Cellulitis Optimal Antibiotic Treatment - COAT

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FUNDER

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Protocol Information

This protocol describes the COAT trial and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other non-trial participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the trial, but sites entering participants for the first time are advised to contact Southampton Clinical Trials Unit to confirm they have the most recent version.

Compliance

This trial will be conducted in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

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LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
DMEC	Data Monitoring and Ethics Committee
DMP	Data Management Plan
DLQI	Dermatology Life Quality Index
EQ-5D-5L	EuroQol Five dimension Five Levels
GCP	Good Clinical Practice
GP	General practitioners
IB	Investigator Brochure
IMP	Investigational Medicinal Product
ISF	Investigator Site File
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
NCI	National Cancer Institute
NRS	Numeric rating scale
PI	Principal Investigator
PIS	Participant Information Sheet
QALYs	Quality Adjusted Life Years
QDS	Four times a day
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SCTU	Southampton Clinical Trials Unit
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

KEYWORDS
Cellulitis, primary care, antibiotic treatment, antibiotic resistance, pain, cost consequences

TRIAL SYNOPSIS

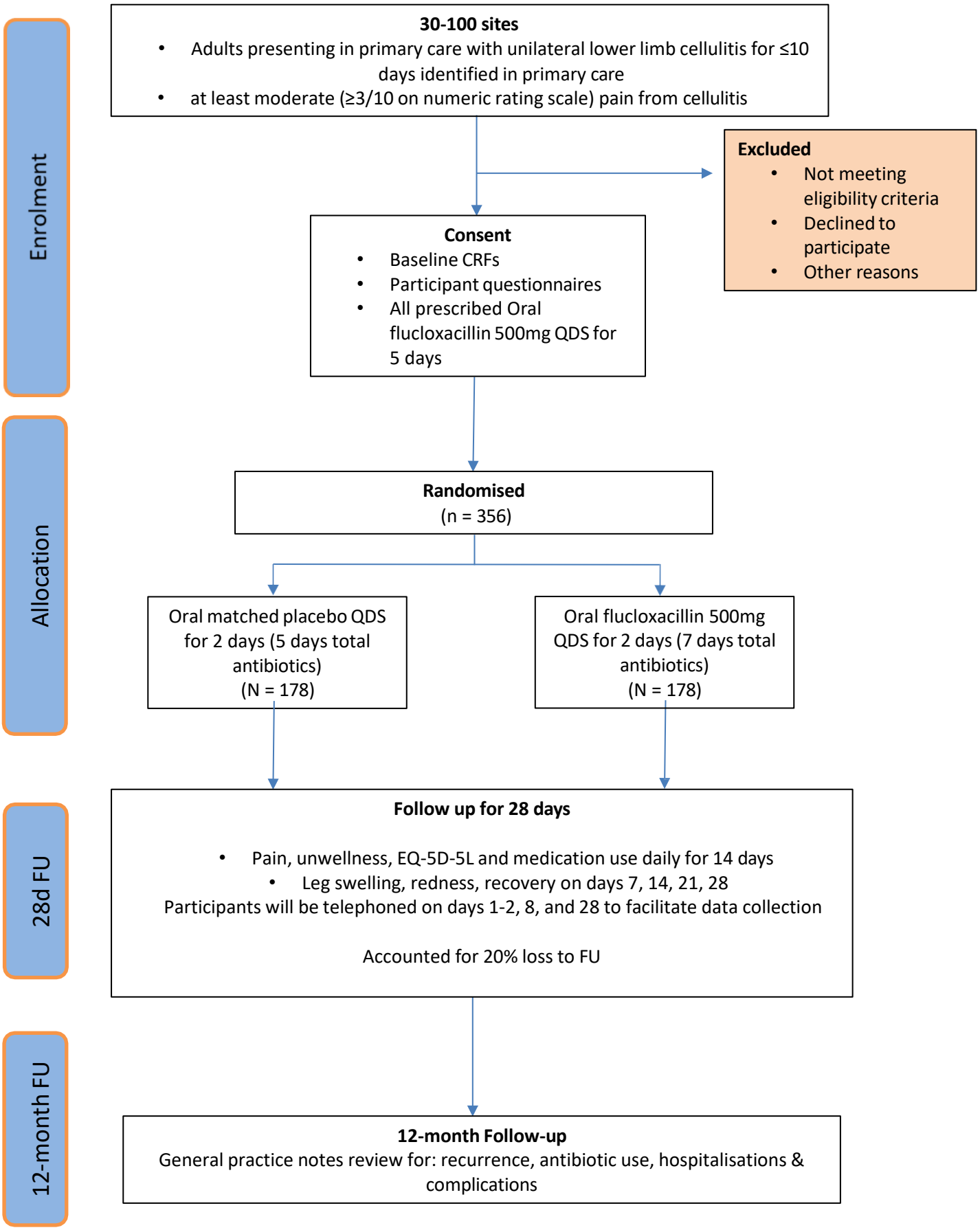
Short title:	Cellulitis Optimal Antibiotic Treatment: COAT
Full title:	A blinded, non-inferiority phase III trial of 5 versus 7 days of oral flucloxacillin in primary care patients with lower limb cellulitis

Phase:	Phase III
Population:	Adults presenting in primary care with unilateral cellulitis of the leg
Primary Objective:	Assess the effectiveness and safety of 5 days vs standard 7 days of oral flucloxacillin for lower leg cellulitis
Secondary Objective:	Evaluate the cost-consequences of a shorter course from an NHS and personal perspective.
Rationale:	Large numbers of antibiotics are prescribed each year for suspected or confirmed cellulitis in primary care. The duration of antibiotic treatment is frequently determined not by evidence from research but by custom, much of it shaped by deeply ingrained warnings against stopping too soon. However, there is increasing evidence that shorter courses are as effective as longer courses and that longer courses may increase risks for individual patients, as well as the entire healthcare system.
Trial Design:	Randomised, 2-arm, blinded, multi-centre, phase III non-inferiority trial with a 6 month internal pilot.
Sample size:	356 (178 in each arm)
Investigational Medicinal Product:	Oral flucloxacillin 500 mg
Dosage Regimen / Duration of Treatment:	**Intervention:** Flucloxacillin 500mg four times a day (QDS) for 5 days (unblinded NHS prescription) followed by *placebo* QDS for 2 days (5 days of antibiotic) **Control:** Flucloxacillin 500mg QDS for 5 days (unblinded NHS prescription) followed by *flucloxacillin 500mg* QDS (blinded) for 2 days (7 days of antibiotic)

URL for Database:	https://sctu.build.openclinica.io/
URL for randomisation:	https://prod.tenalea.net/ciru/DM/

Primary Trial Endpoints:	• Self-reported pain over days 6-14
Secondary Trial Endpoints:	• Total number of days of antibiotics taken days 0-28 • Use of any additional antibiotics (other than the initial 5-day course and IMP) as a binary outcome • Patient-reported rating of feeling unwell • EQ-5D-5L (includes mobility, self-care, usual activities, pain/discomfort, anxiety/depression) • Self-reported leg redness and swelling over time, • Time until self-reported start of improvement, • Time until self-assessed full recovery, • Hospital admissions, complications, and recurrent cellulitis episodes (up to 12 months) *Health economic endpoints including:* • Change in resource use including hospital admissions, consultations, and medication use • Number of recurrent cellulitis episodes over 12 months • Change in Health-related quality of life
Total Number of Sites:	30 - 100

TRIAL SCHEMA



SCHEDULE OF OBSERVATIONS AND PROCEDURES

Visit	Baseline	Daily	Weekly (+2 Days)	12 Months
Time (days):	**Day 0-4**	**Days 1-14**	**Days 7, 14, 21, 28**	
Informed consent	**X**			
Eligibility evaluation	**X**			
Clinical Features of Current Illness	**X**			
Symptoms	**X**[1]		**X**	
Demographics	**X**[1]			
Comorbid conditions and concomitant medications				**X**[3]
NRS[2] for pain	**X**[1]	**X**	**X**	
Wellness	**X**[1]	**X**	**X**	
EQ-5D-5L	**X**[1]	**X**	**X** Day 21 & 28	
DLQI	**X**[1]		**X** Day 28	
Initial antibiotic course and IMP	**X**	**X**		
Use of analgesics	**X**[1]	**X**		
Leg swelling and redness	**X**[1]		**X**	
Day cellulitis started to improve (self-assessed)			**X**	
Day felt recovered			**X**	
Participant travel and other out of pocket costs	**X**[1]		**X** Day 14 & 28	
Use of additional antibiotics		**X**	**X** Day 21 & 28	**X**[3]
Primary care consultations				**X**[3]
Hospital admissions				**X**[3]
Complications				**X**[3]
Recurrent episodes of cellulitis				**X**[3]

1. Collected at recruitment or by ePRO/telephone following informed consent
2. NRS= Numeric rating scale 3. Collected from participants' primary care record

NB: The Participant/legal representative is free to withdraw consent at any time without providing a reason. When withdrawn, the participant will continue to receive standard clinical care. Follow up data will continue to be collected (unless the participant/legal representative has specifically stated that they do not want this to happen).

1 INTRODUCTION

1.1 BACKGROUND

Cellulitis is a deep infection of the skin and subcutaneous tissues and most often occurs in the legs. The term erysipelas is sometimes used to describe a more superficial skin infection, but the two are caused by similar organisms and can be difficult to distinguish from each other, and therefore we will use the term cellulitis to include erysipelas. Cellulitis is a common but under researched condition (1). It occurs as a result of bacteria (most commonly *Streptococcus pyogenes* and *Staphylococcus aureus*) breaching the skin barrier and starting to spread in the dermis and subcutaneous tissues. Conditions leading to a breach of the skin barrier, such as toe web intertrigo or common dermatoses such as eczema, increase the risk of cellulitis, as do obesity, lymphoedema, and chronic venous insufficiency (2).

The incidence of cellulitis in UK primary care is about 25/1000 patient-years, (3, 4) meaning an average general practice of 10,000 patients will see about 250 cases a year. Cellulitis accounts for 3% of A&E attendance (5) and during 2014-15 cellulitis was the reason for 114,190 patients to be admitted to hospital, with a median hospital stay of 6 days (6). A study from the US found that the incidence of skin and soft-tissue infections (SSTI) increased between 2000 and 2012 and that this was associated with a tripling in the cost of treating the condition (7). We were not able to find comparable incidence trend data for the UK, but our study of flucloxacillin prescribing (used almost exclusively for skin and soft-tissue infections) in primary care found a 21% increase in prescribing between 2004 and 2013 (8) suggesting that cellulitis incidence is increasing in the UK as well.

Skin infections are the third most common reason for antibiotics to be prescribed in primary care (after respiratory and urogenital) with about one in six antibiotic prescriptions being for a skin or wound infection (9). The leg is the most common site for cellulitis, accounting for approximately half of all cases (3, 10). The incidence of lower limb cellulitis increases with age (11) and obesity (2), and therefore it is likely to continue to be a major problem given our ageing population and the rising prevalence of obesity. Cellulitis is a painful condition that is associated with inflammation and swelling of the site, and often systemic symptoms such as fever, headache, muscle aches, malaise and fatigue. Patients report feeling generally unwell and that it has a significant impact on their mobility and ability to carry out their usual activities.

As our PPI co-applicant said, “it is a lot worse than chest infections or sore throat - I'd put it alongside sciatica or back spasms, as it affects mobility as well as bringing pain and the inconvenience of not being able to wear anything that rubs the leg”. Cellulitis can be severe, progressing to the need for hospitalisation and even sepsis or death in the most severe cases. The infection can also spread through the lymphatic system and damage to the lymphatic system can result in chronic lymphoedema, which causes persistent leg swelling and an increased risk of recurrent cellulitis. Approximately a third of patients who experience cellulitis will have recurrent episodes (12) causing further distress and morbidity. Cellulitis has been shown to cause significant anxiety and impact on quality of life, as well as substantial periods of work absence (13).

Current management of cellulitis

Cellulitis is mainly managed in primary care by multidisciplinary teams, including doctors, nurses, paramedics and pharmacists. Cellulitis is most commonly caused by Streptococci species and Staphylococcus aureus which are susceptible to flucloxacillin, and in the UK this is generally the first-line antibiotic for cellulitis and other skin infections. Indeed, in primary care flucloxacillin is used almost exclusively for skin infections (8). NICE recommends oral flucloxacillin 500–1000 mg four times daily for 5-7 days as first-line treatment for most patients with cellulitis in the community (14). However, most patients are prescribed 7 days or more of antibiotics. Our study of flucloxacillin prescribing in 1.7M primary care patients found that the vast majority were prescribed 500mg QDS and 90% were given initial courses of 7 days or more (81% 7 days and 9% longer than 7 days) (8). We surveyed 24 GPs, 1 nurse practitioner and 1 other primary care prescriber in early 2021 and found that 96% reported normally prescribing a 7-day course of flucloxacillin for cellulitis. In addition,

88% of participants attending a session on skin infections at the Royal College of GPs Conference 2021 (~280 attendees) said they would prescribe a course of 7 days or longer for an afebrile 83 year-old with suspected leg cellulitis in an informal survey (personal communication with session organisers). Despite NICE guidance, clinicians are generally not prescribing 5 days, and this is not surprising given the lack of evidence supporting a 5-day course.

Evidence for duration of antibiotic course in cellulitis

NICE cite two systematic reviews in support of their advice to use a 5-7 day course of flucloxacillin as first-line treatment for cellulitis. The reviews were published in 2010 (15) and 2018 (16) and between them include evidence from 3 RCTs. One RCT compared levofloxacin (a fluoroquinolone) for 5 vs 10 days in 87 patients (17). They reported no difference between groups in clinician-assessed resolution of infection on day 14, however participants were randomised on day 5 (with those having a more complicated course being excluded) and the study was not powered as a non-inferiority study. The other two trials both compared 6 days of intravenous (with step-down to oral if indicated) tedizolid vs 10 days of linezolid (oxazolidinone antibiotics, generally reserved for resistant infections) in hospitalised patients (18, 19). These were large, multicentre non-inferiority trials that both found 6-days of once-daily intravenous tedizolid to be non-inferior to 10-days of twice-daily linezolid in terms of 'early clinical response'.

Two further systematic reviews (20, 21) have considered duration of antibiotic treatment for cellulitis, which between them identified a further five studies. One conducted a meta-analysis showing no evidence of benefit from longer courses. All the included studies were conducted in the hospital setting and included patients with severe/complicated cellulitis (and therefore different from the mild-moderate cellulitis managed in primary care), and all apart from one compared different antibiotics at different durations rather than the same antibiotic at different durations. The one study comparing different durations of the same antibiotic included 248 hospitalised patients with severe cellulitis and treated them with an initial 6 days of intravenous flucloxacillin. They were then randomised to an additional 6 days of oral flucloxacillin (total 12d course) or 6 days of oral placebo (total 6d course). The study found no difference in 'cure by day 14 with no relapse by day 28', but failed to recruit their target and therefore did not have power to conclude non-inferiority (22).

Finally, a systematic review of evidence for different antibiotic regimens for lower limb cellulitis, led by two of our team, found no evidence that longer courses or higher doses were associated with improved outcomes and concluded that lower limb cellulitis may be overtreated and that there was a 'profound gap in the literature' and 'a need for trials comparing lower intensity antibiotic regimens' (23). In summary, the evidence to date suggests that shorter courses are non-inferior to longer courses. However, only two trials have compared different durations of the same antibiotic, none of the trials have been based in primary care, and none of the trials have compared different durations of oral flucloxacillin (or similar penicillinase-resistant penicillin).

1.2 RATIONALE AND RISK BENEFITS FOR CURRENT TRIAL

Our research demonstrated that flucloxacillin use in primary care increased by 21% between 2004 and 2013, and is particularly high in older patients who are at greater risk of polypharmacy and adverse effects.(8) Antibiotic consumption risks adverse effects, such as nausea, diarrhoea, thrush and rashes, and affects the gut microbiome, which may increase risk of long-term conditions, such as diabetes and obesity (24). Use of antibiotics, including beta-lactam antibiotics such as flucloxacillin, (25) promotes the development of antimicrobial resistance (AMR), including methicillin-resistant Staphylococcus aureus (MRSA). MRSA is a major public health threat that are associated with difficult to treat skin infections, as well other severe infections such as sepsis and pneumonia.

The UK government report on antimicrobial resistance published in 2016 gives an indication of the costs and potential risks of not tackling AMR (26). At the time of publishing 700,000 people a year were dying of resistant infections, and the number is rising rapidly. The authors estimate that by 2050, 10 million lives a

year and 100 trillion USD of economic output would be at risk as a result of AMR if it is not adequately tackled. One of the reasons why AMR is predicted to have such profound effects is because many modern medical procedures, such as surgery and chemotherapy, rely on the effectiveness of antibiotics. Key to reducing the threat of AMR, as highlighted in the UK government's five-year action plan(27), is reducing unnecessary consumption of antibiotics. In England, around three quarters of all antibiotics consumed are prescribed in primary care (28). Systematic reviews of clinician-focused interventions aimed at reducing antibiotic use for respiratory tract infections have shown that most reduce antibiotic use by about 25% or less (29). Therefore, a reduction in antibiotic use from 7 days to 5 days (a 29% reduction) is important. In a survey of 25 primary care clinicians (23 GPs, 1 Nurse Practitioner and 1 other primary care prescriber; conducted March 2021 through UK Dermatology Clinical Trials Network and Clinical Research Network Wessex), 72% said that a comparison of 5 vs 7 days would be extremely or very useful in informing their practice, and 5 vs 7 days was the comparison they selected as most informative. Two of the top ten research priorities identified in a James Lind Alliance research priority setting partnership on cellulitis involved selecting optimal dose and duration of antibiotic treatment (30). This shows that evidence on optimal duration of treatment is important for patients and clinicians.

2 TRIAL OBJECTIVES AND ENDPOINTS

2.1 AIM

To assess the effectiveness and safety of 5 days vs 7 days of flucloxacillin for lower leg cellulitis, and to evaluate the cost-consequences of a shorter course from an NHS and personal perspective.

2.2 PRIMARY OBJECTIVE

Assess whether 5 days of oral flucloxacillin is non-inferior to 7 days in terms of pain over days 6-14 in people presenting in primary care with lower leg cellulitis.

2.3 SECONDARY OBJECTIVES

To compare use of antibiotics and analgesics, symptoms, and complications in those prescribed an initial 5 vs 7 days of oral flucloxacillin.

2.3.1 Health economic objective

Evaluate the cost-consequences of a shorter course from an NHS and personal perspective.

- Change in resource use including hospital admissions, consultations, and medication use
- Number of recurrent cellulitis episodes over 12 months
- Change in Health-related quality of life

2.4 PRIMARY OUTCOME

Self-reported pain (measured using the Pain Numeric Rating Scale (NRS) (0-10)) over days 6-14. Our public contributors are very clear that pain is the most important outcome for this study. Cellulitis is a very painful condition and our public contributors report that resolution of pain is more important than resolution (or early recurrence) of other symptoms. Pain is also the patient-reported outcome most used in other trials of interventions for cellulitis (31), and the 11-point Numeric Rating Scale for Pain is widely used and has good evidence of validity and responsiveness to change (32). Most participants will start their antibiotics part-way through day 1 and therefore would complete a 5-day course on day 6, and therefore this is the first point at which the groups differ.

2.5 KEY SECONDARY OUTCOME

Demonstrating that the intervention is non-inferior in terms of pain is not sufficient – there needs to be some benefit if the intervention is to be recommended. In this trial the anticipated benefit is a reduction in use of antibiotics, which has beneficial effects as outlined in the introduction section. However, although participants in the intervention group will be given less initial antibiotics, this does not necessarily mean

that they will consume less antibiotics. Therefore, we propose using total antibiotic consumption (defined as the total number of days (days 0-28) that one or more doses of antibiotics are consumed) as a key secondary outcome. We have not powered the study on this secondary outcome but would not conclude that the intervention should be adopted if the point estimate for this secondary outcome suggests that antibiotic use in the intervention group is greater than in the control group.

2.6 ADDITIONAL SECONDARY OUTCOMES

Additional secondary outcomes and their associated objectives are listed in table 1.

Table 1: Secondary outcomes

Objective	Measure	Source
To compare use of antibiotics and analgesics, symptoms, and complications in those prescribed an initial 5 vs 7 days of oral flucloxacillin.	Use of additional antibiotics	Any reported use of antibiotics other than the initial 5 days of flucloxacillin and 2 days of IMP up to day 28)
	Patient-reported assessment of how well they are feeling	Categorical scale from Extremely unwell to 'not at all unwell' rated daily for days 1-14 and then on days 21 and 28.
	Health related quality of life	EQ-5D-5L - values over days 6-14, and individual dimension (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) level scores over days 6-14 using repeated measures.
	Leg swelling and redness Time until self-reported recovery Time until starting to recover (self-reported)	Participant reported on days 7, 14, 21 and 28.
Evaluate the cost-consequences of a shorter course from an NHS and personal perspective.	Hospital admissions Recurrent cellulitis episodes over 12 months (number of episodes) Complications (e.g., lymphoedema, leg ulceration, venous insufficiency, sepsis, death) over 12 months	Participant primary care notes review at 12 months
	Health related quality of life used to estimate Quality Adjusted- Life Years (QALYs)	EQ-5D-5L - values over days 6-14, and individual dimension (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) level scores over days 6-14 using repeated measures.
	Participant travel and other costs including over the counter purchases and time off work	Participant reported at day 14 and 28

3 OVERALL TRIAL DESIGN

A phase III blinded, multi-centre, non-inferiority trial assessing the effectiveness and safety of 5 days vs 7 days of oral flucloxacillin 500mg QDS for lower leg cellulitis, and to evaluate the cost-consequences of a shorter course from an NHS and personal perspective. Participants will be recruited in NHS primary care settings in England and Wales. We will primarily recruit through general practices, out of hours and urgent care settings.

Participants will be randomised 1:1 into 2 arms:

> **Intervention:** Flucloxacillin 500mg four times a day (QDS) for 5 days (unblinded NHS prescription) followed by blinded *placebo* QDS for 2 days (5 days of antibiotic)
> **Control:** Flucloxacillin 500mg QDS for 5 days (unblinded NHS prescription) followed by *flucloxacillin 500mg* QDS (blinded) for 2 days (7 days of antibiotic)

To facilitate ease of recruitment and avoid treatment delay, participants will be provided with an NHS prescription for flucloxacillin 500mg QDS for the first 5 days. A blinded medication pack will be sent by next day delivery, containing flucloxacillin 500mg QDS, or matched placebo QDS for the final 2 days. Participants will be informed that the capsules in this pack may look different from the capsules they were taking on days 1-5. Participants experiencing significant clinical deterioration, as judged by their healthcare team, may have their antibiotic treatment changed or be prescribed additional antibiotic courses. Any changes or additional use of antibiotics will be recorded, and the patient and recruiting centre will remain blinded unless unblinding is deemed necessary.

The trial will include a 6-month internal pilot with clear stop-go criteria* based on recruitment rates and data completeness:

Progression criteria	Red	Amber	Green
Total number of participants recruited	<32	32-39	40+
Recruitment rate (Participants/Site/month)	0.7	0.8-0.9	1+
Sites open	<8	8-9	10+
Proportion of participants with acceptable adherence from participant diary (≥75% doses taken) of initial treatment course (5d antibiotic course +2d IMP)	<60%	60-79%	80%+
Primary outcome data available (overall % of days 6-14 with a pain score)	<60%	60-79%	80%+

Following the submission of the 6-month internal pilot progress report, it has been agreed with the funder that the trial will include a further 6-month internal pilot with clear stop-go criteria* based on the total number of participants recruited, dose adherence and data completeness:

Progression criteria	Red	Amber	Green
Total number of participants recruited	<124	124-154	≥155
Proportion of participants with acceptable adherence from participant diary (≥75% doses taken) of initial treatment course (5d antibiotic course +2d IMP)	<60%	60-79%	80%+

Primary outcome data available (overall % of days 6-14 with a pain score)	<60%	60-79%	80%+

* Green = Progress as planned to full RCT, Amber = review with funder and TSC actions required, Red = urgent review with funder and oversight committees

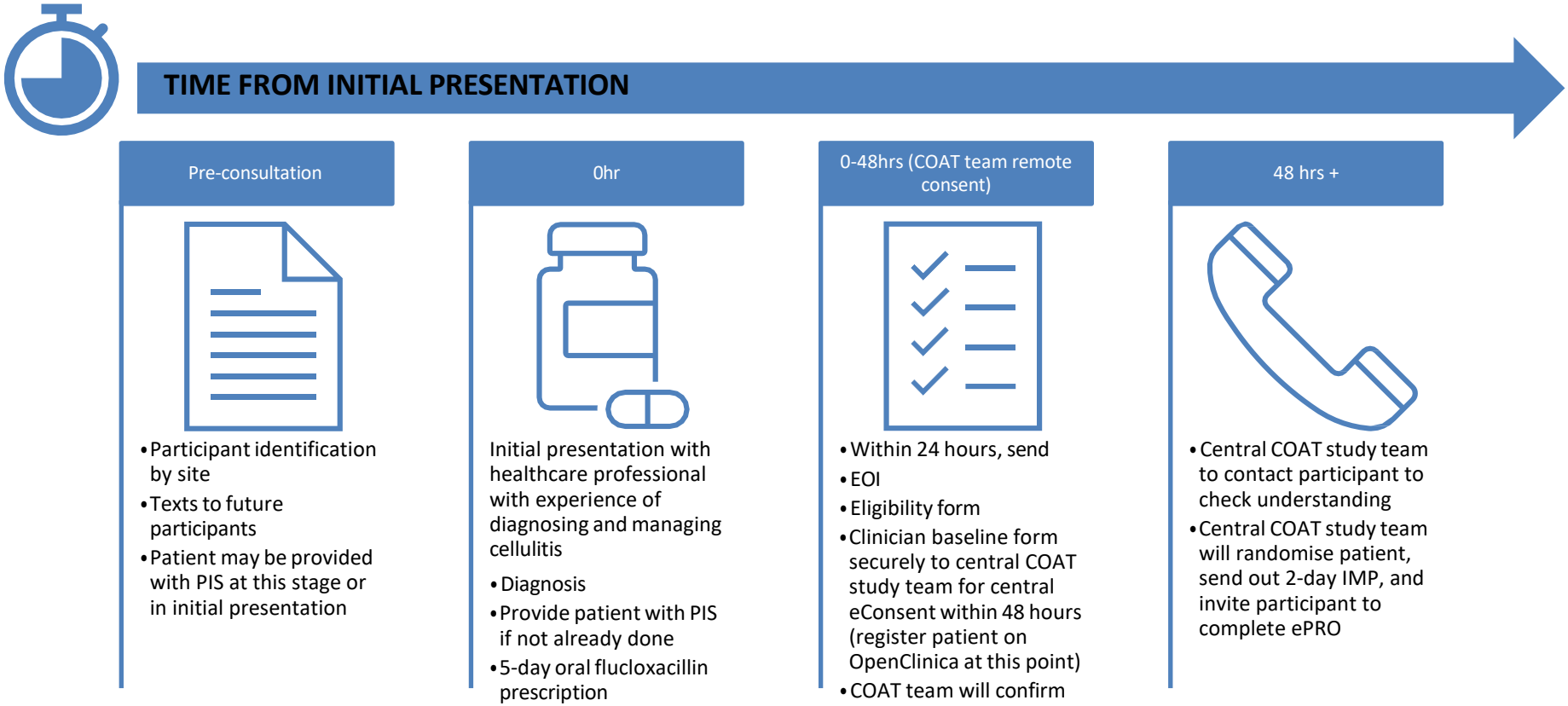
4 SELECTION AND ENROLMENT OF PARTICIPANTS

Due to the nature of the trial, participants will not start taking their IMP until day 5 at the earliest. Therefore, although study teams should aim to complete all study processes to allow for randomisation to occur within 72 hours from patient initial presentation (shown in Figure 1 below), the critical question is whether IMP can be delivered to the participant to be started by day 5. It may be possible to recruit patients rapidly and provide them with IMP by same-day delivery, so if in doubt sites should contact the COAT central study team to clarify whether a patient can be recruited and randomised or not.

A patient presenting at a recruiting centre with cellulitis may be seen by any healthcare professional who (as per standard of care) has experience with diagnosing and managing cellulitis, and is able to prescribe a 5-day course of flucloxacillin (e.g. doctor, advanced nurse practitioner, paramedic, etc.).

The general principles of consent, as well as study-specific requirements are detailed in section 4.2 below. Consent must be obtained before any study-specific procedures (including documentation of eligibility confirmation). Confirmation of eligibility assessment (detailed in section 5.1.1) may be made by a healthcare professional (e.g. GP, advanced nurse practitioner, paramedic, pharmacist) who has experience in managing and diagnosing cellulitis in a primary care setting and has been delegated this responsibility by the site principle investigator. Following consent, a patient may be registered on the study database as detailed in section 5.2. Due to the wide variety of healthcare professionals that may treat a patient, and who may be involved in the research process, role-specific patient management flows for the study have been created and copies provided to the site by the COAT central study team.

Figure 1


TIME FROM INITIAL PRESENTATION
Pre-consultation
•Participant identification by site
•Texts to future participants
•Patient may be provided with PIS at this stage or in initial presentation
0hr
Initial presentation with healthcare professional with experience of diagnosing and managing cellulitis
•Diagnosis
•Provide patient with PIS if not already done
•5-day oral flucloxacillin prescription
•In-person consent (paper or electronic)
•Baseline data collection template in patient medical notes
•Eligibility may be confirmed by a suitably trained healthcare professional at initial presentation
0-48hrs (COAT team remote consent)
•Within 24 hours, send
•EOI
•Eligibility form
•Clinician baseline form securely to central COAT study team for central eConsent within 48 hours (register patient on OpenClinica at this point)
•COAT team will confirm consent with site
•COAT team will randomise patient and send out IMP
48 hrs +
•Central COAT study team to contact participant to check understanding
•Central COAT study team will randomise patient, send out 2-day IMP, and invite participant to complete ePRO

4.1 PARTICIPANT IDENTIFICATION

Potentially eligible participants will be initially identified by appropriate site staff. Where possible, potential participants will be directed to our study website where they can access information about the study and watch a short video explaining the study or be sent information about the study prior to their consultation. We may translate the PIS into various languages to help increase diversity and inclusivity.

We will also provide a template text message to participating sites with a link to the PIS and video, should they wish to send information about the trial to patients with a history of cellulitis, to make them aware of the trial should they be diagnosed at a future consultation.

The initial consultation with a participant, as well as the eligibility assessment, should ideally take place face to face but can be done virtually as per normal clinical practice for the recruiting site. Three models for recruiting participants will be available to sites:

1. Participant is recruited during the initial consultation (in person or virtual).
2. Participant is recruited by a member of the site/hub study team after the initial consultation.
3. Participant is recruited by a member of the COAT central study team after the initial consultation.

4.2 CONSENT

General consent principles for COAT study

In all cases a trained researcher will explain the trial to potential participants with the aid of participant information sheets.

The Principal Investigator (PI) retains overall responsibility for the conduct of the research at their site, including the receiving of informed consent of participants. They must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained, and competent to participate.

Consent to enter the trial must be sought from each participant only after a full explanation has been given and PIS offered. This can be done either face to face or virtually, depending on the site that the patient is treated at. Due to the acute nature of cellulitis and the need to start treatment as soon as possible, informed consent will be expedited, and ideally completed during the consultation. However, informed consent can be obtained up to 48 hours from the participant's initial presentation at the GP surgery or their participating site.

The right of the participant to refuse to participate without giving reasons will be respected. After the participant has entered the trial, the treating team remains free to give alternative treatment to that specified in the protocol at any stage if they feel it is in the participant's best interest, but the reasons for doing so should be recorded.

Paper consent

Upon completion of a paper informed consent form, a copy will be given to the participant, a copy stored in the participant's medical notes, and the original filed in the site trial file. A copy of the consent form should also be sent to the COAT central study team via the University of Southampton's SafeSend service or the University approved secure email address to allow for central monitoring. The paper consent form may be translated into various languages to help increase diversity and inclusivity.

eConsent process

Online participant eConsent will be obtained by the COAT study team using AdobeSign or other SCTU approved central eConsent/eSignature systems according to local procedures). Sites will be required to send

the participant expression of interest form to the COAT study team (within 48 hours) if they wish for a participant to be consented remotely. The patient will be sent a PDF version of the COAT informed consent form to their email address and therefore, must have access to a mobile phone or computer with internet connection and an up-to-date web browser. The patient will be guided through the consent process via phone call or video call with an appropriately trained and delegated member of the COAT central study team if required. Once the patient has signed consent, the consenter will also electronically counter-sign the electronic informed consent form (eICF). When consent is completed by a member of the COAT central study team, a telephone call log should be completed and filed with trial documentation according to local standard procedures. Upon completion of the eICF, a copy will be sent to the; the site (who will print and file copies in the participant's medical notes and in the ISF); and a copy saved in an access restricted electronic folder ar the SCTU.

Potential participants can be supported by carers/family members/others to use the eConsent system as appropriate.

4.3 INCLUSION CRITERIA

1. Adult (age ≥18 years) with symptoms suggestive of cellulitis (pain, tenderness, redness or other change in skin colour, and warmth to touch) in one leg for 10 days or less, and where the clinical impression is of cellulitis as the most likely diagnosis.
2. Pain rated ≥ 3/10 on a numeric rating scale (0-10) at baseline assessment.
3. Able to complete trial procedures in English language (could be through the assistance of an interpreter).

4.4 EXCLUSION CRITERIA

4. Has had antibiotics for cellulitis within the past month
5. Bilateral cellulitis#
6. Post-operative cellulitis (within 30 days of operative procedure on same leg)*
7. Cellulitis resulting from a human/animal bite injury (cellulitis following an insect bite is eligible for inclusion)
8. Cellulitis associated with chronic (>6 weeks) leg ulceration*
9. Patient requires immediate hospital admission or out-patient intravenous antibiotic therapy
10. Known true allergy to penicillin or cephalosporins. (Guidance will be provided on assessing penicillin allergy. Prospective participants will be questioned as to the nature of any potential allergic reactions to assess whether it was likely to be a true allergy. If a true allergy is thought to be unlikely then the likely risks and benefits should be discussed with the patient to allow them to come to an informed, shared decision.)

True bilateral cellulitis is extremely rare and therefore patients with bilateral leg inflammation are more likely to have pseudo-cellulitis.
* Associated with different organisms and different illness course compared with normal cellulitis.

5 TRIAL PROCEDURES

5.1 SCREENING PROCEDURES

All patients who present at a participating centre with suspected lower leg cellulitis should be screened for trial eligibility. A screening log should be completed detailing each time a potential participant is approached and document whether they agree to participate or not, and the reasons if they are not enrolled. Anonymised, aggregate site level data may also be sought from sites to review numbers of patients presenting with cellulitis.

5.1.1 Trial Eligibility Assessments

General eligibility principles for COAT study

Eligibility must be confirmed by a healthcare professional (e.g. GP, advanced nurse practitioner, paramedic, pharmacist) who has experience in managing and diagnosing cellulitis in a primary care setting in line with standard practice.

Confirmation of patient eligibility will be documented by the treating healthcare professional, using the paper eligibility form or the eligibility form within the study database, once informed consent has been given from the patient.

If a patient is not to be consented during the initial consultation (e.g. will later go through the consent process with another member of the research team or with the central COAT study team), the treating healthcare clinician may pre-screen the patient for eligibility, and make a statement in the patient notes confirming that the patient is eligible for the trial. Following the successful consent of the participant, any member of the research team at site (who is delegated to do so) may complete either the paper or electronic eligibility form on behalf of the treating healthcare provider using the statement in the medical notes.

In all cases, the name and role of the treating healthcare provider who has confirmed eligibility will be recorded (either on paper or electronic eligibility form) to ensure that this has been confirmed by an appropriate individual.

The Principal Investigator (PI) retains overall responsibility for the conduct of research at their site, including ensuring recruited participants meet the eligibility criteria.
Where the Principal Investigator at a site is not a medically qualified doctor, the Chief Investigator (CI) for the study retains this responsibility.

5.1.2 Screen Failures

Screen failures are defined as patients with whom the COAT trial is discussed but who do not go on to be enrolled in the trial. This will include patients who consented but were not eligible for inclusion. Screen failures will be documented in screening logs, together with reasons for exclusion. Site screening logs will be filed in the ISF.

5.2 REGISTRATION AND RANDOMISATION PROCEDURES

5.2.1 Registration

Participants will be registered either during their initial consultation or remotely during their consent phone/videocall with either a member of delegated site staff or a member of the COAT central study team.

5.2.2 Randomisation

Randomisation will occur as soon as possible following consent but may occur during a 72 hour+ window, if medication can be sent via courier after initial presentation. It will be undertaken by the COAT central study team using a web-based system.

We will use block randomisation stratified by obesity (BMI≥30) and prior history of leg cellulitis. Participants will be allocated IMP containing either 2 days' worth of flucloxacillin 500mg or placebo capsules provided in identical packaging to ensure blinding. Neither the trial staff dispensing the IMP, the participant nor the trial site will know to which arm the participant has been randomised.

5.3 BLINDING AND PROCEDURES FOR EMERGENCY UNBLINDING

An emergency unblinding service is not required for this trial due to the low risk associated with the trial. This will be documented in the trial risk assessment. Emergency clinical decisions can be made without knowledge of the treatment group that the participant is allocated to. If unblinding is required this can be done by the Trial Statisticians at the SCTU during normal working hours (9am to 5pm, Monday to Friday).

All participants will carry a trial card with relevant phone numbers to call in the event of any serious adverse events (see Section 7).

5.4 TRIAL PROCEDURES

5.4.1 Baseline (Up to randomisation)

Standard of care procedures (site):

- Cellulitis diagnosis/pre-screen eligibility assessment in line with COAT inclusion/exclusion criteria
- Prescription of 5-day oral flucloxacillin
- Baseline clinical features (incl. pain score) documented in patients notes

Trial-specific procedures:

- Contact details documented on either participant expression of interest form or participant contact details form
- Informed consent (site or central)
- Eligibility confirmation (to be documented in the patients electronic medical records and only sent securely to the COAT central study team only once consent is received/confirmed)
- Baseline documents sent to COAT central study team via Safesend or the University approved secure email address
- Registration on OpenClinica (site or central)
- Randomisation on ALEA (central)

All participants will be invited to complete further baseline data using an online electronic data collection tool, and will be contacted by a member of the central trial team as soon as possible after recruitment to check understanding, answer any questions they may have, encourage completion of the electronic data collection, or collect data over the phone if not willing or able to complete the online form. The following baseline data will be collected using the electronic data collection tool (estimated completion time 10 minutes) or over the phone:

- Demographics (Month & year of birth, sex at birth, ethnicity, employment status, postcode.)
- Pain score at the time of recruitment (numeric rating score (NRS))
- Rating of unwellness
- Leg swelling and redness
- Other symptoms
- EQ-5D-5L
- DLQI
- Consumption of analgesics specifically for cellulitis pain
- Participant travel and other costs including over the counter purchases and time off work

5.4.2 Days 1-14

The IMP, alongside the patient infographic will be sent to the participant via recorded delivery for receipt within 5 days of the baseline visit

The following participant reported data will be collected daily until day 14 days via an ePRO web-based system (estimated completion time 5 minutes) or via a paper diary (if requested during the baseline appointment):

- NRS for pain
- Rating of unwellness
- EQ-5D-5L
- Use of initial antibiotics and IMP (day 0-10)
- Use of any additional antibiotics
- Use of analgesics for cellulitis pain

In order to maximise collection of primary outcome data, participants who are not providing regular data via the online form, and all participants who have opted for paper diary completion, will be sent daily text message reminders or email reminders to prompt them to complete the relevant questionnaires and/or telephoned on days 7 and 14 to support data completion and/or collect outcomes over the phone.

5.4.3 Days 7, 14, 21, 28

In addition to the daily data during days 1-14, the following data are also reported weekly (by participants) via an ePRO web-based system (estimated completion time 5 minutes) or via paper diary cards:

- Leg swelling and redness
- Other symptoms
- NRS for pain (day 21 and 28)
- Rating of unwellness (day 21 and 28)
- Day the cellulitis started to improve
- Day the participant felt recovered
- Participant travel and other costs including over the counter purchases and time off work (day 14 and 28)
- Use of additional antibiotics (day 21 and 28)
- EQ-5D-5L (day 21 and 28)
- DLQI (day 28)

Participants who do not complete the online assessments and all participants who have opted for paper diary completion will be sent daily text and/or email reminders to prompt them to complete the relevant questionnaires and/or will be telephoned to collect outcomes over the phone.

5.4.4 12 Months

A review of the participants' primary care medical records will be conducted to obtain additional baseline data (use of antibiotics for any reason in 28 days prior to enrolment for cellulitis, past medical history), document any additional medication for cellulitis prescribed during the baseline consultation, identify additional primary care consultations or hospitalisations (day cases, admissions or A&E visits), identify antibiotics or other medications prescribed for cellulitis (from 3 months prior to randomisation), and identify further episodes of cellulitis or complications occurring during the 12 months following recruitment.

5.5 TRIAL INTERVENTION DISCONTINUATION AND PARTICIPANT WITHDRAWAL

Participants may withdraw voluntarily from the trial or the Principal Investigator/Treating Healthcare Provider may discontinue a participant from the trial treatment for appropriate medical reasons.

5.5.1 Discontinuation of Trial Intervention

Participants may be discontinued from the trial in the event of:

- Significant trial intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the trial would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognised) that precludes further trial participation

Where possible, participants discontinued from the IMP only should continue with the trial-associated processes as per the Schedule of Observations and Procedures.

Full details of the reason for trial treatment discontinuation should be recorded in the eCRF and the participant's medical record.

5.5.2 Trial Withdrawal

The participant/legal representative is free to withdraw consent from the trial at any time, without providing a reason, and without their medical care or legal rights being adversely affected.

Investigators should explain to participants the value of remaining in trial follow-up and allowing this data to be used for trial purposes. Where possible, participants who have withdrawn from trial treatment should remain in follow-up as per the Trial Schedule of Observations and Procedures. If participants additionally withdraw consent for this, they should revert to standard clinical care/follow-up as deemed by the responsible healthcare provider. It would remain useful for the trial team to continue to collect any routine data (i.e., data that can be collected with no impact on the participant beyond standard clinical care/follow-up), and this will continue unless the participant explicitly requests otherwise. If this is requested, this constitutes complete withdrawal from the trial and should be recorded as end of trial for the participant in the relevant eCRF and in their medical record, and no further data should be collected for this participant.

Participants will have the following options of withdrawal:

- Withdrawal from treatment and all follow up assessments
- Withdrawal from follow up (ePRO) assessments only
- Complete withdrawal from all study procedures and data collection

In the event of any form of withdrawal, data obtained up to this point will be retained for analysis, as advised in the Patient Information Sheet. We would also like to have the option to collect data from their electronic records, in the future, unless they request otherwise.

Following withdrawal from the study, patient care will be decided by their healthcare provider according to usual practice. Details of trial discontinuation (date, reason if known) will be recorded in the eCRF and medical record.

Participants who do not provide any follow up data between days 1- 28 will be considered lost to follow up. However, we will still attempt to obtain 12-month follow-up data for these participants unless they have specifically withdrawn consent for this aspect of the study.

Participants who are lost to follow up will not be replaced, but we will closely monitor follow up rates and if these are less than anticipated, we may make the case to independent monitoring committees, funder and sponsor for increasing our sample size.

5.6 DEFINITION OF END OF TRIAL

Participants end their involvement with the trial when their last follow up questionnaire is completed (or efforts to obtain final questionnaire have been unsuccessful), or they have withdrawn from the trial.

The end of trial will be when the last participant has completed their last follow-up questionnaire and a 12-month review of their medical records has been completed and this data has been entered onto the database and cleaned.

6 TRIAL TREATMENTS

6.1 DESCRIPTION OF INVESTIGATIONAL MEDICINAL PRODUCT(S)

Within the trial, the following are classed are as IMPs:

- Flucloxacillin 500mg, over encapsulated to match the appearance of the placebo capsule.
- Placebo: formulated and manufactured according to a standard placebo composition to match the appearance of the over encapsulated flucloxacillin.

All participants will be prescribed a 5-day course of Flucloxacillin 500mg Capsules BP QDS by their GP, or an appropriate healthcare professional. Following randomisation each participant will then sent either blinded *placebo* QDS for 2 days (receiving 5 days of antibiotic) or *flucloxacillin 500mg* QDS (blinded) for 2 days (receiving 7 days of antibiotic). The Chief Investigator or an appropriate delegate will take overall responsibility for the provision of IMP to study participants once it has been confirmed by the COAT central study team that a healthcare professional (e.g. GP, advanced nurse practitioner, paramedic, pharmacist) who has experience in managing and diagnosing cellulitis in a primary care setting has confirmed eligibility and the participant has been prescribed an initial 5-day course of oral flucloxacillin.

The COAT central study team will send the IMP package via a secure recorded method to participants to arrive before day 5.

6.2 REGULATORY STATUS OF THE DRUG

The flucloxacillin 500mg capsules used for the first five days will be prescribed by the recruiting site and commercially available flucloxacillin 500mg capsules will be used in their respective marketed presentations.

For the final two days, the flucloxacillin 500mg IMP will consist of over-encapsulated flucloxacillin 500mg capsules licensed in the Netherlands. The active and placebo IMP will be manufactured in the UK in accordance with Good Manufacturing Practices (GMP) and Qualified Person (QP) certified for clinical trial use.

6.3 PRODUCT CHARACTERISTICS

Flucloxacillin Sodium is indicated for the treatment of infections due to sensitive Gram-positive organisms, including β-lactamase producing staphylococci and streptococci infections, in primary care flucloxacillin is used almost exclusively for skin infections[8].

Flucloxacillin should not be given to participants with a history of hypersensitivity to β-lactam antibiotics (e.g. penicillin, cephalosporin) or excipients. Therefore, we will screen for and exclude participants with a known Penicillin allergy

6.4 INVESTIGATIONAL MEDICINAL PRODUCT(S) SUPPLY

6.4.1 Drug Storage and Supply

The initial 5-day course of flucloxacillin will be prescribed by the participants' recruiting site and provided as per standard of care by local pharmacies.

The remaining 2 days of IMP (flucloxacillin or matching placebo) capsules will be arranged by MODEPHARMA. The IMPs will be packed in HDPE bottles (8 active or placebo capsules per bottle) with child resistant caps, tamper-evident sealed and labelled according to Annex 13 guidelines. The active and placebo IMPs will be visually identical and each bottle will have a uniquely assigned bottle number.

IMP will be stored securely in a locked storage location at room temperature at Primary Care Research Centre, Aldermoor Health Centre, Southampton. Access will be limited to trial staff based at the Primary Care Research Centre. IMP will be sent to participants after randomisation using a secure recorded delivery service, following confirmation of their address and willingness to continue in the trial. Participants should only be randomised if IMP can be delived to them before their initial 5-days of antibiotics have been completed.

6.4.2 Preparation and Labelling of Investigational Medicinal Product(s)

Preparation and labelling of the investigational medicinal products will be completed in accordance with the relevant GMP guidelines. The IMPs (flucloxacillin or matching placebo) capsules will be arranged by MODEPHARMA. The IMPs will be packed in HDPE bottles (8 active or placebo capsules per bottle) with child resistant caps, tamper-evident sealed and labelled according to Annex 13 guidelines. The active and placebo IMPs will be visually identical and each bottle will have a uniquely assigned bottle number.

Further details about the IMP manufacturing can be found in the IMP dossier.

6.4.3 Accountability

As a pragmatic trial, a full reconciliation is unnecessary and would be difficult to undertake. Drug accountability records of IMP stored centrally will be maintained throughout the course of the trial by the COAT central study team. Designated staff will document the date and quantity of IMP as it is received and dispensed to trial participants.

Participants will be asked to safely dispose of unused trial medication by returning them to a local pharmacy or disposing of them at home. Individuals who are sent trial medication but change their mind before starting the medication will also be asked to return these to a local pharmacy or dispose of these at home.

If the trial medication is lost or damaged between randomisation and the end of the participant's treatment period, the trial medication will be replaced by using the kit allocation system, which will allocate new IMP.

6.5 TREATMENT SCHEDULE

Participants will have a 5-day course of oral Flucloxacillin 500mg capsules, to be taken 4 times daily. Followed by a 2-day course of IMP (Flucloxacillin 500mg capsules or placebo), to be taken 4 times daily as per standard care instructions.

Compliance will be participant reported and recorded on the trial database.

6.6 KNOWN DRUG REACTIONS AND INTERACTION WITH OTHER THERAPIES

Common side effects of flucloxacillin happen in more than 1 in 100 people and include nausea, vomiting, diarrhoea, bloating, and indigestion.

6.7 CONCOMITANT MEDICATIONS

Information on any other medicine(s) prescribed during the initial consultation for the management of the participant's cellulitis and over the counter medication participants are taking for their cellulitis (including analgesics and additional antibiotics) used by the participant from the first administration of the NHS flucloxacillin prescription up to 28 days will be recorded in the eCRF.

7 SAFETY

7.1 DEFINITIONS

The Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, provides the following definitions relating to adverse events in trials with an investigational medicinal product:

Adverse Event (AE)	Any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. *An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.*
Adverse Reaction (AR)	All untoward and unintended responses to an IMP related to any dose administered. *All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.*
Unexpected Adverse Reaction (UAR)	An AR, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure (IB) for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product). *When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected. Side effects documented in the IB/SmPC which occur in a more severe form than anticipated are also considered to be unexpected. Reports which add significant information on specificity or severity of a known documented adverse event are to be considered unexpected.*

Serious Adverse Event (SAE)	Any untoward medical occurrence or effect that at any dose: • Results in death • Is life-threatening* • Requires hospitalisation, or prolongation of existing hospitalisation • Results in persistent or significant disability or incapacity • Is a congenital anomaly or birth defect • Important medical events*** *'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. ** Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE. ***Other important medical events may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A Serious Adverse Reaction, the nature and severity of which is not consistent with the information about the medicinal product in question as set out in the Reference Safety Information.

7.2 TRIAL SPECIFIC REQUIREMENTS

The safety profile of Flucloxacillin is well known and AEs will not be reported for this trial.

For this trial, the following events **<u>do require reporting</u>**:

- Serious Adverse Reactions. These should be reported on the trial specific serious adverse event report form.

All serious adverse reactions occurring from the first administration of the participants NHS antibiotic prescription up to 28 days will be reported.

7.2.1 Seriousness

An assessment of the seriousness must always be assessed by a medically qualified doctor who is registered on the delegation of responsibility log; this is usually the investigator.

All trial related reportable adverse events that fulfil the criteria definition of 'serious' in protocol section 7.1, must be reported to SCTU using the Serious Adverse Event Report Form.

7.2.2 Exceptions:

For the purposes of this trial, the following **SAEs do not** require reporting to SCTU using the Serious Adverse Event Report Form:

- Events not deemed to be related to the COAT trial
- Hospitalisations for elective treatment of a pre-existing condition
- Hospitalisations for progression of cellulitis (these will be documented as a secondary outcome)

7.3 CAUSALITY

A complete assessment of the causality must always be made by a medically qualified doctor who is registered on the delegation of responsibility log; this is usually the investigator.

If any doubt about the causality exists, the local investigator should inform SCTU who will notify the Chief Investigator. Other medically qualified doctors may be asked for advice in these cases.

In the case of discrepant views on causality, SCTU will classify the event as per the worst case classification and if onward reporting is required, the MHRA will be informed of both parties' points of view.

Relationship	Description	Denoted
Unrelated	There is no evidence of any causal relationship	SAE
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).	SAE
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).	SAR/ SUSAR
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	SAR/ SUSAR
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR/ SUSAR

7.4 EXPECTEDNESS

Expectedness assessments are made against the approved Reference Safety Information (RSI). The RSI for this trial is specified within the document versions listed in the tables below:

Name of Product	SmPC	Section /Table No.	Manufacturer	Last updated on eMC DD-MMM-YYYY
Flucloxacillin Mylan 500mg Capsules BP	SmPC	4.8	Mylan B.V (Viatris Inc)	25th June 2021

The nature and/or severity of the event should be considered when making the assessment of expectedness. If these factors are not consistent with the current information available, then the AR should be recorded as 'unexpected'.

7.5 REPORTING PROCEDURES

Any questions concerning adverse event reporting should be directed to the SCTU in the first instance. A flowchart will be provided to aid in the reporting procedures.

There are three avenues where SAEs could be identified:

1. Participants' healthcare professional: Participants' GP surgery's will be informed of their patient's participation and will be asked to notify the trial team of any event that falls within the serious classification deemed related to the trial.

2. Participant reported: On the ePRO completed by the participant at Day 28, participants will be asked within the follow up questionnaire if they have been to hospital, and if so where they were hospitalised. The COAT central study team will obtain relevant information and contact the participant's relevant trial site should further information be required.

3. At the 12-month notes review hospital visits (via discharge summaries to GP) within the 28-day reporting period will be captured and recorded on the eCRF.

Upon occurrence of an SAE notified by the GP surgery, identified at the follow up visits or participant reported at Day 28, the PI or named delegate listed on the delegation log will assess seriousness and causality. Any delegated member of local site study team will take the reporting action described in Sections 7.5.1.

7.5.1 Reporting Details

7.5.1.1 Non-serious AEs/ARs

The safety profile of Flucloxacillin is well known and AEs/ARs will not be reported for this trial.

7.5.1.2 Serious Adverse Events

For all reportable SAEs, an SAE report form should be completed with as much detail as possible (including any relevant anonymised treatment forms and/or investigation reports) and emailed to SCTU immediately but at least within 24 hours of site becoming aware of the event.

Or

Contact SCTU by phone for advice and then email a scanned copy of the SAE report form completed as above.

SAE REPORTING CONTACT DETAILS

Please email a copy of the SAE form to
SCTU within 24 hours of becoming aware of the event

Email: ctu@soton.ac.uk

FAO: Quality and Regulatory Team

For further assistance: Tel: 023 8120 5154 (Mon to Fri 09:00 – 17:00)

The event term should be the most appropriate medical term or concept (which the SCTU will code to MedDRA) and grades given in accordance with the grading system referenced in section 7.2 i.e. the NCI CTCAE v5.

Additional information should be provided as soon as possible as it is received if all information was not included at the time of reporting.

7.5.1.3 Reporting Timelines

All protocol reportable SAEs should be reported up to 28 days after the first administration of the participants 5-day NHS flucloxacillin prescription.

All unresolved adverse events should be followed by the investigator until one of the end of trial criteria is met (i.e. lost to follow up, withdrawal etc.). At the last scheduled visit, the investigator should instruct each participant to report any subsequent event(s) that the participant, or the participant's general practitioner, believes might reasonably be related to participation in this trial. The investigator should notify the trial sponsor of any death or adverse event occurring at any time after a participant has discontinued or terminated trial participation that may reasonably be related to this trial.

7.5.2 Pre-existing Conditions

Pre-existing conditions (prior to informed consent) should not be reported as an AE unless the conditions worsen during the trial and is deemed related to the trial or is a clinically relevant AR. The condition, however, must be reported on the Medical History eCRF.

7.5.3 Pregnancy

The safety profile of flucloxacillin is well known, previous studies with flucloxacillin have shown no teratogenic effects. The product has been in clinical use since 1970 and the limited number of reported cases of use in human pregnancy have shown no evidence of untoward effects. Therefore, no additional safety reporting will be carried out for participants who become pregnant while participating in the trial.

7.6 RESPONSIBILITIES

7.6.1 Principal Investigator (PI)

The PI (if a medically qualified doctor), or medically qualified doctor who is registered on the delegation of responsibility log, is responsible for:

1. Using medical judgement in assigning seriousness, causality and referring to the Reference Safety Information for expectedness.
2. Ensuring that all SAEs are recorded and reported to the SCTU immediately, or at a least within 24 hours, of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with the SCTU if a record of receipt is not received within 1 working day of initial reporting.
3. Ensuring that AEs and ARs are recorded and reported to the SCTU in line with the requirements of the protocol. (Not applicable to this study as AEs and ARs are not recorded)

If the PI at a site is not a medically qualified doctor, then they are responsible for passing on all relevant information regarding an adverse event to the Chief Investigator (or his delegate), who will perform the responsibilities listed above. In cases where the Chief Investigator is taking on the role of medically qualified doctor as described above for a particular site, clinical review will be obtained from an appropriately independent reviewer.

7.6.2 Chief Investigator (CI) / delegate or independent clinical reviewer:

The CI, or delegated clinical reviewer, is responsible for:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning the SAEs seriousness, causality and whether if requested, the event was anticipated (in line with the Reference Safety Information) where it has not been possible to obtain local medical assessment.
3. Immediate review of all SUSARs if required.
4. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
5. Upon request review Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding for all coded events.
6. Preparing the clinical sections and reviewing the Development Safety Update Report (DSUR).

7.6.3 Sponsor / delegate

The Sponsor, or delegate, is responsible for:

1. Central data collection and verification SAEs, SARs and SUSARs according to the trial protocol onto a database.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
3. Checking causally related events against the approved RSI, in place at time of event onset.
4. Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring & Ethics Committee (DMEC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
5. Ensuring that expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC are within the required timelines.
6. Notifying Investigators of SUSARs that occur within the trial.
7. The unblinding of a participant for the purpose of expedited SUSAR reporting
8. Regularly checking for and notifying PIs of updates to the Reference Safety Information for the trial.
9. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC.

7.7 REPORTING URGENT SAFETY MEASURES

If any urgent safety measures are taken the CI/Sponsor shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and REC of the measures taken and the circumstances giving rise to those measures.

7.8 DEVELOPMENT SAFETY UPDATE REPORTS (DSUR)

The Sponsor, or delegate, will provide DSURs once a year throughout the trial, or as necessary, to the Competent Authority (the MHRA in the UK), and the appropriate REC.

The report will be submitted within 60 days of the Development International Birth Date of the trial each year until the trial is declared ended.

8 STATISTICS AND DATA ANALYSES

8.1 METHOD OF RANDOMISATION

Randomisation will be handled by the SCTU via an online system. Participants will be individually randomised between the arms, using a 1:1 allocation ratio, and using block randomisation stratified by obesity (BMI≥30)

and prior history of leg cellulitis. On allocation of the pack ID, the Trial Staff will send the package to the participant to arrive before day 5.

8.2 SAMPLE SIZE

Assuming a non-inferiority margin of 1 point on the NRS for pain (0-10), standard deviation of 2.8 and correlation between 9 measures of 0.7, a sample size of 284 would provide 90% power to detect a difference between groups using a one-sided alpha of 0.025. Allowing for 20% loss to follow-up, a sample size of 356 (178 in each arm) needs to be recruited.

Several studies have measured pain in patients with cellulitis using the NRS for pain (0-10) (31). Mean pain scores are typically in the 5-7 range at baseline and reduce to ~3 by days 4-6 and ~2 with a standard deviation of ~2.8 by day 7. Therefore, we expect pain scores in the 7-day group to reduce from ~2.5 on day 6 to ~1-1.5 by day 14. Our PPI group weighed up benefits of reduced exposure to antibiotics and the potential harms of increased pain related to inadequate response or early relapse and agreed that a non-inferiority margin of 1 point was reasonable. We have been unable to find a published minimal clinically important difference (MCID) for pain following cellulitis, and published data on MCIDs for pain more generally are varied, but generally suggest values larger than 1. A systematic review of the MCID for the Pain Visual Analogue Scale (0-100) in patients with arthritis found MCIDs of 7-11, 19-27 and 29-37 (equivalent to 0.7-1.1, 1.9-2.7 and 2.9-3.7 on an NRS) for patients with baseline pain scores of 30-49, 50-65, and >65 respectively (33). Another review of 37 studies on treatment of acute pain reported absolute MCIDs equivalent to 0.8-4 on a NRS and relative MCIDs of 13-85% (34). Therefore, a non-inferiority margin of 1 is towards the bottom end (most conservative) of what is considered to be a clinically meaningful difference in pain scores in published studies.

8.3 INTERNAL PILOT

There will be an analysis of the internal pilot data which will be descriptive with respect to the progression criteria and discussed with our Oversight Committees to inform decisions about trial progression.

8.4 STATISTICAL ANALYSIS PLAN (SAP)

A detailed statistical analysis plan will be developed prior to the final analysis of the trial, however, the main features of the plan are discussed below. Data will be reported and presented according to the revised CONSORT (Consolidated Standards of Reporting Trials) Statement. All results will be reported with 95% confidence intervals and all models will control for the baseline covariates set out in the primary analysis. Any subgroup analyses will be planned and pre-specified in the statistical analysis plan.

8.4.1 Primary endpoint

The primary analysis will use a generalised linear mixed model, controlling for baseline pain NRS and stratification variables and allowing for the clustering of repeated measures within participant over time. The mixed modelling approach will allow participants to contribute data to the model for any days for which they have completed the NRS, with any missing days being treated as missing at random. The structure and pattern of missing data will be explored, and if appropriate, a sensitivity analysis based on data imputed using a multiple imputation model will be presented.

The primary analysis will be completed using ITT, as this is the basis for the sample size calculation. However, since ITT can be anti-conservative for non-inferiority trials, the analysis will also be conducted per protocol as an important secondary analysis, and findings interpreted cautiously in light of any differences between approaches that emerge. A standard per protocol analysis, which excludes those who take additional antibiotics during days 6 to 14, will be carried out. In addition, a modified per protocol analysis, which censors those who take additional antibiotics from the day they start the additional course, will also be conducted.

8.4.2 Key Secondary endpoint

The total number of days of antibiotic consumption will be compared using either Poisson or negative binomial regression as appropriate to the data, adjusting for the same covariates as the primary analysis.

8.4.3 Additional secondary endpoints

Use of additional antibiotics (as a binary outcome) in the first 28 days will be assessed using logistic regression, adjusting for the same covariates as the primary analyses. How unwell patient felt over days 6-14, and leg swelling and redness over days 7, 14, 21 and 28 will be analysed by repeated measures linear regression models adjusting for baseline scores and other baseline covariates as per the primary analysis. Time until self-reported recovery, and time until self-assessed start of improvement, will be treated as time to event outcomes and analysed using appropriate survival modelling approaches, most likely Cox regression. Adverse reactions of special interest and SAEs will be summarised by group with frequencies and percentages and compared with Pearson's χ^2 tests.

12-month follow-up analyses

At 12 months, the number of antibiotic prescriptions, primary care consultations, hospital admissions (including A&E visits), complications and recurrent cellulitis episodes will be treated as count outcomes or binary outcomes as appropriate to the distribution and a suitable regression modelling strategy chosen, i.e. logistic regression for binary distribution or mostly likely Poisson or negative binomial for a count distribution.

8.5 ECONOMIC EVALUATION

We will conduct a cost-consequence analysis to describe and compare resource use (primary, community and secondary care), costs (including intervention and participant costs (our PPI colleagues have said it is impossible to work when experiencing cellulitis and that it may have implications for travel costs)) and selected outcomes in a disaggregated form over the time horizon of 12 months. We hypothesise that the mean cost per participant in the 5- day course will be less than that for the 7-day course, and that health-related quality of life does not differ between treatment arms. Participants will be asked to self-report their personal resource use (e.g. out of pocket expenses such as for over the counter analgesics, time off work and travel costs to appointments) until day 28 whilst NHS resource use between baseline and 12 months will be collected via a review of GP electronic medical records.

The EQ-5D-5L will be asked daily for the first 14 days and again on days 21 and 28, and this will be used to estimate the utility loss associated with an episode of cellulitis. Since it will not be possible to ask participants the EQ-5D-5L after day 28 this estimate of utility loss will be used to help estimate Quality-Adjusted Life Years over the 12 months based on the number of recurrences recorded. We will use an approach akin to that used in Mason et al (2014) which was a within-trial economic evaluation comparing low dose penicillin V in patients following a first episode and more recurrent cellulitis compared to a placebo for participants who had suffered a recent episode of cellulitis of the leg (35). In those who had an infection, the difference between their initial EQ-5D score (during infection) and follow-up EQ-5D score (after resolution of infection) provided an estimate of the loss in quality of life associated with an infection, and was subsequently used to estimate the quality-adjusted life-year (QALY) loss associated with a recurrence of cellulitis (what Mason et al (2014) call a QALY 'tariff' for a recurrence). These QALY scores were then used to estimate the QALY gain due to recurrence prevention within the trial in question. In a similar way we will apply a "QOL tariff' to each cellulitis recurrence recorded in our study where the QOL tariff will be estimated using the EuroQol EQ-5D-5L scores collected daily from baseline to day 14 and then on day 21 and 28. A case of cellulitis typically lasts 7-10 days with effective treatment meaning that the daily collection of utility over the first 14 days and then again at day 21 and 28 is sufficient for this purpose. The QALY loss due to recurrence will be used to model QALY gains resulting from the prevention of recurrence in the trial phase should there be a difference in recurrence between the shorter and standard course of flucloxacillin. The analysis assumes that the utility loss associated with an occurrence of cellulitis is constant over time i.e. that utility loss doesn't increase with each subsequent reoccurrence.

Mean differences and 95% confidence intervals between treatment arms for healthcare resource use, costs and EQ-5D-5L scores will be estimated using parametric methods. Sensitivity analyses will be conducted in line with best practice to explore any uncertainties, for instance, how to deal with missing data should that be a problem or the impact of perspective on results. Costs related to antibiotic resistance will not be fully captured given the timeframe for the study and the difficulties of measuring these effects. Whilst undertaking economic modelling could capture a longer time horizon, the evidence to inform this approach would be beyond the scope of this trial. Presenting the costs and outcomes in a disaggregated format will allow future studies modelling the costs of antibiotic resistance to incorporate evidence from this study if appropriate. A detailed Health Economic Analysis Plan (HEAP) will be written and reviewed prior to the trial database being locked.

9 REGULATORY COMPLIANCE

9.1 CLINICAL TRIAL AUTHORISATION

This trial has a Clinical Trial Authorisation from the UK Competent Authority the Medicines and Healthcare products Regulatory Agency (MHRA) and a Favourable Research Ethics Committee (REC) Opinion

9.2 DEVIATIONS AND SERIOUS BREACHES

9.2.1 Protocol Compliance

A protocol deviation is any noncompliance with the trial protocol, GCP, or Manual of Procedure requirements. Any deviation occurring at sites should be reported to the SCTU and the local R&D Office immediately. As a result of deviations SCTU will advise of and/or undertake any corrective and preventative actions as appropriate. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

9.2.2 Serious Breaches

A "serious breach" is a breach which is likely to effect to a significant degree –
- The safety or physical or mental integrity of the participants of the trial; or
- The scientific value of the trial.

All serious protocol deviations/violations and serious breaches of Good Clinical Practice and/or the trial protocol will immediately be reported to the regulatory authorities and other organisations, as required in the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

10 ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 as revised and recognised by governing laws and EU Directives. Each participant's consent to participate in the trial should be obtained after a full explanation has been given of treatment options, including the conventional and generally accepted methods of treatment. The right of the participant to refuse to participate in the trial without giving reasons must be respected.

After the participant has entered the trial, the treating centre may give alternative treatment to that specified in the protocol, at any stage, if they feel it to be in the best interest of the participant. However, reasons for doing so should be recorded and the participant will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the participant

remains free to withdraw at any time from protocol treatment and trial follow-up without giving reasons and without prejudicing their further treatment.

10.1 RESEARCH ETHICS COMMITTEE REVIEW (REC) AND REPORTS

The trial protocol has received the favourable opinion of a Research Ethics Committee or Institutional Review Board (IRB) in the approved national participating countries.

An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended.

Within one year after the end of trial, the Chief Investigator will submit a final report with the results, including any publication/abstracts, to the REC.

10.2 SPECIFIC ETHICAL CONSIDERATIONS

None.

10.3 INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to the principles of GCP.

Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to the participant by appropriately delegated staff with knowledge in obtaining informed consent with reference to the participant information sheet. This information will emphasise that participation in the trial is voluntary and that the participant may withdraw from the trial at any time and for any reason. The participant will be given the opportunity to ask any questions that may arise and provided the opportunity to discuss the trial with family members, friend or an independent healthcare professional outside of the research team and time to consider the information prior to agreeing to participate.

10.4 DATA PROTECTION AND CONFIDENTIALITY

SCTU will preserve the confidentiality of participants taking part in the trial. The investigator must ensure that participant's anonymity will be maintained and that their identities are protected from unauthorised parties. On eCRFs participants will not be identified by their names, but by an identification code and their initials. Participant's postcodes are collected as a proxy of socioeconomic status, these will be translated into a deprivation code and will not be stored or used in the analysis.

11 SPONSOR

SCTU, Chief Investigator and other appropriate organisations have been delegated specific duties by the Sponsor and this is documented in the trial task allocation matrix.

The duties assigned to the trial sites (NHS Trusts or others taking part in this trial) are detailed in the Non-Commercial Agreement.

11.1 INDEMNITY

The University of Southampton's public and professional indemnity insurance policy provides an indemnity to UoS employees for their potential liability for harm to participants during the conduct of the research. This does not in any way affect an NHS Trust's responsibility for any clinical negligence on the part of its staff.

11.2 FUNDING

The NIHR Health Technology Assessment Programme are funding this trial.

11.3 SITE PAYMENTS

The payments assigned to the trial sites (NHS Trusts or others taking part in this trial) are detailed in the Site Agreement.

This trial is adopted onto / automatically eligible for the NIHR portfolio. This enables Trusts to apply to their comprehensive local research network for service support costs, if required.

11.4 PARTICIPANT PAYMENTS

Participants will not be paid for participation in this trial.

12 TRIAL OVERSIGHT GROUPS

The day-to-day management of the trial will be co-ordinated through the SCTU and oversight will be maintained by the Trial Management Group, the Trial Steering Committee and the Data Monitoring and Ethics Committee. An executive management group comprised of a core group of co-applicants and SCTU staff will also meet regularly during key stages of the trial.

12.1 TRIAL MANAGEMENT GROUP (TMG)

The TMG is responsible for overseeing progress of the trial, including both the clinical and practical aspects. The Chair of the TMG will be the Chief Investigator of the trial.

The COAT TMG charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the TMG, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.

12.2 TRIAL STEERING COMMITTEE (TSC)

The TSC act as the oversight body on behalf of the Sponsor and Funder. The TSC will meet (either virtually or in-person) at least yearly and have at least one further teleconference meeting during the year. The majority of members of the TSC, including the Chair, should be independent of the trial.

The COAT TSC charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the TSC, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.

12.3 INDEPENDENT DATA MONITORING COMMITTEE (IDMC) /DATA MONITORING AND ETHICS COMMITTEE (DMEC)

The aim of the DMEC is to safeguard the interests of trial participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the trial.

The COAT DMEC charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the DMEC, including the timing of meetings, methods of providing information to and from the DMEC, frequency and format of meetings, statistical issues and relationships with other trial committees.

13 DATA MANAGEMENT

Participant data will be entered remotely at site, by the COAT central study team and by participants via ePRO and retained in accordance with the current Data Protection Regulations. Informed consent may also be collected via the current trial database in accordance with current Data Protection Regulations. The PI and/or trial coordinator is responsible for ensuring the accuracy, completeness, and timeliness of the data entered.

The participant data is pseudo anonymised by assigning each participant a participant identifier code which is used to identify the participant during the trial and for any participant- specific clarification between SCTU and site.

The Participant Information Sheet and Informed Consent Form will outline the participant data to be collected and how it will be managed or might be shared; including handling of all Patient Identifiable Data (PID) and sensitive PID adhering to relevant data protection law.

Trained personnel with specific roles assigned will be granted access to the eCRF. eCRF completion guidelines will be provided to the investigator sites to aid data entry of participant information.

Only the Investigator and personnel authorised by them including the COAT central study team should enter or change data in the eCRFs.

A Data Management Plan (DMP) providing full details of the trial specific data management strategy for the trial will be available and a Trial Schedule with planned and actual milestones, CRF tracking and central monitoring for active trial management created. Timelines for key tasks will be specified in the DMP and shared with sites during the Site Initiation Visits.

Data queries will either be automatically generated within the eCRF, or manually raised by the trial team, if required. All alterations made to the eCRF will be visible via an audit trail which provides the identity of the person who made the change, plus the date and time.

At the end of the trial after all queries have been resolved and the database frozen, the PI will confirm the data integrity by electronically signing all the eCRFs. The eCRFs will be archived according to SCTU policy and a PDF copy including all clinical and Meta data returned to the PI for each participant.

Data may be requested from the Data Access Committee at SCTU. Any request will be considered on a monthly basis.

14 DATA SHARING REQUESTS FOR RESULTS THAT ARE AVAILABLE IN THE PUBLIC DOMAIN

In order to meet our ethical obligation to responsibly share data generated by interventional clinical trials, SCTU operate a transparent data sharing request process. As a minimum, anonymous data will be available for request from three months after publication of an article, to researchers who provide a completed Data Sharing request form that describes a methodologically sound proposal, for the purpose of the approved proposal and if appropriate a signed Data Sharing Agreement. Data will be shared once all parties have signed relevant data sharing documentation.

Researchers interested in our data are asked to complete the Request for Data Sharing form (CTU/FORM/5219) [template located on the SCTU web site, www.southampton.ac.uk/ctu] to provide a brief research proposal on how they wish to use the data. It will include; the objectives, what data are requested, timelines for use, intellectual property and publication rights, data release definition in the contract and participant informed consent etc. If considered necessary, a Data Sharing Agreement from Sponsor may be required.

15 MONITORING

15.1 CENTRAL MONITORING

Data stored at SCTU will be checked for missing or unusual values and checked for consistency within participants over time. Any suspect data will be returned to the site in the form of data queries, or ePRO entry clarifications may be sought from the participant over the phone. There are a number of monitoring principles in place at SCTU to ensure reliability and validity of the trial data, which are detailed in the trial monitoring plan.

A copy of the consent form will be sent to the SCTU using the University of Southampton's SafeSend service or the University approved secure email address, to allow for central monitoring.

15.2 CLINICAL SITE MONITORING

The Trial will be monitored and audited in accordance with SCTU procedures as detailed in the Trial Monitoring Plan.

All trial related documents will be made available on request for monitoring and audit by SCTU, UoS and REC and for inspection by other relevant bodies. Prior to the trial start, the trial site will be advised of the anticipated frequency of the monitoring visits. The Site Lead will receive reasonable notification prior to any monitoring visits.

15.2.1 Source Data Verification

Upon receipt of a request from SCTU, the PI will allow the SCTU direct access to relevant source documentation for verification of data entered onto the eCRF (taking into account data protection regulations). Access should also be given to trial staff and departments (e.g. pharmacy).

The participants' medical records and other relevant data may also be reviewed by appropriate qualified personnel independent from the SCTU appointed to audit the trial, including representatives of the Competent Authority. Details will remain confidential and participants' names will not be recorded outside the trial site without informed consent.

15.3 SOURCE DATA

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

15.4 AUDITS AND INSPECTIONS

The trial may be participant to inspection and audit by University of Southampton (under their remit as Sponsor), SCTU (as the Sponsor's delegate) and other regulatory bodies to ensure adherence to the principles

of GCP, Research Governance Framework for Health and Social Care, applicable contracts/agreements and national regulations.

16 RECORD RETENTION AND ARCHIVING

Trial documents will be retained in a secure location during and after the trial has finished.

The PI or delegate must maintain adequate and accurate records to enable the conduct of the trial to be fully documented and the trial data to be subsequently verified. After trial closure the PI will maintain all source documents and trial related documents. Archiving will be authorised by the Sponsor following submission of the end of trial report. All source and trial related documents will be retained for a period of 25 years following the end of the trial.

Sites are responsible for archiving the ISF and participants' medical records. Following the period of retention destruction of essential documents will require authorisation from the Sponsor.

The Sponsor is responsible for archiving the TMF and other relevant trial documentation.

17 PUBLICATION POLICY

Data from all centres will be analysed together and published as soon as possible.

Individual investigators may not publish data concerning their patients that are directly relevant to questions posed by the trial until the Trial Management Group (TMG) has published its report. The TMG will form the basis of the Writing Committee and advise on the nature of publications. All publications shall include a list of investigators, and if there are named authors, these should include the Chief Investigator, Co-Investigators, Trial Manager, and Statistician(s) involved in the trial. Named authors will be agreed by the CI and Director of SCTU. If there are no named authors then a 'writing committee' will be identified.

If they consent to receiving the information, participants will be notified of the results of the trial via the site where they were recruited or from the COAT central study team. The data will be published in a peer reviewed journal and available in the public domain. Our PPI group will assist with writing the report to ensure the language is appropriate and accessible.

18 REFERENCES

1. Bakhit M, Hoffmann T, Santer M, Ridd M, Francis N, Hummers E, et al. Comparing the quantity and quality of randomised placebo-controlled trials of antibiotics for acute respiratory, urinary, and skin and soft tissue infections: a scoping review. BJGP Open. 2020;4(4).
2. Dupuy A, Benchikhi H, Roujeau JC, Bernard P, Vaillant L, Chosidow O, et al. Risk factors for erysipelas of the leg (cellulitis): case-control study. BMJ. 1999;318(7198):1591-4.
3. Ellis Simonsen SM, van Orman ER, Hatch BE, Jones SS, Gren LH, Hegmann KT, et al. Cellulitis incidence in a defined population. Epidemiol Infect. 2006;134(2):293-9.
4. Miller LG, Eisenberg DF, Liu HH, Chang CL, Wang Y, Luthra R, et al. Incidence of skin and soft tissue infections in ambulatory and inpatient settings, 2005-2010. Bmc Infect Dis. 2015;15.
5. Haydock SF BS, Wall EC, Connick RM. Admissions to a U.K. teaching hospital with nonnecrotizing lower limb cellulitis show a marked seasonal variation. Br J Dermatol. 2007.
6. Smith E PM, Thomas K. Which outcomes are reported in cellulitis trials? Results of a review of outcomes included in cellulitis trials and a patient priority setting survey. British Journal of Dermatology. 2018.
7. Tun K, Shurko JF, Ryan L, Lee GC. Age-based health and economic burden of skin and soft tissue infections in the United States, 2000 and 2012. PLoS One. 2018;13(11):e0206893.
8. Francis NA, Hood K, Lyons R, Butler CC. Understanding flucloxacillin prescribing trends and treatment non-response in UK primary care: a Clinical Practice Research Datalink (CPRD) study. J Antimicrob Chemother. 2016;71(7):2037-46.
9. Dolk FCK, Pouwels KB, Smith DRM, Robotham JV, Smieszek T. Antibiotics in primary care in England: which antibiotics are prescribed and for which conditions? J Antimicrob Chemoth. 2018;73:2-10.
10. Corwin P, Toop L, McGeoch G, Than M, Wynn-Thomas S, Wells JE, et al. Randomised controlled trial of intravenous antibiotic treatment for cellulitis at home compared with hospital. Brit Med J. 2005;330(7483):129-32b.
11. McNamara DR, Tleyjeh IM, Berbari EF, Lahr BD, Martinez JW, Mirzoyev SA, et al. Incidence of lower-extremity cellulitis: A population-based study in Olmsted County, Minnesota. Mayo Clin Proc. 2007;82(7):817-21.
12. Oh CC, Ko HC, Lee HY, Safdar N, Maki DG, Chlebicki MP. Antibiotic prophylaxis for preventing recurrent cellulitis: a systematic review and meta-analysis. J Infect. 2014;69(1):26-34.
13. Carter K, Kilburn S, Featherstone P. Cellulitis and treatment: a qualitative study of experiences. Br J Nurs. 2007;16(6):S22-4, S6-8.
14. (NICE) NIfHaCE. Cellulitis and erysipelas: antimicrobial prescribing 2019 [Available from: https://www.nice.org.uk/guidance/NG141.
15. Kilburn SA, Featherstone P, Higgins B, Brindle R. Interventions for cellulitis and erysipelas. Cochrane Database Syst Rev. 2010(6):CD004299.
16. Hanretty AM, Gallagher JC. Shortened Courses of Antibiotics for Bacterial Infections: A Systematic Review of Randomized Controlled Trials. Pharmacotherapy. 2018;38(6):674-87.
17. Hepburn MJ, Dooley DP, Skidmore PJ, Ellis MW, Starnes WF, Hasewinkle WC. Comparison of short-course (5 days) and standard (10 days) treatment for uncomplicated cellulitis. Arch Intern Med. 2004;164(15):1669-74.
18. Prokocimer P, De Anda C, Fang E, Mehra P, Das A. Tedizolid Phosphate vs Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections The ESTABLISH-1 Randomized Trial. Jama-J Am Med Assoc. 2013;309(6):559-69.
19. Moran GJ, Fang E, Corey GR, Das AF, De Anda C, Prokocimer P. Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a randomised, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis. 2014;14(8):696-705.
20. Cross ELA, Jordan H, Godfrey R, Onakpoya IJ, Shears A, Fidler K, et al. Route and duration of antibiotic therapy in acute cellulitis: A systematic review and meta-analysis of the effectiveness and harms of antibiotic treatment. J Infect. 2020;81(4):521-31.
21. Brindle R, Williams OM, Barton E, Featherstone P. Assessment of Antibiotic Treatment of Cellulitis and Erysipelas: A Systematic Review and Meta-analysis. JAMA Dermatol. 2019;155(9):1033-40.
22. Cranendonk DR OB, van Agtmael MA,. Antibiotic treatment for 6 days versus 12 days in patients with severe cellulitis: a multicentre randomized, doubleblind, placebo-controlled, non-inferiority trial. Clin Microbiol Infect. 2020.

23. Mistry K, Sharma S, Patel M, Grindlay D, Janjuha R, Smart P, et al. Clinical response to antibiotic regimens in lower limb cellulitis: a systematic review. Clin Exp Dermatol. 2021;46(1):42-9.
24. Langdon A, Crook N, Dantas G. The effects of antibiotics on the microbiome throughout development and alternative approaches for therapeutic modulation. Genome Med. 2016;8(1):39.
25. Tacconelli E DAG, Cataldo MA, Pozzi E, Cauda R. Does antibiotic exposure increase the risk of methicillin-resistant Staphylococcus aureus (MRSA) isolation? A systematic review and meta-analysis. J Antimicrob Chemother. 2008.
26. J. ON. Tackling drug-resistant infections globally: final report and recommendations. 2016.
27. Government H. Tackling antimicrobial resistance 2019-2024: The UK's five-year national action plan.; 2019.
28. Agency UHS. Public Health England. English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR): Report 2019 to 2020.; 2020.
29. Sarah Kg Tonkin-Crine PST, Oliver van Hecke, Kay Wang, Nia W Roberts, Amanda McCullough, Malene Plejdrup Hansen, Christopher C Butler, Chris B Del Mar. Clinician-targeted interventions to influence antibiotic prescribing behaviour for acute respiratory infections in primary care: an overview of systematic reviews. Cochrane Database Syst Rev. 2017
30. Thomas KS, Brindle R, Chalmers JR, Gamble B, Francis NA, Hardy D, et al. Identifying priority areas for research into the diagnosis, treatment and prevention of cellulitis (erysipelas): results of a James Lind Alliance Priority Setting Partnership. British Journal of Dermatology. 2017;177(2):541-3.
31. E Smith MP, K S Thomas Which outcomes are reported in cellulitis trials? Results of a review of outcomes included in cellulitis trials and a patient priority setting survey. Br J Dermatol. 2018.
32. Gillian A Hawker SM, Tetyana Kendzerska, Melissa French. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res (Hoboken). 2011.
33. Melissa E Stauffer 1 SDT, Douglas J Watson, Paul M Peloso, Alan Morrison. Definition of nonresponse to analgesic treatment of arthritic pain: an analytical literature review of the smallest detectable difference, the minimal detectable change, and the minimal clinically important difference on the pain visual analog scale. Int J Inflam. 2011.
34. Mette Frahm Olsen EB, Maria Damkjær Hansen, Jørgen Hilden, Nino Emanuel Landler, Britta Tendal, Asbjørn Hróbjartsson Pain relief that matters to patients: systematic review of empirical studies assessing the minimum clinically important difference in acute pain. BMC Med. 2017.
35. Mason JM, Thomas KS, Crook AM, Foster KA, Chalmers JR, Nunn AJ, et al. Prophylactic antibiotics to prevent cellulitis of the leg: economic analysis of the PATCH I & II trials. PLoS One. 2014;9(2):e82694.

19 APPENDICES

None.

20 SUMMARY OF SIGNIFICANT CHANGES TO THE PROTOCOL

Protocol date and version	Summary of significant changes
V1 06-Dec-2022	First written
V2 11-Dec-2023	1) :Section 5.5.2 of the protocol has been updated to include that the new infographic will be sent to participants at the same time as the IMP. The ISRCTN registration number and full funder acknowledgement has also been added. The sponsor's room number has been removed. We have also updated the reporting procedures in the protocol to ensure consistency for AE reporting. The sentence "all adverse events will need to be reported from the day of consent up to 28 days" has been updated to "all adverse events will need to be reported from the first administration of the participants NHS antibiotic prescription up to 28 days". Subsequent sections of the reporting timeline have also been changed to "Day 28", where "28 days" is mentioned. 2) : Section 4.1 has been updated to reflect that a longer consenting window and different models of recruitment to reflect that participants can be consented remotely via the trial database (Openclinica) either by the participating GP practice, or by a member of the COAT central study team at SCTU. Participants can also be assessed for eligibility virtually by their practice.
V3 – 19-July-2024	The main changes are to sections 4 and 5 of the protocol which have been updated to clarify and separate out the study processes in terms of screening, confirming eligibilityand consenting. Section 4 now includes an infographic for sites which outlines time frames and study procedures. In addition, the protocol also now states that the COAT central study team will send daily text messages/emails to participants to remind them about completing their questionnaire. Exclusion criteria list updated so that insect bites is added to the body of the text, instead of the sub section to make it more visible. New progress criteria table added to reflect outcome of the 6-month pilot funder report. The term clinician has been removed and replaced with either a medically qualified doctor or another suitable term to avoid ambiguity. 72 hour randomisation window updated to 72+ hours.
V4 16-Dec-2024	Method of sending PID to the COAT study team has changed from Safesend to secure email. eConsent method has been changed from Openclinica to Adobesign and this will be done by the central team only. Study team will also explore the possibility of using translated PIS and ICF.