The DANCE study:
Duration of ANtibiotic therapy for CEllulitis
(2013)

PROTOCOL

VERSION 9.4
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PROTOCOL TITLE: The DANCE study: Duration of ANtibiotic therapy for CEllulitis

Protocol ID	NL44512.018.13
Short title	DANCE study
Title used in information for volunteers	Antibiotica voor cellulitis: 6 of 12 dagen? (Antibiotics for cellulitis: 6 or 12 days?)
EudraCT number	2013-002106-31
ABR number	NL44512.018.13
ClinicalTrials.gov number	Trial will be entered after approval of METC, and before inclusion of the first patient
Version	9.4
Date	July 27th, 2017
Study type	A multicentre, randomized, double-blind, placebo-controlled non-inferiority trial
Target sample size	316 patients
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TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
DSMB	Data Safety Monitoring Board
EudraCT	European drug regulatory affairs Clinical Trials
GCP	Good Clinical Practice
IB	Investigator's Brochure
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
(S)AE	(Serious) Adverse Event
SPC	Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
Wbp	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: Cellulitis is among the most common infections leading to hospitalization, yet the optimal duration of therapy remains ill defined. Pragmatically Dutch guidelines advise 10 to 14 days of treatment with flucloxacillin, which is currently standard of care. Recently it has been shown that antibiotic treatment for pneumonia and urinary tract infections can safely and significantly be shortened. Importantly, in an outpatient setting, treatment of uncomplicated cellulitis with 5 days of antibiotics was as effective as 10 days. We hypothesize that there is no difference in outcomes when patients hospitalized with cellulitis are treated with either a short-course (6 days) or standard-course (12 days) of antibiotics.

Objective: To determine whether 6 days of flucloxacillin has equal efficacy compared to 12 days in patients hospitalized with cellulitis who after 5 days of initial therapy have substantially improved, defined as absence of fever (temp > 38.0°C) and improvement in cellulitis severity score (self-reported or investigator-assessed).

Study design: Multicentre, randomized, double-blind, placebo-controlled non-inferiority trial.

Study population: Patients hospitalized for cellulitis, > 18 years of age.
Power calculation (non-inferiority design): a total sample size of 316 randomized patients gives 80% power to reject the null hypothesis of non-inferiority assuming a 15% failure rate, considering a difference of 10% as equivalence limit, with a 0.05 significance level.

Intervention: 6 days of flucloxacillin followed by another 6 days of flucloxacillin or placebo.

Main study parameters/endpoints: The primary endpoint is resolution of cellulitis at 14 days, defined as disappearance of warmth and tenderness at the site of infection, with substantial improvement in eythema and edema, and without recurrence by day 28, defined as the need of additional antibiotic therapy for cellulitis.
Secondary study endpoints include a test of cure with a different set of criteria for cure by day 14 and relapse by day 28, recurrence of cellulitis by day 90, speed of recovery as determined by improvement in cellulitis severity score and self assessment of subjective pain and swelling on VAS scales (0-10), Health-related Quality of Life (Dutch SF-36 questionnaire), and health care resource utilisation as determined by total antibiotic use and effect on direct and indirect health-care associated costs (economic evaluation and budget impact analysis).

Statistical analysis: Analysis will be based on intention-to-treat basis. Groups will be compared for the primary endpoint with Chi-squared test and Cochran-Mantel-Haenszel test for adjustment for the baseline covariates to evaluate the non-inferiority hypothesis. Secondary outcome parameters will be analyzed using Chi-squared test, two group t-test or Mann-Whitney test when appropriate.

Nature and extent of the burden and risks associated with participation: All study participants will have to complete a maximum of five sets of questionnaires (some by phone) and a maximum of five venous punctures. Potential risks include inferiority of 6 days of antibiotics compared to 12 days of treatment, i.e. a slower recovery of patients in the intervention group. Given the results of earlier trials on shortening of antibiotic therapy in pneumonia and urinary tract infections, we do not expect this to be the case. In our view the

small risk that 6 days will be inferior compared to 12 days offsets the profits which a shortening of antibiotic therapy for cellulitis potentially yields.

1. INTRODUCTION AND RATIONALE

Cellulitis

Cellulitis is a common acute, spreading pyogenic inflammation of the skin (dermis) and subcutaneous tissue, usually complicating a wound, ulcer or dermatosis.[1] Erysipelas, while originally a separate disease entity with a well-defined raised edge and more prominent systemic symptoms, is now considered a manifestation of cellulitis, due to the ability of cellulitis to extend to the dermal layers, making it practically impossible to make a meaningful distinction[2]. Cellulitis is considered to be severe if the patient is admitted to the hospital to receive intravenous antibiotics (please refer to Appendix I for the background of the definition of cellulitis used). Cellulitis is among the most frequent infections leading to hospitalization.[3,4] The incidence of bacterial skin infection in the Netherlands has increased considerably in recent years, up to 32 per 1000 patients per year (Landelijk Medische Registratie, 2012). This is probably due to an increase in both the elderly population and the number of patients with immunosuppressive conditions such as diabetes.[5] In addition, clinical relapse occurs in 12 to 20% of patients.[6,7] 6% of all patients with a bacterial skin infection who consult the general practitioner will be hospitalized. In the USA alone it is estimated that cellulitis results in more than 600,000 hospitalizations per year, which represents more than a 50% relative increase in the past decade.[3] In the Netherlands the diagnosis bacterial cellulitis and erysipelas are made approximately 28.000 times each year, resulting in over 2500 hospitalizations. Total health-care associated costs, mostly due to costs of hospitalisation, were estimated to be over 17 million euro each year during 1998-2000[8].

Antibiotic treatment

For cellulitis initial antibiotic treatment is given intravenously (i.e., the patient is hospitalized) if the lesion is spreading rapidly, if the systemic response is prominent with fever and general malaise, when oral antibiotic therapy has failed, or if there are coexisting conditions such as immunodeficiency, neutropenia, asplenia or pre-existing edema.[1,3] As most cases of cellulitis are caused by Gram-positive bacteria (*Streptococci* and *Staphylococcus aureus*), beta-lactam antibiotics with activity against penicillinase-producing *S. aureus* are the drugs of choice. In the Netherlands, flucloxacillin is the recommended treatment regiment for hospitalized patients with cellulitis (dose: po 500 mg 4dd1 or iv 1000 mg 4dd1; www.swab.nl). Clindamycin is given in case of an allergy to beta-lactam antibiotics.[9] Recommended treatment duration for all antibiotics is 10 to 14 days.[9] However, the duration of therapy required remains ill defined*:* the need for 10-14 days of treatment is not evidence based. A recent systematic review concluded that there is little evidence for duration of antibiotic therapy[10]. Of note, antibiotic resistance of *S. aureus* (MRSA, Methicillin Resistant *S. aureus*,) is an increasing problem in many parts of the world. In the Netherlands, MRSA prevalence is still well below 5%.[9,11]

Justification of therapeutic intervention

It has previously been postulated that after several days of therapy residual symptoms persist due to inflammation rather than active infection, which means that prolonged antibiotic therapy is not indicated. This notion is underscored by a clinical study in which 5 days of antibiotic therapy proved to be equally effective for uncomplicated cellulitis in an outpatient setting compared to 10 days of therapy.[12] In addition, more recent studies have shown that antibiotic treatment for pneumonia[13,14], urinary tract infections[15,16] and acute

pyelonephritis[17] can safely and significantly be shortened. Still, optimal treatment strategies in terms of duration of antibiotic therapy for cellulitis warranting hospitalization are still ill defined. In light of the aforementioned studies, it is likely that the currently advised 10-14 days of antibiotic therapy can be safely and significantly reduced as well. It is important that evidence-based strategies are developed to optimize outcome, antibiotic use, and use of health care resources.

Hypothesis
We hypothesize that there is no difference in outcomes when patients hospitalized with cellulitis are treated with either a short-course (6 days) or standard-course (12 days) of antibiotics.

2. OBJECTIVES

2.1 Primary objective

- To determine whether 6 days of flucloxacillin has equal efficacy compared to 12 days in patients hospitalized with cellulitis who after 5 days of initial therapy have substantially improved, defined as absence of fever (temp > 38.0°C) and improvement in cellulitis severity score.

2.2 Secondary objectives

- To assess differences in the frequency of relapse by day 90
- To assess differences in (A) speed of improvement of symptoms and (B) quality of life
- To assess the effects of 6 days of antibiotics compared to 12 days on total antibiotic use and health care costs

2.3 Tertiary objectives

- To analyse inflammatory and microbiological parameters in the (epi)dermis and blood during cellulitis, to explore markers of disease severity, determinants of therapeutic failure, and tools for pathogen detection

3. STUDY DESIGN

3.1 Design

The DANCE study is a prospective, randomized, observer, physician and patient blinded, placebo-controlled, multicentre non-inferiority trial with two parallel groups. Patients hospitalized with cellulitis and responding to initial therapy, defined as absence of fever (temp > 38.0°C) and improvement in cellulitis severity score (self-reported or investigator-assessed) by day 5, will be randomized with a 1:1 allocation into one of two groups, who will receive different treatments after the 6th day:

- Regular treatment group: after the initial 6 days of flucloxacillin, another 6 days of oral flucloxacillin.
- Intervention group: after the initial 6 days of flucloxacillin, 6 days of oral placebo.

Study protocol is based on the SPIRIT 2013 guidance for clinical trial protocol development[18].

3.2 Duration and setting

The estimated duration of the study is three and a half years (see also 3.4 and 4.1); for individual patients the study duration will be 90 days. The trial will be performed in the Internal Medicine and Dermatology departments of the hospitals mentioned above, and their respective outpatient clinics after discharge. Depending on patient preference and availability of clinical examination rooms at the outpatient clinics, the dedicated research nurse/investigators can also visit participants at their home address. Informed consent will be obtained by the dedicated research nurse/ investigators, after the attending physician inquires about willingness to participate in a clinical trial.

3.3 Time schedule of study procedures for participants

	Day 0	Day 2-3	Day 5-6	Day 14-15	Day 28-29	Day 90
Informed consent	X					
In- and exclusion criteria	X					
Physical examination	X		X	X	X	
Laboratory measurements (usual care)	X					
Venous puncture	X	X	X	X	X	
Skin biopsy (see chapter 7)	X					
Clinical cellulitis score	X	X	X	X	X	
Self assessment score (0-10 scale)	X	X	X	X	X	X
SF-36 questionnaire & EQ-5D	X				X	X
Health care utilization questionnaire			X		X	X
Skin swabs (see chapter 7)	X			X		

Table 1. Time table of study procedures for participants

Up to day 28-29, patients will be evaluated face to face either in the clinic or at home. Self assessment scores and questionnaires to be performed on day 90 will be mailed to patients beforehand. On day 90, the investigators will review the answers and scores by telephone. Laboratory measurements collected through usual care will be collected when available. In exceptional cases, where inclusion would be hampered by people's willingness or ability to have so many follow-up visits, the decision can be made by the investigators to perform the day 28-29 visit solely by telephone. In this case the primary endpoint, questionnaires and medication information would be assessable. Physical examination, cellulitis severity score measurement and blood collection will not be possible.

The above table displays the ideal time schedule for participants. However, patients can be included until 72 hours after admission. When patients are included during 24-72 hours, the day 2-3 visit is skipped. The check for improvement on day 5-6 then also allows for self-reported improvement as marker for clinical improvement, due to the investigator not being present at the time when the disease was likely at its most severe. Self-reported improvement is also rated using the seven aspects of the cellulitis severity score; patients will be asked if they think that they have improved, taking all those aspects into account.

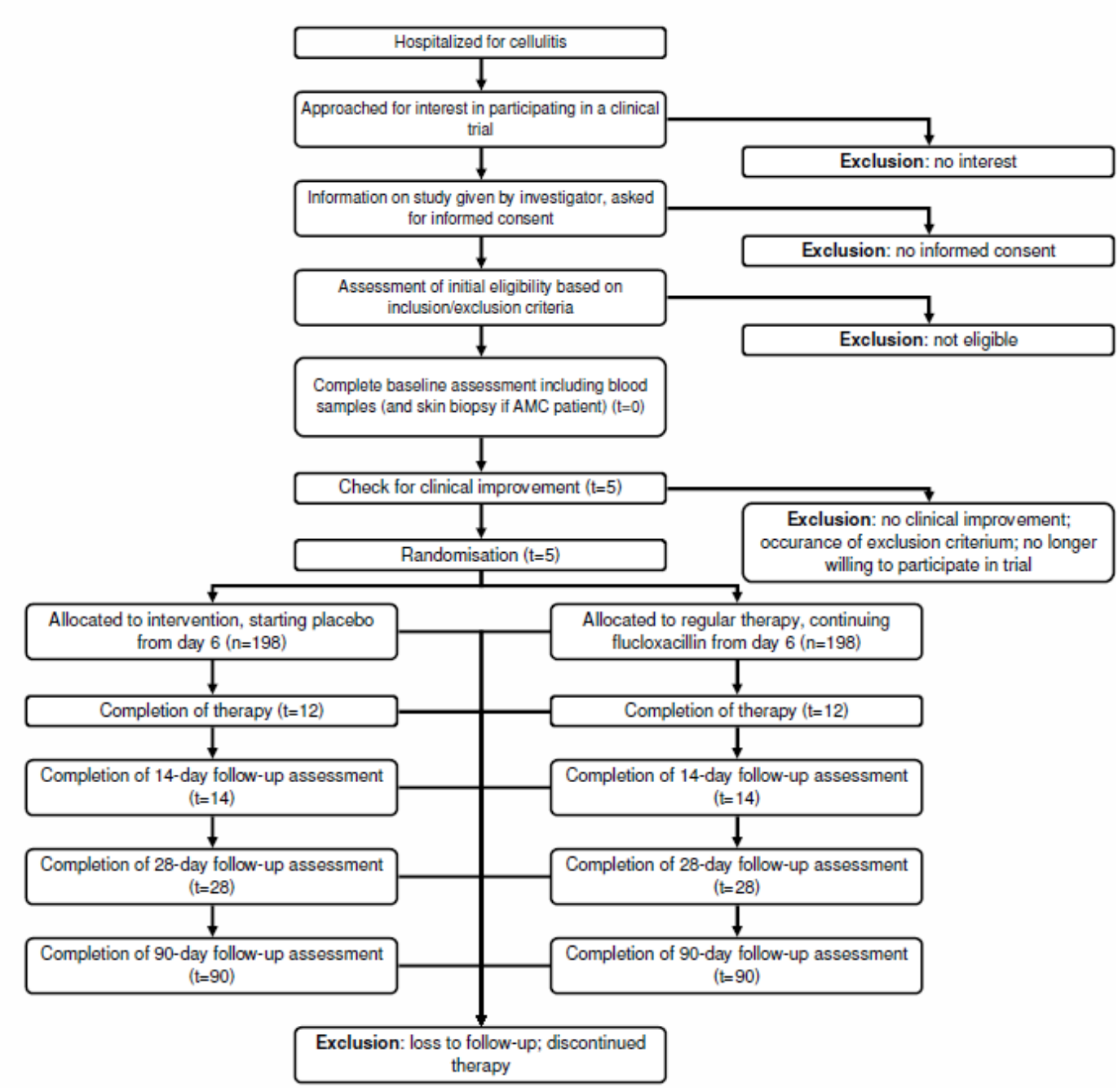

Figure 1. Flow diagram for study participants

3.4 Time schedule of the study

Months 1-4:	Preparation of study and obtaining ethical approval
Months 5-44:	Enrolment of patients
Month 44:	Last patient enrolled
Month 47:	Last follow-up visit of last enrolled patient
Months 47-48:	Analysis of results

4. STUDY POPULATION

4.1 Population

We plan to randomize 316 patients. All adult patients admitted to the hospital with cellulitis (see definition in appendix I) will be eligible for inclusion. The cohort comprises 316 subjects to be recruited by the Departments of Infectious Disease and Dermatology at the Academic Medical Center, the VU Medical Center and the University Medical Center Utrecht in collaboration with 8 affiliated teaching hospitals as mentioned above. These hospitals provide secondary and tertiary care to a large heavily populated urban region of the Netherlands. Participating hospitals have declared that they expect to admit at least 20 suitable cellulitis patients yearly. Assuming that 75% of patients will partake in this study, this brings the estimated recruiting period to approximately 3.5 years (396 patients / (8 centers * 15 patients yearly) = 3.3 years → this number has been adjusted to 316 as of July 2015, which puts the estimated deadline at April 2017). A dedicated research nurse will help with patient enrolment.

If during the enrolment process it is expected that the recruiting period will last longer than 3.5 years, additional hospitals will be approached to participate in the study. The number of inclusions will be evaluated on at least a yearly basis.

As control group for the microbiota analysis from the skin swabs (see 7.3.6), we will include 20 healthy volunteers who are age- and gender-matched to the population of whom the skin swabs are analysed. Eligible volunteers are aged 18 or older, and should not have had cellulitis, abscesses, dermatitis, or psoriasis in their leg in the past 3 months. The rest of the protocol is not applicable to these volunteers, except when specifically mentioned. These patients will have completed their participation in this study, as soon as the skin swab has been taken.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria. Subjects must be:

- Admitted to the hospital to receive intravenous antibiotics for cellulitis/erysipelas. Cellulitis is the general descriptive term suggesting infection and indicating the warmth, erythema and induration of skin and/or subcutaneous tissue, with or without pain (this also includes erysipelas, see appendix I).
- 18 years of age or older
- Capable of giving written informed consent and able to comply with the requirements and restrictions listed in the informed consent form

4.3 Exclusion criteria

As this study focuses on the treatment of cellulitis requiring hospitalization without additional complicating factors, a potential subject who meets any of the following criteria will be excluded from participation:

- Allergy for flucloxacillin, other beta-lactam antibiotics or one of the additives, or flucloxacillin induced hepatitis or liver enzyme disorders.
- Concurrent use of antibiotics for other indications
- Alternative diagnosis accounting for the clinical presentation.
- All cases involving any of the following complicating factors:
    - Use of antibiotics with Gram-positive activity for more than 4 days in the past 7 days
    - Intensive care unit admission during the last 7 days
    - Risk factors associated with Gram-negative pathogens as a causative agent[19]:
        - Chronic or macerated infra-malleolar ulcers, or infra-malleolar ulcers with previous antibiotic treatment, in patients with diabetes mellitus [20]
        - Neutropenia
        - Cirrhosis (Child-Pugh class B or C)
        - Intravenous drug use
        - Human or animal bite
        - Skin laceration acquired in fresh or salt open water
        - Fish fin or bone injuries
    - Severe peripheral arterial disease (Fontaine IV)
    - Severe cellulitis necessitating surgical debridement or fascial biopsy
    - Necrotizing fasciitis
    - Periorbital or perirectal involvement
    - Surgery
    - Life expectancy less than one month

4.4 Sample size calculation

The sample size calculation of is based on three large randomised clinical trials which were published in high impact journals in 2014. From the DISCOVER, ESTABLISH and SOLO trials, information was gathered on cellulitis clinical cure rates as assessed by investigators after therapy:

DISCOVER[21] (dalbavancin vs vancomycin-linezolid): (information from supplementary data)

- Clincal status evaluation at the end of therapy (day 14) of cellulitis patients:
    - Cured: 297/324 and 276/301

ESTABLISH[27] (tedizolid vs linezolid): (information received from authors via e-mail)

- Investigator assessed response at post-therapy evaluation (7-14 days after end of therapy) of cellulitis patients:
    - Cured: 265/301 and 263/307

SOLO[28] (oritavancin vs vancomycin): (information received from authors via e-mail)

- Investigator assessed clinical cure rates at the post-therapy evaluation (7-10 days after end of therapy) of cellulitis patients:
    - Cured: 294/387 and 315/400

Total cure rates:

- (297+276+265+263+294+315) / (324+301+301+307+387+400) = 1710 / 2020 = 84,65% cure rate

A two-group large-sample normal approximation test of proportions with a one-sided 0.050 significance level will have 80% power to reject the null-hypothesis, assuming a success rate

of 85% and considering a difference of 10% between the two groups as equivalence limit, if the sample size of each group is 158. This gives a total sample size of 316 patients.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

After 5-6 days of treatment, patients who respond to therapy – defined as absence of fever (defined as temp > 38.0°C) and clinical improvement since admission (either self-reported or investigator-assessed using the cellulitis severity score) – will be randomized in a blinded fashion with a 1:1 allocation ratio to receive 6 more days of (A) oral flucloxacillin or (B) oral placebo (both starting after day 6):

(A) Regular treatment group: after the initial 6 days of flucloxacillin, another 6 days of oral flucloxacillin.
(B) Intervention group: after the initial 6 days of flucloxacillin, 6 days of oral placebo.

Flucloxacillin treatment is administered as currently advised by the SWAB[9]: flucloxacillin intravenously 1000mg 4dd or orally 500mg 4dd, as a minimum. Some physicians will decide to dose differently, such as intravenously 1000mg 6dd, or orally 1000mg 4-6dd. This is allowed, but will be documented and can be taken into account during the analyses. No added benefit is to be expected from higher or more frequent dosing. Empirical treatment on admission can differ from flucloxacillin, provided it contains a beta-lactam antibiotic with anti-staphylococcal activity. Switch from intravenous medication to the oral route can be initiated before the 6th day of treatment at the discretion of the attending physician, but only if the patient has no fever (temp > 38.0°C) and when the physician is convinced the cellulitis is improving. Patients who do not respond to treatment or whose blood cultures became positive (excluding contamination related positive blood cultures) will not be randomized and will be treated at the discretion of the attending physician. Their definitive diagnosis upon discharge, definitive antibiotic treatment and discharge date will be recorded.

5.2 Use of co-intervention

Other treatment will not be different from daily practice (e.g. diet, contraception, other therapies). Compression therapy should be encouraged, but is not obligatory, and is at the discretion of the attending physician.

5.3 Escape medication

Not applicable.

5.4 Adherence to investigational treatment

As there are only 6 days of trial medication use, we don’t expect there to be issues with adherence. Nevertheless, patients will be thoroughly informed about the necessity of adherence to trial medication. To register the rate of adherence, patients will be asked how many capsules of the trial medication they have left at day 14-15. Reasons for non-adherence will be recorded.

5.5 Retention of participants

Once enrolled, every reasonable effort to follow the participant until the end of study will be made by the investigators. To diminish possible loss to follow-up due to travelling, we primarily visit patients at home for follow-up assessments, but also extend the offer to visit our outpatient clinic.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational products

1. Flucloxacillin tablet 500 mg capsule, ATC code J01CF05

2. Placebo capsule, currently being procured by dr. E.M. Kemper, hospital pharmacist and trial medication specialist

6.2 Summary of findings from non-clinical studies

1. See Summary of Product Characteristics (SPC) of flucloxacillin, paragraph 5.3.

2. Once finished, this will be available in the placebo's IMPD.

6.3 Summary of findings from clinical studies

1. See SPC of flucloxacillin, paragraph 5.1.

2. Not applicable.

6.4 Summary of known and potential risks and benefits

1. See SPC of flucloxacillin, paragraph 4.4 through 4.9. The most frequently seen side effects are gastro-intestinal upset or skin rash, occurring in 0,1-1% of the patients.

2. Not applicable.

6.5 Description and justification of route of administration and dosage

1. See SPC of flucloxacillin, paragraph 4.2. The 500 mg capsules will be administered orally four times/day, as the SWAB guidelines dictate[9]. Some physicians might alter dosing within a certain range as per the "Farmacotherapeutisch Kompas", this will be documented but allowed, although a minimum of 4dd 1000mg i.v. and 4dd 500mg p.o. are maintained.

2. These capsules should likewise be administered orally four times/day.

6.6 Dosages, dosage modifications and method of administration

1. With diminished kidney function (creatinine clearance <10 ml/min or hemodialysis): 500 mg orally every 8 hours.

2. Identical dosage modifications for placebo: one capsule every 8 hours.

6.7 Preparation and labelling of Investigational Medicinal Product

Preparation and labelling of study drugs will be done according to the relevant GMP guidelines by the AMC trial pharmacy.

6.8 Drug accountability

Drug accountability will be done according to the relevant GMP guidelines.

7. METHODS

7.1 Study endpoints

7.1.1 Main study endpoint

The primary endpoint is resolution of cellulitis at 14-15 days, defined as disappearance of warmth and tenderness at the site of infection, with substantial improvement in erythema and edema, and without recurrence by day 28-29, defined as the need of additional antibiotic therapy for cellulitis.

This endpoint is in accordance with the study by Hepburn et al[12], and assumes that erythema and edema take longer to resolve than warmth and tenderness as seen in clinical practice.

7.1.2 Secondary study endpoints

- Resolution of cellulitis at 14-15 days, defined as the absence of fever and an improvement of the combined symptom score of warmth, tenderness, erythema and edema by 2 or more points since patient inclusion (or it has reached 0), and without recurrence by day 28-29, defined as a stable or further improved combined symptom score, absence of fever and no need of additional antibiotic therapy for cellulitis.
    - A per protocol analysis of this endpoint (see paragraph 9.1).
    - Sensitivity analyses with two modifications to the day 28 criteria:
        - Resolution of cellulitis at 14 days, defined as the absence of fever and an improvement of the combined symptom score of warmth, tenderness, erythema and edema by 2 or more points since patient inclusion (or it has reached 0), and with further improvement of the combined symptom score of 1 or more point(s) (or it has reached 0), absence of fever, and no need of additional antibiotic therapy for cellulitis by day 28
        - Resolution of cellulitis at 14 days, defined as the absence of fever and an improvement of the combined symptom score of warmth, tenderness, erythema and edema by 2 or more points since patient inclusion (or it has reached 0), and with further improvement of the combined symptom score of 2 or more point(s) (or it has reached 0), absence of fever, and no need of additional antibiotic therapy for cellulitis by day 28
- Recurrence of cellulitis by day 90 after inclusion, defined as the need of additional antibiotic therapy for cellulitis
- Speed of recovery, as determined by improvement in cellulitis severity score, and self assessment of subjective pain and swelling on Visual Analog Scales scales (0-10), assessed at baseline (day 0), days 2-3, 5-6, 14-15, 28-29 and 90 (day 90 self-assessment only)[12]
- Mean health-related Quality of Life (using the Dutch SF-36 questionnaire and the EQ-5D) at day 0, 28-29 and 90.

- Health care resource utilisation, as determined by total antibiotic use and effect on direct and indirect health-care associated costs

7.1.3 Tertiary study endpoints

- Inflammatory parameters as measure for disease severity derived from whole blood (e.g. sTREM-1, procalcitonin)
- Microbiome analysis, by analysing skin swabs and comparing it with deeper cultures and blood markers
- Single Nucleotide Polymorphisms (SNP's) associated with higher disease severity, analysed in whole blood

7.2 Randomisation, blinding and treatment allocation

Patients who respond to initial therapy will be randomized in a 1:1 ratio at day 5 by the commonly used online ALEA® randomisation software to one of two arms (starting at day 6):

(A) Standard course: after 6 days of flucloxacillin, another 6 days of oral flucloxacillin.

(B) Short course: after 6 days of flucloxacillin, 6 days of oral placebo.

The independent central randomisation service will create a computer generated random schedule in permuted blocks, stratified for diabetes mellitus (yes or no) and study site. The code will only be broken in case the DSMB advises to do so.

Hospital pharmacies are closed during the weekends, but there is a possibility that patients need to be evaluated for their day 5-6 timepoint somewhere during the period between Friday 16:00, and Monday 9:00, while they also need to receive their first dose of study medication in that period. For those patients, normal randomisation would be unfit because the study medication can't be delivered in time. For this minor group of patients, a different method of randomisation is used:

- Before Friday afternoon (ideally on the day 2-3 visit), the researchers will evaluate if the patient is likely to be randomised during the weekend period. If that is the case, the default checks in the eCRF are bypassed, and the patient is preliminarily randomised, thus assigning a randomisation number, and allowing the pharmacy to prepare the appropriate medication.
- Medication for these patients will be prepared by the AMC pharmacy, even if patients are admitted to other study sites. The researchers will collect the medication and store it in their workspace.
- Upon evaluation of the patient during the day 5-6 timepoint, the researchers will judge if the patient is able to be randomised according to the randomisation criteria.
    - If the patient **can** be randomised, the medication will be given as if the patient was randomised as normal. Data entry will be done on the same day, and the built-in eCRF checks will automatically be performed during the night, confirming the appropriate randomisation.

- If the patient **cannot** be randomised, the patient will be treated as any other person unfit for randomisation. Medication will be returned to the AMC pharmacy at the earliest convenience, for reuse if possible, and the drug accountability list entries will be undone. A form will be submitted to the Clinical Research Unit, requesting the undoing of the randomisation, to free up the used randomisation number. This way, the block randomisation will be kept intact without blocks missing patients in the end.
    - Criteria for medication reuse (such as temperature control) will be agreed upon with the pharmacy.

7.3 Study procedures

See paragraph 3.3 for an overview of when study procedures take place.

7.3.1 Baseline characteristics and physical examination

On the first day of enrolment a medical history will be obtained and a physical examination will be performed. The following disease characteristics will be collected:

- Demographic and baseline patient characteristics which might intervene with the main study parameter (confounders), including: age, gender, medication, ethnic background, recreational drug use, comorbidity (including diabetes), smoking, body weight, and residence before hospital admission (e.g. other hospital or nursing home).

- Baseline disease characteristics: cellulitis severity score, cellulitis lesion surface area (cm2)[23], presence of lymphadenopathy (axillary or inguinal), predisposing risk factors for cellulitis[24] (i.e. venous insufficiency, lymphoedema, peripheral arterial disease, immunosuppression, diabetes, trauma, tattoos, ulcers, eczema, tinea pedis and burns), white blood cell count and C-reactive protein (CRP). Photographs will be taken of the laesion as an illustration of the different grades used in scoring. Physical examination will be repeated at day 5-6, 14-15 and 28-29.

- Causative agents: microbiological samples for culture will be collected as aspirates, biopsies, deep swabs or other appropriate methods (superficial swabs are not acceptable) plus blood culture, according to standard of care at each center.

- Hematology and chemistry lab results will be collected through regular care.

- For the 20 healthy volunteers, only basic data such as age, gender, diabetes status and cellulitis history will be recorded.

7.3.2 Cellulitis severity score

The severity of cellulitis will be graded at day 0, 2-3, 5-6, 14-15 and 28-29 using a clinical scoring sheet, in which the investigators assign an assessment (none, mild, moderate, or severe) to each of the following parameters: erythema, warmth, tenderness, edema,

ulceration, drainage, and fluctuance. Grading of each will be standardized among investigators at the beginning of the study by simultaneous readings. The grading designations none through severe are converted into a numerical value of 0 to 3 and these numbers were added to create a physician composite score for purposes of analysis (maximum score 21). This scoring system is the same as used in the most recent therapy duration study.[12] This will allow for measuring of objective (investigator-evaluated) improvement.

Two investigators (the PhD student and the trial nurse) will be responsible for data collection throughout the study. To minimize inter-observer variation and to promote data quality, initial patient assessment will be performed simultaneously by both investigators, and later independently and scores compared/evaluated. When five patients have been assessed independently, resulting in identical scores from both investigators, the investigators will start assessing patients on their own. After 100 patients have been assessed by a single investigator, the investigators will again assess five patients together, to compare scoring and thus improve data quality. During the course of the trial it will be evaluated if additional investigators need to be recruited, due to possible heavy workload and time spent on traveling between sites. Additional investigators will be trained by the PhD student in similar fashion as the trial nurse, with simultaneous and subsequent independent scoring as described above.

Patient self assessment scores will be performed at day 0, 2-3, 5-6, 14-15, 28-29 and 90 by visual Analog Scales (VAS) scores (rated 0-10) in order to determine the amount of pain and swelling patients experience accounting for subjective (patient-evaluated) improvement.

7.3.3 Quality of life

The Dutch SF-36 questionnaire will be used to assess health-related Quality of Life. This will be performed at inclusion and after 28-29 and 90 days. The SF-36 is a validated questionnaire[25], allowing the study population to be compared with equivalent controls in the general Dutch population.

7.3.4 Health care associated costs

Patient information on antibiotic use and health care utilization for cellulitis related complaints (e.g. outpatient services, inpatient admissions, other health care provider services, use of antibiotics and other medication, assist devices or materials) will be collected at certain intervals. This will be collected through Health Care Utilization Questionnaires and patient records at days 5-6, 28-29 and 90. Parallel to this analysis, the EQ-5D-3L questionnaire will be utilized to index the health state of the patients and to accentuate the cost utility analysis.

7.3.5 Blood samples

At day 0, 2-3, 5-6, 14-15 and 28-29 blood will be drawn in order to assess inflammatory markers in blood. This will require extra venous punctures. Up to 42 ml of blood can be taken each visit, adding up to a total of 83,5 ml for non-AMC patients and 99,5 ml for AMC patients (see table for accurate ml per day). Ten (10) ml of EDTA plasma will mainly be

used for measurement of biomarkers and cytokines associated with the inflammatory process, but an extra 10 ml EDTA plasma will be taken from AMC patients on day 0, to be used for RNA and protein analysis in polymorphonuclear (PMN) leukocytes. This will only be done in AMC patients and only on day 0, due to time constraints (preparation for storage of these samples using Ficoll takes several hours and has to be done soon after collection from the patient). After March 30th 2017, no more extra blood will be taken from AMC patients.

Citrated blood will be used to analyze parameters of coagulation that have yet to be determined. An additional PAXgene tube will be taken to be able to isolate RNA from peripheral whole blood leukocytes. To associate certain SNP's in genes encoding for yet to be determined markers (f.e. complement factors), with disease severity and/or outcome, an extra 4,5ml EDTA tube will be collected. Samples will be processed on the day of collection, and stored in -20°C or -80°C (as needed), for analysis at the time that all samples have been collected.

7.3.6 Skin swabs

Using kits bought from Microbiome (Houten, NL), we will explore possible new diagnostic options. Currently, blood cultures and skin cultures are negative more often than not, and (at least for skin cultures) culture results are not always reliable due to uncertainty of contamination. From each patient we'll collect skin swabs (one on the affected limb, one on the contralateral limb), and culture results, and we will process a selected number of skin biopsies for microbiota analysis (protocol is drawn up in collaboration with Microbiome). For a limited number of patients, swabs will be collected from the other limb on day 1 as well (so in case of cellulitis of the leg, swabs will also be taken from each arm), to a total of 4 swabs. After March 9th 2017, no more swabs will be taken from new patients.

From 20 healthy volunteers, which are age- and gender-matched to the population of swabbed patients, one swab will be taken from a(n unaffected) lower leg.

	Volume	Day 0	Day 2-3	Day 5-6	Day 14-15	Day 28-29
Blood						
EDTA tube 10 ml each)	10 ml*	1 tube (AMC: +1)	1 tube	1 tube	1 tube	1 tube
Citrated tube (4.5 ml each)	4,5 ml	2 tubes			2 tubes	
PAXgene tube (2.5 ml each)	2.5 ml	1 tube			1 tube	
EDTA tube for DNA (4,5 ml each)	4,5 ml	1 tube				
Microbiome analysis						
Skin swab	swab	2-4			2 swabs	

		swabs				
Total		26 ml - 36 ml	10 ml	10 ml	21.5 ml	10 mL
Skin biopsy	4 mm	3				

* Depending on study location; AMC patients will have 20 ml taken on the first day, while others have 10 ml taken. The reason for this, is that the extra 10ml takes a lot of time to process, and therefore cannot be done for every patient. Seeing how the quality of this particular sample depends on the time between drawing the blood and processing it, the AMC patients are the best candidates for the best samples. Total blood drawn during the course of the study will thus be 87.5 ml from AMC patients, and 77.5 ml from non-AMC patients. After March 30th 2017, no more extra blood will be taken from AMC patients.

All variables that are going to be analyzed will be on a pre-clinical level and will be of no consequence for individual patients. Only the aggregated information on group level will be important.

7.3.7 Skin biopsies

Skin biopsies will be performed on patients admitted to the AMC (not to other study centers, due to logistic reasons), for use in future studies of the pathobiology of cellulitis. Specific consent will be obtained for the collection of these biopsies. On the day of enrolment, two biopsies (4mm in diameter) will be taken from the afflicted area plus one biopsy (4 mm in diameter) from the contralateral unaffected limb. The majority of the biopsy samples will be formalin fixed and paraffin embedded, or snap-frozen. The formalin-paraffin samples will be used for pathological (immuno)staining, the frozen samples will be used for isolation of mRNA for inflammatory array analysis, selected inflammatory parameters, or microbiome analysis. Additional in-depth immunological analyses can be decided upon during the course of the study.

A deep skin culture will be taken from the biopsy site during the biopsy procedure.

After March 30th 2017, no more skin biopsies will be taken.

7.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

7.5 Replacement of individual subjects after withdrawal

Not applicable, an intention-to-treat analysis will be performed.

7.6 Follow-up of subjects withdrawn from treatment

As per usual care, they might receive an antibiotic treatment schedule at the discretion of their attending physician.

7.7 Premature termination of the study

The sponsor has the right to terminate the study prematurely if there are any relevant medical or ethical concerns, or if completing the study is no longer feasible. If such action is taken, the reasons for terminating the study must be documented. All study subjects still under treatment at the time of termination must undergo a final examination, which must be documented. The METC must be informed without delay if any investigator has ethical concerns about continuation of the trial.
Premature termination of the trial will be considered if:

- The risk-benefit balance for the study subjects changes markedly;
- It is no longer ethical to continue with the shorter duration of antibiotics strategy, as decided by the DSMB;
- It is no longer feasible to complete the study.

8. SAFETY REPORTING

8.1 Section 10 WMO event (temporary halt for reasons of subject safety)

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

8.2 AEs, SAEs and SUSARs

8.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product or experimental interventions. All adverse events, reported by the subject or observed by the investigators, meeting all of the following criteria will be recorded:

- Severity: grade 2, or grade 1 lasting longer than 1 week, graded by the CTCAE (Common Terminology Criteria for Adverse Events, v4.03, June 2010)
- Causality: there needs to be a reasonable suspicion of the AE being an effect of the medical treatment
- Time window: between the moment of inclusion and the day 28 follow-up visit

8.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that at any dose:

-results in death;

-requirement of hospitalisation or prolongation of existing inpatients' hospitalisation for reasons not related to cellulitis

- is life threatening (at the time of the event);

-results in persistent or significant disability or incapacity;

-is a congenital anomaly or birth defect;

- any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse reactions. This holds true for both the coordinating center as well as the participating centers (see PIs as stated above).

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

Of note, since a significant part of included patients is expected to be readmitted to the hospital due to relapse of cellulitis, the requirement of hospitalisation or prolongation of existing inpatients' hospitalisation due to cellulitis is not considered a SAE and will not be reported to the METC but will be subjected by monitoring by the DSMB. SAE's will be reported until the patient reaches the end of study. To facilitate SAE reporting in the period between day 28 and day 90, participants will receive a card on day 28 with instructions to contact the study team in case any SAE occurs.

8.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 8.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
   - Summary of Product Characteristics (SPC) for an authorised medicinal product;
   - Investigator's Brochure for an unauthorised medicinal product.

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.
The expedited reporting of SUSARs through the web portal ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report. This holds true for both the coordinating center as well as the participating centers (see PIs as stated above).

8.3 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.
This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

8.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

8.5 Data Safety Monitoring Board (DSMB)

The assessment of data quality and the monitoring of compliance with the protocol, monitoring of trial conduct and monitoring of evidence for treatment harm will be performed by an independent data monitoring team of the AMC, Amsterdam, the Netherlands.

A Data Safety Monitoring Board (DSMB) will receive and review the progress and accruing data of this trial and will provide advice on the conduct of the trial to the Trial Steering Committee (TSC).

An independent DSMB will evaluate mortality after 198 patients have completed the trial. Given the expected low mortality rates[10,19], the power to detect differences in mortality at this stage will be very low. Therefore, the DSMB will qualitatively evaluate all deaths for their possible relation with the given treatment. Only in case of striking differences between the two arms they will inform investigators and the METC.

Members of the DSMB will be:

- Chair: prof. dr. J. T. van Dissel, internist-infectiologist, President of the Dutch Association for Infectious Diseases (VIZ), LUMC, Leiden, the Netherlands
- Dr. S. Geerlings, internist-infectiologist, President of the Dutch Association of AIDS-treating Physicians (NVHB), AMC, Amsterdam, the Netherlands
- Dr. M. G. W. Dijkgraaf, methodologist, Clinical Research Unit, AMC, Amsterdam, the Netherlands

A separate Charter will describe the roles and responsibilities of the independent DMC, including the timing of meetings, methods of providing information to and from the DMC, frequency and format of meetings and relationships with other committees.

9. STATISTICAL ANALYSIS

9.1 General considerations

For the modified intention to treat analysis, all randomized patients who received at least one dose of study medication will be included. Missing data will be handled with multiple imputation, due to its nature of giving standard errors and P values that incorporate missing-data uncertainty[22].

For the per protocol analyses, only randomized patients whose compliance was clear, and who received at least four days of trial medication (in clinical successes), or one day of trial medication (in clinical failures) will be included.

For the per protocol analysis of our primary outcome, patients are considered clinically cured if there is resolution of cellulitis at 14 days defined as disappearance of warmth and tenderness at the site of infection, with substantial improvement in erythema and edema, and without recurrence by day 28, defined as the need of additional antibiotic therapy for cellulitis. Clinical failure is defined as the persistence or progression of signs and symptoms of the acute process after randomization, or the inability to complete the study owing to adverse events. The response is deemed indeterminate when the patient (i) received less than 80% of the study drug for reasons other than clinical failure, (ii) acquired a concomitant infection outside of the skin requiring antibiotic treatment, (iii) was lost to follow-up, or (iv) died unrelated to the primary diagnosis.

For the per protocol analysis of our first secondary outcome (paragraph 7.1.2), patients are considered clinically cured if there is resolution of cellulitis at 14 days, defined as the absence of fever and an improvement of the combined symptom score of warmth, tenderness, erythema and edema by 2 or more points since patient inclusion (or it has reached 0), and without recurrence by day 28, defined as a stable or further improved combined symptom score, absence of fever and no need of additional antibiotic therapy for cellulitis. The response is deemed indeterminate when the patient (i) received less than 80% of the study drug for reasons other than unblinding / requiring new antibiotics for cellulitis / being unable to continue due to adverse effects, (ii) acquired a concomitant infection outside of the skin requiring antibiotic treatment, (iii) was lost to follow-up, or (iv) died unrelated to the primary diagnosis. Those whose outcomes are not cured or indeterminate are considered clinical failures.

We plan to conduct two subgroup analyses, based on biological plausible explanations, and statistically tested with interaction effects. Diabetes mellitus has recently been shown to affect outcome in patients treated for complicated skin and skin structure infections, through multiple suggested mechanisms[26]. A high cellulitis severity score reflects an extensive local inflammatory response to infection, which might indicate a higher grade of infection that possibly requires more intensive or prolonged antibiotic therapy.

9.2 Baseline characteristics

Statistical analysis will be based on the intention-to-treat principle. Baseline assessments and outcome parameters will be summarized using simple descriptive statistics.

Continuous variables will be summarized with standard descriptive statistics (e.g. mean, median, interquartile ranges, etc). Categorical variables will be summarized with frequencies and percentages. Ninety-five percent confidence intervals will be provided for descriptive statistics, as warranted.

Characteristic	**6-day group**	**12-day group**
Age (yr)		
Male sex (%)		
Ethnicity/race (white/black/asian/other)		
BMI (kg/m^2)		
No. of days of symptoms before presentation (days)		
Antibiotic treatment preceding presentation (%)		
Risk factors: - diabetes mellitus (%) - peripheral arterial disease (%) - lymphoedema (%) - non-diabetic ulcer (%) - venous insufficiency (%) - eczema / dermatitis (%) - trauma (%) - immunosuppression (%) - tattoos (%) - burns (%) - tinea pedis (%) - none (%)		
Cellulitis laesion surface area at presentation (cm^2)		
Axillary or inguinal lymphadenopathy (%)		
Resident at health care centre (%)		
Previous episode(s) of cellulitis (%)		
Smoker (%)		
Temperature at presentation (^oC)		
Leukocyte count ($x10^9/l$)		
C-reactive protein (mg/l)		
Initial cellulitis severity score (score)		
Total % of positive cultures (%) - Streptococcus pyogenes (%) - Staphylococcus aureus (%) - MRSA (%) - Other Gram+ (%) - Gram- (%)		
Duration of hospital stay (days)		

Table 2. Baseline characteristics to be collected

9.3 Primary study parameter(s)

For the primary outcome, the proportion of successful treatments will be calculated for the two groups, and the absolute risk difference (with one sided 95% confidence limit) will be estimated to evaluate the non-inferiority hypothesis. In a secondary analysis, the difference in proportion in the two groups will be adjusted for relevant baseline covariates, using a logistic regression analysis. The difference in proportion of successful treatments will be estimated at mean values for the covariates.

9.4 Secondary study parameter(s)

Differences in secondary outcome parameters will be reported as relative risk or mean difference (with 95% confidence interval), and p-values for statistical significance estimated with the Chi-square test, t-test or Mann-Whitney test, where appropriate. A Kaplan-Meier analysis will be performed to compare the time to relapse (defined as requiring additional antibiotics for cellulitis) between the two groups.

Variable/outcome	Hypothesis	Outcome measure	Methods of analysis
1. Primary			
Resolution without relapse	Intervention not inferior to control	Percent cured on day 14 without relapse by day 28 [binary]	Absolute risk difference
2. Secondary			
Resolution without relapse (per definition of protocol version 9.4, see paragraph 7.1.2, including both sensitivity analysis and per protocol analysis)	Intervention not inferior to control	Percent cured on day 14 without relapse by day 28 [binary]	Absolute risk difference (Per protocol analysis: Chi^2 → Relative Risk)
Relapse by day 90	No difference	Percent with relapse [binary]	Chi^2 → Relative Risk
Time to relapse	No difference	Relapse after cure [time to event]	Kaplam-Meier survival analysis
Objective speed of recovery	No difference	Cellulitis severity score [continuous]	Student's T-test or Mann-Whitney U test
Subjective speed of recovery	No difference	Visual analogue scales of pain and swelling [continuous]	Student's T-test or Mann-Whitney U test
Quality of life	No difference	SF-36 questionnaire score at day 0 and 90 compared to population, day 14 and 28 compared to day 5-6 [continuous]	Student's T-test or Mann-Whitney U test
Antibiotic usage	No difference	Total costs of antibiotic use [continuous]	Student's T-test or Mann-Whitney U test
Health care utilization	No difference	Total treatment associated costs, Health Care Utilization Questionnaire [continuous]	Student's T-test or Mann-Whitney U test
3. Subgroup analyses			
Cellulitis severity score on a continuous scale	Severity score affects rate of cure		Regression analysis, with interaction term for severity score
Diabetes mellitus vs no diabetes mellitus	Diabetes affects rate of cure		Regression analysis, with interaction term for (no) diabetes
4. Sensitivity analyses	Intervention not inferior to	All outcomes	

	control		
Per protocol analysis			Chi^2 → Relative Risk
Primary outcome adjusted for baseline covariates			Cochran-Mantel-Haenszel → Relative Risk

Table 3. Analysis methods per outcome measures or variables

9.5 Other study parameters

Not applicable.

9.6 Interim analysis

An interim analysis will be performed on mortality after 198 patients have completed the trial. If mortality has occurred in the course of the trial, the two treatment groups will be compared for rate of mortality. If one group has a higher rate of mortality, an independent researcher with unblinded access to the allocation of patients will be asked to compile a report for the DSMB. The DSMB will convene and evaluate the unblinded results, and present their recommendations to the trial steering committee. Only the sponsor has the authority to stop or modify the trial. Criteria to prematurely stop the trial are listed in paragraph 7.7. For more information on interim analyses, see paragraph 8.5 and the DSMB charter.

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

Full medical confidentiality will be preserved. The Declaration of Helsinki, the Note for Guidance on Good Clinical Practice (ICH GCP; CPMP/ICH/135/95, step 5 consolidated guideline) and the EU Directive for clinical trials (2001/20/EG) are followed.

10.2 Recruitment and consent

Eligible patients will be informed by the study coordinator, informed colleague and/or research nurse about the study. If they are interested, they will be given the patient information letter, and the principle investigator/trial nurse will be summoned to visit the patient to discuss all questions patients might have. Patients will be given some time to consider their decision, keeping in mind that the baseline assessment has to be performed within 24h of admittance.

10.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable.

10.4 Benefits and risks assessment, group relatedness

The use of antibiotics is associated with multiple side-effects such as gastrointestinal complaints, the selection of resistant micro-organism and depletion of the gut microbiota. Therefore, strategies to lower the duration of antibiotic therapy are both of direct benefit to the patients and the society as a whole. The individual risk might be that shorter duration of antibiotics for cellulitis might lead towards relapse of the disease after which a new course of antibiotics is needed. In the current trial we want to evaluate whether short duration of antibiotics is equally effective as long duration of antibiotics for patients hospitalized with cellulitis.

10.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7, subsection 6 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as ‘verrichter’ in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study. For additional information, see document G1.

10.6 Incentives

Not applicable.

10.7 Risk assessment

The main risks of this study are a lower cure rate and a higher relapse rate of cellulitis in the 6-days treated arm. Keeping studies in other infectious diseases in mind, this risk seems small. Only clinically stable patients are included, critically ill patients as well as patients not responding to therapy the first 6 days are excluded. The small remaining risk is acceptable to us in view of the great advantages that a general shortening of antibiotic treatment of cellulitis would yield.

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

Patient data will be centralized by the Principal Investigator and kept under strict confidentiality.

The following data sources will be used;

- Demographic data, cellulitis history, and general medical history will be collected from the hospital records, either digital or paper. When unavailable or incomplete, it will be collected directly from the patient him-/herself.
- Physical examination results will be taken from hospital records, when performed by the attending physician. If unavailable or incomplete, one of the investigators will perform the physical examination to complete the results. These additional results will be recorded on the paper version of the eCRF (see below), and then entered in the eCRF. Cellulitis surface area, and the maximum height and width of the laesion are generally not clinically relevant, and will therefore not be noted in the records.
- The cellulitis severity score will be recorded on the paper version of the eCRF before being entered in the eCRF. It will not be mentioned in the hospital records.
- Lab and culture results will be collected from the hospital records.
- VAS scores and questionnaires will be entered straight into a digital survey tool (LimeSurvey, provided by the Clinical Research Unit) on a computer, by the patient. In some cases, a digital survey tool will be unfit for the patients, and bedside paper questionnaires (which the digital survey is based on) can be used. The answers of this questionnaire will directly be entered into the digital survey tool by the investigators, at the same time that other eCRF data is entered. These paper questionnaires will all be kept at the primary study site (AMC, due to logistic reasons) with denomination of study ID and study timepoint.
- Medication information will be registered using the hospital records, as well as entered manually by patients themselves in one of the questionnaires.
- Information on additional antibiotics received after discharge, will be collected from patients themselves or, when in doubt on the validity of statements made by patients, checked with the pharmacy.
- Information on day 90, such as medication changes, readmissions, adverse events, etc, will be collected by telephone from patients themselves, and recorded on a single paper CRF before entering in the eCRF. Day 90 information from before 15-9-2016 have been subject to direct entry, during/right after the telephone call. In both cases, information from hospital records can/could also be used as source data. When information sources conflict(ed), the investigators would assess which was more likely to be correct.

Data will be collected in an electronic CRF (eCRF) directly, in a digital survey tool, or written on a printed and modified version of the eCRF which will be used in bedside evaluations The printed version of the eCRF will be stored in the primary study site (AMC) regardless of the admitting hospital, for logistic reasons (investigators visit multiple patients daily, from different hospitals, often at home, and returning each CRF to it's respective study site would take too much time and effort). These CRF's will be anonymous using only the patient study ID. In regards to storage location, temporary exceptions can be made when practical reasons demand otherwise. Alternate locations are other study sites, but the final storage location is the AMC. Information can be entered into the eCRF directly without writing it down on the paper CRF first, this can be

marked as such on the paper CRF. Informed consent forms will be kept at the local study site. All patients will have access to their own information through their physician. During the study, the anonymity and confidentiality will be guaranteed and patient identification will be coded. All subjects will be identified by patient identification number on all (case report) forms, laboratory samples or source documents forwarded to the sponsor. No subject names will be disclosed. The key to the code will be safeguarded by the principal investigator and study coordinator.

For the 20 healthy volunteers, only basic demographic data (such age, sex, diabetes status and cellulitis history) will be recorded. These will be asked verbally and entered straight into a separate Microsoft Excel file.

Representatives of regulatory agencies, as allowed by local regulations, may review clinical information. The handling of personal data will comply with the Dutch Personal Data Protection Act (in Dutch: De Wet Bescherming Persoonsgegevens, Wbp).

11.2 Monitoring and Quality Assurance

A data management system will be designed, developed and maintained in house at the AMC Clinical Research Unit. Mandatory study monitoring and reporting will be performed in accordance with the ICH Good Clinical Practice (GCP) guidelines. See also above at DSMB.

11.3 Amendments

A ‘substantial amendment’ is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor. The DSMB will also be informed of any substantial amendments.

11.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

11.5 End of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient’s last study day.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

11.6 Public disclosure and publication policy

The principal investigators will be responsible for publication of the study results. The results of the study will be disclosed unreservedly.The principles of generally accepted specifications for authorship shall be followed in the appointing of authors and co-authors. All contributors to a specific publication (abstract, original report) will have a true opportunity for full evaluation of the final text before submission to a scientific meeting or an editor. Of note, this concerns an investigator initiated study.

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Appendix I: the definition of cellulitis

The terminology used to describe different types of skin and soft tissue infections can be confusing because different terms are used in various countries to describe skin and soft tissue infection.[1,3,20] The term erysipelas is mainly used in northwestern European countries to describe a specific type of cellulitis mainly caused by *S. pyogenes* involving superficial dermal structures distinguished clinically by raised borders and clear demarcation between involved and uninvolved skin. Cellulitis is less clearly marked and involves the dermis and subcutaneous tissues and may be caused by various microorganisms that are indigenous to the skin (most frequently *S. aureus*).[1,3,20] To further complicate this, Dutch dermatologists reserve the term cellulitis for non-infectious inflammation of the lower legs.
Here, we use the international definition of cellulitis used for clinical trials: cellulitis is a general descriptive term suggesting infection and indicating the warmth, erythema, and induration of skin and/or subcutaneous tissue, with or without pain (this also includes erysipelas).[10,21] Cellulitis is considered to be severe if the patient is admitted to the hospital to receive intravenous antibiotics.