capacity their active participation in the research will stop but we will continue to gather information from their health records to answer the study questions
- that the data collected during the study may be looked at by individuals from the Sponsor, NHS Trust and regulatory authorities to check that the study is being carried out correctly
- that anonymous information may be used to support other research in the future and shared with the companies that make the temperature measurement devices, so they can improve the use of their device for cellulitis
- that their General Practitioner (GP) will be contacted about their participation in the study and information about antibiotics prescribed by their GP will be accessed
- that they agree to being sent a summary of the results of the study.

If they agree to join, they will sign and date the consent form. There will be an optional point regarding whether they consent to the photographs of their leg being used for future teaching and research purposes. After having received consent, the original ICF will be filed in the medical notes, a copy given to the participant, and a copy filed in the researcher site file. All members of the research team seeking informed consent will have up to date Good Clinical Practice (GCP) training. If verbal translation is needed this will occur via a hospital interpreter by phone.

After receiving informed consent potential participants will be asked if they would like to provide contact details for a family member, friend, carer or other suitable person to assist in providing their patient-reported symptoms and other information on their behalf where necessary. This is not a requirement for participation but may help to facilitate the participation of participants who are frailer.

5.3 Study assessments

The following assessments will be undertaken as soon as possible after the participant has provided their consent to participate in the study. Baseline is referred to as day 0, see Table 1 Schedule of Assessments. If patients are not recruited to the study on day 0 then data for most assessments will still be available and can be collected retrospectively for the day 0 timepoint. However, day 0 skin surface temperature measurement and physical examination of affected skin **cannot** be collected retrospectively and data will be missing for that timepoint. According to the exclusion criteria, the latest timepoint at which a patient will be eligible for recruitment is the end of day 2. Similarly, for patients recruited on a Friday, only day 0 and day 3 skin surface temperature measurement and physical examination of affected skin can be taken.

Study assessments are as follows:

Data from medical and laboratory records:

- Demographics for day 0 only
- Medical history (including previous episodes of cellulitis) for day 0 only
- Admission details (admitting and discharging specialty, intensive care stay, length of stay)
- Vital signs (e.g. heart rate, temperature) daily on days 0-3
- Antibiotic data: Total IV and oral antibiotic use as inpatient and to take out (TTO) on day 0 and daily until discharge or completion of antibiotic treatment, antibiotic use immediately prior to admission, antibiotic allergies
- Antibiotic-associated adverse events on day 0 and daily until discharge or completion of hospital antibiotic treatment
- Microbiology, haematology & biochemistry results will be extracted from laboratory records on days 0-3.

Physical assessments:

- Skin surface temperature measurement daily on days 0-3 (see 5.3.1 Skin surface temperature measurements)
- Physical examination of affected skin daily on days 0-3 (see 5.3.2 Physical examination of affected skin)

Table 1. Schedule of Assessments

Assessment	Day 0	D1 to D3 post-antibiotic treatment initiation	D1 to discharge	Day 28 (+/- 3 days) post-antibiotic treatment initiation	Day 90 +/- 180 (+/- 5 days) post-antibiotic treatment initiation †
Setting	Trust (inpatient / ambulatory care)			Trust (clinic) or virtual	Telephone-based
Informed consent	X				
Medical and laboratory records					
Demographics	X *				
Medical history	X *				
Vital signs	X *	X *			
Antibiotic use	X *	X *	X *	X *	X *†
Antibiotic-related adverse events	X *	X *	X *	X	
Routine microbiology, haematology & biochemistry	X *	X *			
Admission details				X *	
Readmission and mortality					X *†
Physical assessments					
Skin surface temperature measurement (includes time	X ^	X			

taken to measure and failed measurements)					
Physical examination of affected skin	X ^	X		X	
Patient-reported					
Symptoms of pain & swelling	X	X	X[#]	X	
Recurrence of symptoms				X	X [†]
Exacerbation of other medical conditions				X	
Quality of life	X				X [†]
Return to normal activities					X [†]

* Information available as part of routine care.

^ Day 0 data for these assessments needs to be collected at actual day 0, not retrospectively.

[#] Patient-reported symptoms will continue to be recorded daily until either they feel they have recovered or they reach their 28-day follow-up.

[†]Measured at 180 days for the subset of patients in whom there is >180 days available before the study ends.

Patient-reported:

- Symptoms - patients will report the severity of their pain and swelling due to cellulitis on a 10-point verbal and numerical scale. They will also report on whether they feel recovered from their cellulitis. Responses will be recorded from day 0 until either they feel they have recovered or reach their day 28 follow-up appointment. They will be given access to an online symptom diary, but a paper-based option will be available if the participant does not have access to a computer or smartphone. If participants have not filled in their online symptom diary for one or more days and they have not reported that they feel recovered, they can be sent a reminder to do so (text/email, phone call, depending on their preference). Participants with paper diaries will be reminded to complete their diary on alternate days from either the date of discharge or day 4 (whichever is earliest) to day 7 (+/- 1 day to account for weekends). They will then receive reminders each week until their 28-day appointment. If they are still an inpatient and cannot be contacted by other means they can be reminded in-person.
- Recurrence of symptoms of cellulitis at 28, 90 +/- 180 days.
- Whether the cellulitis has exacerbated their other medical conditions.
- Whether they experienced any antibiotic adverse events (e.g. diarrhoea or rashes).
- Quality of life - assessed using the SF-12 at day 0, 90 days +/- 180 days.
- Return to normal activities - assessed at day 90 days +/- 180 days.

5.3.1 Skin surface temperature measurements

Temperature measurement devices will be compared for measuring skin surface temperature on days 0-3. For settings outside of the hospital in which access to and storage of all three devices may not be feasible (e.g., Outpatient Parenteral Antibiotic Therapy), skin temperature measurements may be taken with device A or C only:

Device A - The Extech® IR200 non-contact infrared thermometer.[36] Non-contact infrared thermometers have previously been used to monitor clinical response in cellulitis.[29,37] This device can measure temperature over areas of the body other than the forehead and the temperature range is larger than that of other noncontact infrared thermometers.[36,38]

Device B - The FLIR One Generation 3 thermal camera for smartphones.[39] Thermal imaging cameras have previously been used in studies investigating the diagnostic utility of skin surface temperature in cellulitis (Generation One; FLIR Systems).[31,32] Benefits over non-contact infrared thermometers include easier determination of the point of the maximum temperature of the lesion.

Device C - The Thermofocus® 0800 is a non-contact infrared thermometer similar to device A that has been extensively evaluated in settings other than cellulitis. [40,41] A recent study found that the device has good reproducibility of measurements, with very small differences between the first and the second readings.[40]

Skin surface temperature measurement daily on days 0-3:

- All patients will have their skin temperature measured but at least the first 50 patients recruited will have the first measurement repeated (twice for device A and C) by the same member of research staff in order to calculate repeatability of the measurements, interim analyses of variability will be used to determine whether repeated measurements continue or not (see section 6.2.2 Technology comparison analysis for justification of sample size). The measurement will be taken at the point of maximal temperature on the affected limb and at the corresponding point on the non-affected limb to allow for calculation of temperature difference:
    - For **device A and C**, determination of the point of maximal temperature will not be exact and will involve taking up to 3-5 'test' measurements at different points of the lesion. Device A should be held approximately 5 cm and 3cm from the skin, respectively.
    - For **device B**, the point of maximal temperature on the affected lesion will be determined by localising the warmest point on the live thermal image.
- In patients in whom both legs are affected, the unaffected skin surface temperature of an arm will be taken.
- The time taken to measure and record skin surface temperature using each device will be measured (including the time taken for test measurements using device A) to provide 50 comparisons, this serves to provide an estimate of the average resource use required.
- Each time a device fails to obtain a temperature measurement will also be recorded.

5.3.1 Physical examination of affected skin

A physical examination of the affected skin will be performed on days 0-3:

- The area of the affected lesion will be measured (i.e. acute colour change, oedema, or induration, whichever is largest) with a flexible disposable tape measure, by multiplying the longest head-to-toe length of the lesion with the widest width perpendicular to that length.

- A cellulitis severity score (CSS) will also be measured. This is a descriptive symptom score, with 7 items (colour change, oedema, warmth, pain, ulceration, discharge and fluctuance) being scored on a 4-point scale (none = 0, mild = 1, moderate = 2, severe = 3), creating a total score between 0 and 21.
    - To minimise inter-observer variation for the CCS, the Chief Investigator will perform this assessment in addition to another member of the research team until assessments performed independently match consistently.

5.4 Longer-term follow-up assessments

Day 28 follow-up
All participants will be seen at 28 days (+/- 3 days) post-treatment initiation for follow-up. A physical examination of the leg affected by cellulitis will take place to assess recovery, defined as the absence of warmth and tenderness at the site, with improvement in swelling and acute colour change, that did not require new antibiotic treatment. While in-person assessments will be attempted there is a possibility, given the COVID-19 pandemic, that this appointment will need to be virtual, using NHS-approved video conferencing software. If this is the case and a participant is using a paper-based symptom diary then a stamped addressed envelope will be sent to them so that it can be returned.

Electronic health records will also be used to assess for any antibiotic use for cellulitis within secondary and primary care, for the latter this will involve accessing the participant's Summary Care Record (SCR). The SCR is accessible to the hospital-based research team through NHS smartcards, so participants' GPs will not need to be contacted for this information. In the rare situation where a patient cannot recall if they have received a new prescription of antibiotics for cellulitis and is opted out of the SCR, the general practice will be contacted. An email will be sent from an NHS email account to the Practice Manager with the participant's ICF attached asking for details on acute antibiotic prescriptions for cellulitis.

At the 28-day follow-up, participants will also be asked whether the cellulitis has exacerbated their other medical conditions, whether they experienced any antibiotic adverse events, and their daily patient-reported symptoms of pain and swelling will be reviewed.

Day 90 follow-up
The primary outcome of sustained recovery, defined as no initiation of new antibiotic treatment for cellulitis at the same site through to 90 days, will be assessed during the follow-up and through electronic health records. Electronic health records will also be accessed to assess cellulitis readmissions and mortality within 90 days. Participants will also be asked about their return to normal activities and answer the SF-12 (quality of life questionnaire) during a telephone follow-up at day 90 (+/- 5 days).

Day 180 follow-up
Participants recruited within the first year of the study will be telephoned at 180 days (+/- 5 days) and be asked about any recurrence in their symptoms, their return to normal activities and answer the SF-

12 (quality of life) questionnaire. The trust's Patient Administration System will be checked prior to calling the patient to check that they are still alive.

An attempt will be made to book follow-up appointment dates during the initial study visits. If this is not possible, participants will be contacted a maximum of six times by phone from a non-withheld number to arrange each follow-up appointment. On enrolment into the study, participants will be asked which phone number they prefer to be contacted on and whether voice messages are acceptable. If they do not respond to any of these contact attempts, they will be identified as lost to follow-up. Data that can be collected from electronic health records will be used. These follow-up appointments would not usually be undertaken as routine standard of care.

5.5 Withdrawal of participants

Participants are free to withdraw their consent for the study at any time. No further data will be collected from the time of withdrawal. However, de-identified data that have already been collected will continue to be used (and any person-identifiable data will be destroyed).

In addition, the Chief Investigator may discontinue a participant from the study at any time if they consider it necessary for ineligibility (either arising during the study or retrospectively having been overlooked at screening). The reason for withdrawal will be recorded.

5.6 Definition of End of Study

The study will end at the completion of all primary and secondary, endpoints and their corresponding analyses.

6 STATISTICS & DATA ANALYSIS

6.1 Sample size calculation

Cellulitis recurrence rates range from 11-18% within 6-12 months,[9,42,43] with the most recent trial reporting an overall 90-day recurrence rate of 14%.[21] We do not know the prevalence of the different factors that we will investigate. We, therefore, consider factors present in the final sample size at prevalence 10%, 20%, 30%... 90%. We assume that the overall event rate is 14%, and differences in this event rate between those with and without the factor of interest is 15%. We can use this 15% difference and the prevalence of the factor to work out the event rates in those with and without the factor that would give us 14% overall. We then conduct a standard two group binomial proportion sample size assuming 80% power and 2-sided alpha to detect this difference between two groups of the relevant size. We repeat this for a 20% difference in event rate between those with and without the factor of interest. See Stata program in Appendix 2.

With a 10% loss to follow-up, 220 patients provide 80% power to detect differences in recurrence rates of 15% associated with high-risk exposures prevalent at >30% and of 20% associated with high-risk exposures prevalent at 15-30%. During 2018, 741 patients were discharged from Brighton and Sussex University Hospitals NHS Trust with a primary diagnosis code of lower limb cellulitis, so over 18-months, this would require recruiting ~20% of cases.

The loss to follow-up rate for the most recent randomised controlled trial for antibiotic treatment duration in cellulitis was <5%. Therefore, the loss to follow-up for this study has been conservatively estimated as potentially being higher than this (10%). The project supervisors agree with this figure based on their research experience of conducting observational studies within the NHS.

Patients who die before experiencing a recurrence or before reaching the 90-day primary endpoint will be unable to contribute to the study data, due to competing risks between death and recurrence. As of July 2022, 5% (5/100) of study patients died (unrelated to the study) before they developed a recurrence or reached the 90-day primary endpoint, therefore a larger sample size target of up to 240 patients will be used.

6.2 Statistical analysis plan

6.2.1 Cohort primary and secondary outcome analysis

Descriptive summaries of the data, including antibiotic treatment, will be performed. Continuous variables will be reported as means with standard deviations or medians with interquartile range and categorical variables as proportions.

The primary analysis method for the primary outcome will be standard logistic multivariable regression. Backwards elimination will be used to identify the most important predictors. As there will be a large number of factors to investigate, newer variable selection techniques including elastic net/lasso will be used. Time-to-event methods will be used to assess the prognostic value of time-updated measures of response to treatment. Similar predictive models will be fitted for secondary outcomes, as suitable for the nature of the endpoint (binary, categorical, continuous, time-to-event).

The performance of a previously developed predictive model for recurrence or death in cellulitis will be assessed using receiver-operating characteristic analysis on this dataset. The net reclassification index will be used to assess whether the current model improves outcome prediction. Changes in patient-reported symptoms over time will be calculated and their temporal association with the duration of antibiotics assessed.

6.2.2 Technology comparison analysis

Repeatability of the measurements will be assessed on at least the first 50 patients recruited to estimate the within-person standard deviation to within 20% of the population value. Sample size justification:

s_w = within-subject standard deviation

n = number of subjects

m = number of observations per subject

1.96 x $s_w / \sqrt{(2n(m-1)}$

After the first 50 patients, based on the estimates of the standard deviation obtained, either repeated measurements will be continued to improve study power to identify effects or halted. Time taken for repeated measurements will also be taken into consideration. One-way analysis of variance (ANOVA) models will be fitted to the data to estimate the between-person SD, which can be used to estimate the repeatability coefficient. The repeatability of the measurement difference between the affected and unaffected limbs will also be quantified.

A methods comparison will be undertaken, using device A as the more established method as it is the only device previously used to measure clinical response in cellulitis.[29] The difference in each patient's measurements from devices A and B will be plotted against the mean of their measurements to create a Bland-Altman plot.[44] The variability of the differences will be visually inspected to indicate how well device B agrees with device A. The agreement between the methods will be quantified by estimating the limits of agreement (the range within which 95% of future differences in measurements between the two methods are expected to lie). This will be repeated comparing devices A and C.

The mean time taken to measure and record skin surface temperature will be compared using one-way ANOVA. Failure rates in obtaining a measurement of skin surface temperature will be compared using the Chi-squared test. Changes over time in the three temperature measurement technologies will also be summarised to investigate whether they improve the predictive ability of the model using the same methods as 6.2.1.

7 DATA MANAGEMENT

The plans for the data management of the study are outlined below. There is not a separate Data Management document in use for the study.

7.1 Source data

Source documents are where data are first recorded, and from which participants' data are obtained. For this study, these include but are not limited to, medical records (demographics, comorbidities), medication charts (antibiotic use), vital signs charts, laboratory records, electronic health records (cellulitis readmissions and mortality), and symptom diaries. Electronic Case Report Form (eCRF) entries will be considered source data if the eCRF is the site of the original recording (e.g. there is no other written or electronic record of data). On all study-specific documents, other than the signed consent, the participant will be referred to by their study number, not by name.

7.2 Case Report Forms

All data will be transferred into an eCRF which will be labelled using a pseudo-anonymised study number. All study data in the eCRF will be extracted from and be consistent with the relevant source documents. Data from the online symptom diary will be imported into the eCRF. If a paper-based diary is used, then a member of the research team will manually enter data into the eCRF. The eCRFs will be completed by a member of the research team in a timely manner.

7.3 Data handling and record-keeping

Participants will be identified only by a pseudo-anonymised study number only in study data. The only person-identifiable data will be held on consent forms (name) and in a log linking hospital number to pseudo-anonymised study number (necessary to link to electronic healthcare records). These will be stored in a locked room on the research site and a password-protected file on a secure NHS server, respectively. De-identified study data will be stored within secure University servers and retained for 10 years after the end of the study.

7.4 Access to Data

All documents will only be accessible by authorised members of the research team. Access will be granted to authorised representatives from the sponsor, host institution and regulatory authorities, for monitoring and/or audit of the study to ensure compliance with regulations.

8 MONITORING, AUDIT & INSPECTION

The research team will meet monthly throughout the study to discuss the conduct of the research and ensure that it is progressing as expected. Agenda items will include a review of progress against the research timetable, an update on the recruitment and follow-up of patients, and a review of the monthly expenditure reports. The Sponsor will audit and monitor the research in accordance with the risk assessment and Sponsor Standard Operating Procedures. The Trust will also monitor the research as part of their routine research monitoring of active research studies. Periodic reports will also be submitted to the National Institute for Health Research.

9 ETHICAL & REGULATORY CONSIDERATIONS

9.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

9.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice (GCP).

9.3 Research Ethics Committee (REC) approvals

Following Sponsor approval, the protocol, PIS, ICF and other relevant material (e.g. questionnaires) will be submitted to an appropriate Research Ethics Committee (REC), Health Research Authority (HRA) and host institution for written approval. The Chief Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents. All correspondence with the REC will be retained in the Investigator Site File.

9.4 Reporting

The Chief Investigator shall submit once a year throughout the study, or on request, an Annual Progress report to the REC, Sponsor, host organisation and NIHR. Recruitment data with be uploaded as part of the NIHR Clinical Research Network (CRN) Portfolio of studies. An End of Study notification and a final report will be submitted to the same parties.

9.5 Data protection and patient confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by using a pseudo-anonymised study number only in study data. The only person-identifiable data will be held on consent forms (name) and in a log linking hospital number to pseudo-anonymised study number (necessary to link to electronic healthcare records). These will be stored in a locked room on the research site and a password-protected file on a secure NHS server, respectively. All documents will only be accessible by authorised members of the research team. Access will be granted to authorised members of the sponsor, host institution and regulatory authorities if required.

9.6 Public and Patient Involvement

This study has involved patients and the public in the design of the research through the James Lind Alliance Cellulitis Priority Setting Partnership and the NIHR Community Healthcare MIC ‘appropriate antibiotic prescribing’ patient and public involvement group. Another public involvement group consisting of people with prior cellulitis have worked through the proposed outcome measures, identified additional outcomes to measure and improved upon the data collection methods for some of the outcomes. The members of this group will continue to work throughout the study on:

- Foreseeing and managing barriers to recruitment.

- Checking that patient information materials are understandable and contain relevant information.
- Understanding the results of the research from a patients' perspective.
- Ensuring that the presentation of results is clear and highlights findings that are more relevant to the public.
- Planning dissemination activities to communicate findings with the wider public.

The INVOLVE resources have been used to calculate reimbursement of their travel costs, refreshments and time (£20 per hour).

9.7 Payments

All participants will be reimbursed for travel to and from the 28-day follow-up appointment. A £20 voucher will also be provided for the inconvenience of attending as a token of recognition of giving their time and contribution to the study.

9.8 Financial and other competing interests

There are no financial or competing interests to disclose.

9.9 Indemnity

The insurance to meet the potential legal liability of the sponsor(s) for harm to participants arising from the *management* of the research will be covered by University of Sussex insurance policies. The insurance to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the *design* of the research will be covered by University of Sussex insurance policies.

NHS indemnity will apply to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research.

10 DISSEMINATION & PUBLICATION POLICY

10.1 Dissemination policy

The findings of the study will be shared with all of the study participants and public involvement group via a letter. The study findings will also be presented in-person to the public involvement group. They will help to ensure that the presentation of results is clear. They will also work with the research team on planning dissemination activities to communicate findings with the wider public. This will include publishing results through the Modernising Medical Microbiology newsletter, the Lymphoedema Support Network charity's newsletter and website, social media and other public engagement events.

The research findings will also be disseminated at the local Trusts and universities; regionally, at the CRN Kent, Surrey & Sussex Regional Infection Specialty Days; and nationally/internationally, at key infection, acute/general medicine, dermatology and diagnostic conferences. The write-ups of the research will also be submitted to peer-reviewed journals.

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines will be used for reporting the cohort study. The National Institute for Health Research will be acknowledged as the funding source in any publications.

10.2 Publication policy

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. The authors will acknowledge study funding by the National Institute for Health Research. Authorship will be determined in accordance with the International Committee of Medical Journal Editors (ICMJE) guidelines and other contributors will be acknowledged.

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12. APPENDICES

12.1 Appendix 1 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	1.1	03 JUN 2021	Elizabeth Cross	Minor change to inclusion and exclusion criteria so that days 0, 1, 2, 3 are defined by calendar days (as opposed to 24 hours periods) Performing 2 instead of 1 repeat temperature measurements for device A
2	1.2	25 JUN 2021	Elizabeth Cross	Minor changes to inclusion criteria and exclusion criteria to better define the study population Replacement of quality of life questionnaire (SF-36) with the shorter version (SF-12) Time given to read the PIS prior reduced from 30 to 10 minutes, as all participants enrolled thus far have taken less than 5 minutes Reminders for participants if they have not filled in their symptom diary for two or more days To clarify that data on antibiotic-related adverse events will be collected from the medical notes, laboratory records and patient-reported at 28 days When repeating measurements, holding the device approximately '5cm' from the skin (as opposed to the '10cm' specified) Repeated skin temperature measurements will be continued for at

				least the first 50 participants (as opposed to only the first 50) The time taken to measure and record skin surface temperature using each device will be measured to provide 50 comparisons (as opposed to for all participants) Due to numbers of available devices, storage and cost implications, skin temperature measurements in these settings may be taken with device A only in follow-up settings outside of the hospital
3	1.3	15 NOV 2021	Elizabeth Cross	Minor change to the exclusion criteria to exclude those who have been treated for a previous episode of cellulitis within the past 28 days An amendment to the PIS to explain that if they are no longer thought to have cellulitis then they would be excluded from the study A clarification on the inclusion criteria that the clinicians' diagnosis of cellulitis (or change to an alternate diagnosis) applies from days 0-3 (relates to above change)
4	1.4	17 FEB 2022	Elizabeth Cross	Reminders for participants if they have not filled in their symptom diary, to avoid missing patient-reported outcomes data. Previous reminders had focused on participants filling in the online diaries (as the research team are able to monitor remotely whether or not this has been filled in). To prevent missing patient reported data for participants filling in a paper diary a more regular system of reminders is required.
5	1.5	07 APR 2022	Elizabeth Cross	Due to delays acquiring device C (Kronikare), from the company's end due to Brexit and COVID-19, to add the Thermofocus® 0800 device to measure skin temperature change to the nested technology comparison.
6	1.6	25 JUL 2022	Elizabeth Cross	Patients who die before experiencing a recurrence or before reaching the 90-day primary endpoint will be unable to contribute to the study data, due to

				competing risks between death and recurrence. As of July 2022, 5% (5/100) of study patients died (unrelated to the study) before they developed a recurrence or reached the 90-day primary endpoint, therefore a larger sample size target of up to 240 patients will be used. Outcomes are measured at 90 days (+/- 180 days on a subset of patients recruited in the first year). This will be changed to the outcomes being measured at 90 days (+/- 180 days on a subset of patients in whom there is >180 days available before the study ends). This will allow for the more accurate measurement of longer term outcomes on a larger proportion of the study population.

12.2 Appendix 2 – Sample size Stata program

```
* difference in outcome rate of 15% - only works for prevalence of first
factor 30-70%
noi di _n _dup(80) "*" _n "15% difference in outcome" _n _dup(80) "*"
forval i=0.1(0.1)0.9 {
   * proportion in second group
   local j=1-`i'
   * overall event rate is 0.14: find power to detect 0.15 difference
between groups
   * so if x is rate in higher risk group with prevalence `i'
   *       y is rate in lower  risk group with prevalence `j'
   * x-y=0.15, then
   local y=0.14-0.15*`i'
   local x=0.15+`y'
   local nratio =`j'/`i'
   noi power twoprop `x' `y', n(200) nratio(`nratio')
}

* difference in outcome rate of 20% - only works for prevalence of first
factor 30-70%
noi di _n _dup(80) "*" _n "20% difference in outcome" _n _dup(80) "*"
forval i=0.1(0.05)0.3 {
   * proportion in second group
   local j=1-`i'
   * overall event rate is 0.14: find power to detect 0.20 difference
between groups
   * so if x is rate in higher risk group with prevalence `i'
   *       y is rate in lower  risk group with prevalence `j'
   * x-y=0.20, then
```


```
    local y=0.14-0.20*`i'
    local x=0.20+`y'
    local nratio =`j'/`i'
    * can't make this work for all values
    if `y'>0 noi power twoprop `x' `y', n(200) nratio(`nratio')
}
```