CLINICAL TRIAL REPORT

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Trial Title	Penicillin For The Emergency Department Outpatient Treatment Of Cellulitis (PEDOCELL) Study: A Non-Inferiority Randomised Controlled Trial
EudraCT Number	2016-001528-69
Study Ref. No.	Emergency Medicine Trial 001
Sponsor	**Royal College of Surgeons Ireland (RCSI)**
CT Ref. No.	ClinicalTrials.gov ID: NCT02922686
Date of Report	**23/12/2020**

CONFIDENTIAL

Signature pages for clinical trial report

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Signed: Abel Wakai' Abel Wakai (Feb 17, 2021 17:05 GMT) Date: Feb 17, 2021

Print name: Professor Abel Wakai

Position: Chief Investigator

Address: Department of Emergency Medicine, Beaumont Hospital, Dublin 9

Feb 18, 2021

Signed: Maurice Dowling Maurice Dowling (Feb 18, 2021 10:59 GMT) Date: ___/____/_____

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1 TITLE PAGE

Study title: Penicillin for the Emergency Department Outpatient Treatment Of Cellulitis (PEDOCELL) Study

Name of Test Drug: Oral flucloxacillin

Indication studied: Cellulitis

Study description: A Non-Inferiority Randomised Controlled Trial

Sponsor: Royal College of Surgeons Ireland (RCSI)

Protocol: Pedocell Version 5 (22-Jan-2020)

Clinical Phase: IV

Study dates: First patient first visit: 4-Feb-2019
Last patient last visit: 9-Feb-2020

Investigators: Chief Investigator: Professor Abel Wakai
Address:
Department of
Emergency
Medicine,
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Hospital,
Dublin 9

Study Site Principal Investigators

Beaumont Hospital
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Department of Emergency Medicine,
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Mater Misericordiae University Hospital
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Contingency Sites Principal Investigators

Midlands Regional Hospital, Tullamore	Dr. Robert Eager Department of Emergency Medicine, Midlands Regional Hospital, Arden Road, Tullamore, Co. Offaly.
Our Lady of Lourdes Hospital, Drogheda,	Dr. Niall O'Connor Consultant in Emergency Medicine Our Lady of Lourdes Hospital Drogheda, Co Louth.

Medical Monitor:	Dr. Muiris Dowling
Sponsor signatory:	Dr. Muiris Dowling
GCP Statement:	This study was performed in compliance with ICH Good Clinical Practice (GCP) including the archiving of essential documents
Date of report:	23/12/2020

2 SYNOPSIS

NAME OF SPONSOR:	Royal College of Surgeons in Ireland (RCSI)
NAME OF FINISHED PRODUCT:	1. Oral flucloxacillin Capsules 500mg. 2. Oral Penicillin VK Tablets 250mg.
NAME OF ACTIVE INGREDIENT(S)	1. Oral flucloxacillin. 2. Oral Phenoxymethylpenicillin (Penicillin V).
Title of Study	Penicillin for the Emergency Department Outpatient Treatment Of Cellulitis (PEDOCELL) Study
Phase:	IV
Investigator(s)	Site Principal Investigators *Beaumont Hospital, Dublin* Professor Abel Wakai Department of Emergency Medicine, Beaumont Hospital, Dublin 9. *Mater Misericordiae University Hospital, Dublin* Dr Adrian Moughty, Department of Emergency Medicine, Mater Misericordiae University Hospital, Eccles St, Dublin 7. *Connolly Hospital, Dublin* Mr Joseph McKeever, Department of Emergency Medicine, Connolly Hospital, Blanchardstown, Dublin 15. *Cork University Hospital, Cork* Dr Conor Deasy, Department of Emergency Medicine, Cork University Hospital, Wilton, Cork. *Mercy University Hospital, Cork* Dr Adrian Murphy, Department of Emergency Medicine, Mercy University Hospital, Greenville Place, Cork. Contingency Sites Principal Investigators *Midlands Regional Hospital, Tullamore* Dr Robert Eager, Department of Emergency Medicine, Midlands Regional Hospital, Arden Road, Tullamore, Co.Offaly. *Our Lady of Lourdes Hospital, Drogheda, Co. Louth* Dr Niall O'Connor, Consultant in Emergency Medicine, Our Lady of Lourdes Hospital, Drogheda, Co Louth.

Study centre(s)	Study Sites 1. Beaumont Hospital, Dublin. 2. Mater Misericordiae University Hospital, Dublin 3. Connolly Hospital, Dublin. 4. Cork University Hospital, Cork. 5. Mercy University Hospital, Cork. Contingency Sites 1. Midlands Regional Hospital, Tullamore. 2. Our Lady of Lourdes Hospital, Drogheda,
PubMed Identifier (PMID)	PMID: 28836993
Publication	Boland F, Quirke M, Gannon B, Plunkett S, Hayden J, McCourt J, O'Sullivan R, Eustace J, Deasy C, Wakai A. The Penicillin for the Emergency Department Outpatient treatment of CELLulitis (PEDOCELL) trial: update to the study protocol and detailed statistical analysis plan (SAP). *Trials* 2017 Aug 24;18(1):391. doi: 10.1186/s13063-017-2121-2
ISRCTN number	Not applicable
ClinicalTrials.gov identifier (NCT number)	ClinicalTrials.gov ID: NCT02922686
WHO universal trial number (UTN)	Not applicable
Study period	First patient first visit: 4-Feb-2019 Last patient last visit: 9-Feb-2020
Date of interim analysis	Not applicable
Date of final analysis	Not applicable (because the study was terminated after the recruitment of only four trial participants)
Objectives	**Primary Objective** To determine the non-inferiority of oral flucloxacillin alone (monotherapy) compared with a combination of oral flucloxacillin and phenoxymethylpenicillin (dual therapy) for the ED- directed outpatient treatment of cellulitis. **Secondary Objective** 1. To measure adherence and persistence of trial patients with outpatient antibiotic therapy measured by self-report and by counting the number of unused study medications at the end of treatment visit. In addition, to describe adherence and persistence in a sub-study using an electronic medication event monitoring system (MEMS®) 2. To perform a within-trial evaluation of the cost per QALY gained from the use of oral flucloxacillin compared with combination therapy over a one-month time horizon from the perspective of the health-care payer (direct costs). In a secondary analysis the perspective will be extended to consider costs related to the intervention falling on the patient and government.

	3. To externally validate the ESTI-score, a HRQL questionnaire designed to quantify the impact of cellulitis on patient HRQL in clinical trials. Although investigator- determined clinical cure could be considered a composite of objective signs of cure and subjective patient experiences, the ESTI-score will allow for quantification of these experiences and the effects of treatment.
Methodology	The planned trial was a multi-centre, active-controlled, double-blind, parallel arm, non-inferiority randomised trial comparing oral flucloxacillin 500 mg QDS and placebo with oral 500 mg of flucloxacillin QDS and phenoxymethylpenicillin 500 mg QDS for the ED-directed outpatient treatment of cellulitis. The items of the trial protocol were consistent with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 checklist. The trial consisted of a 7-day intervention period and a 2-week follow-up period. Measurements were undertaken at four specific time points: i) baseline, ii) day 2-3 after commencing treatment [ECR], iii) 1-3 days after the end of treatment day (8-10 [EOT]), iv) 7-14 days after the end of treatment (day 14-21 [TOC]). The study design also included a sub-study, within the trial to evaluate patient adherence and persistence with therapy using an electronic monitoring system (MEMS®). The purpose of this was to describe these parameters in the understudied area of short course outpatient antibiotic treatment as well as to provide evidence for any adjustments in analysis based on medication-taking behaviour.

Number of patients	Planned: Given the preferred study power of 90% for non-inferiority trials and a clinical evaluability rate of 80%, it was estimated that a minimum sample size of 207 in each treatment group was required (n=414). Analysed: Not applicable (because the study was terminated after the recruitment of only four trial participants).
Main criteria for inclusion	1. Clinically diagnosed cellulitis, wound infection & abscess affecting any body part, excluding the perineum, and having any two of the following signs: •Erythema •Warmth •Tenderness / Pain of affected area •Oedema / Induration •Regional lymphadenopathy •Purulent drainage 2. Cellulitis, wound infection & abscess deemed treatable with oral antibiotics on an outpatient basis. 3. Patients with cellulitis, wound infection & abscess who have no signs of systemic toxicity and have no uncontrolled co-morbidities. 4. Written informed consent obtained. 5. 16 years of age or older. 6. Fluency in written and spoken English. 7. Willing to return for study follow-up or to have the research nurse or clinical project coordinator visit them. 8. Willing to receive a telephone call from a study investigator.
Test product, dose and mode of administration	Group 1: One 500 mg capsule of flucloxacillin four times daily for 7 days and one 500 mg capsule of phenoxymethylpenicillin four times daily for 7 days. Group 2: One 500 mg capsule of flucloxacillin four times daily for 7 days and one placebo capsule four times daily for 7 days
Duration of treatment	7 days
Criteria for evaluation	The principal secondary outcome measure was a ≥ 20% reduction in lesion surface area on day 2-3 after enrolment compared to the baseline visit. In addition, we planned to assess the following secondary outcome measures: 1. Clinical treatment failure at each follow-up visit 2. Adherence and persistence of trial patients with outpatient antibiotic therapy at EOT (end-of-treatment [day 8-10 post enrolment]). 3. Health-related quality-of-life (HRQL) assessments at each follow-up visit. 4. A pharmaco-economic assessment of cost per quality-adjusted life-year (QALY).

Statistical methods	A trial statistician blinded to the trial arm was to conduct data analysis and reporting. For the first stage of analysis, we planned to use descriptive statistics to describe recruited individuals compared to those eligible; and investigate the trial arms' comparability at baseline. We planned to assess non-inferiority using a 1-sided confidence interval on the difference of proportions between the trial arms for the primary outcome measure. If the upper limit of the CI was less than the non-inferiority threshold of 12.5%, we planned to infer non-inferiority. We planned to perform both intention-to-treat (ITT) and per-protocol analyses. ITT analyses include all patients randomised to a trial regardless of whether they actually satisfied entry requirements, received the assigned treatments, withdrew from the trial or adhered to the protocol. We planned to impute missing values, if possible, using a suitable imputation method. For a per-protocol analysis, we planned to include only patients who completed at least ≥75% of the doses provided during the first 48 hours of the treatment period and adhered to the protocol requirements. In a non-inferiority trial setting, it is suggested that a per-protocol analysis may be more appropriate since it is more likely to reflect actual differences between the two treatments. Also, ITT analysis may be interpreted as being too liberal in a non-inferiority trial and may bias toward making the two treatments appear similar. As a result, we planned to perform both an ITT and per-protocol analysis on the resulting data to assess non-inferiority of the placebo/flucloxacillin combination. In particular, to declare non-inferiority, we planned to exclude the non-inferiority margin in both the ITT and per-protocol analysis. We planned to conduct secondary analyses to investigate the effects of further adjustment for any variables displaying marked imbalance between the trial arms at baseline. We published a full statistical analysis plan in a peer review journal before commencing trial participant recruitment and before undertaking any analysis [1]. We planned to report trial data in line with the Consolidated Standards of Reporting Trials (CONSORT) 2010 Statement [2]. References: 1. Schulz KF, Altman DG, Moher D, Grp C. CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomized Trials. Annals of Internal Medicine. 2010;152(11):726-W293. 2. Boland F, Quirke M, Gannon B, Plunkett S, Hayden J, McCourt J, O'Sullivan R, Eustace J, Deasy C, Wakai A. The Penicillin for the Emergency Department Outpatient treatment of CELLulitis (PEDOCELL) trial: update to the study protocol and detailed statistical analysis plan (SAP). *Trials* 2017 Aug 24;18(1):391. doi: 10.1186/s13063-017-2121-2.

SUMMARY CONCLUSIONS	
Efficacy Results	Not applicable (because the study was terminated after the recruitment of only four trial participants).
Safety Results:	The study was terminated after the recruitment of only four trial participants). No Serious Adverse Events (SAEs) occurred in the four trial participants that were recruited.
Conclusion	Not applicable (because the study was terminated after the recruitment of only four trial participants).
Date of the Report	23/12/2020

Contents

4 LIST OF ABBREVIATIONS & DEFINITION OF TERMS

ABSSSI	Acute Bacterial Skin and Skin Structure Infections
AE	Adverse Event
AR	Adverse Reaction
BH	Beaumont Hospital
CDMS	Clinical Database Management System
CEM	College of Emergency Medicine
CDER	Centre for Drug Evaluation and Research
CHB	Connolly Hospital, Blanchardstown
CI	Confidence Interval
CPG	Clinical Practice Guidelines
CREST	Clinical Resource Efficiency Support Team
CRF	Case Report Form
CRF-C	Clinical Research Facility Cork
CSRI	Client Service Receipt Inventory
CUH	Cork University Hospital
DSMC	Data Safety and Monitoring Committee
DSUR	Data Safety Update Report
ECR	Early Clinical Response
eCRF	electronic Case Report Form
ECRU	Emergency Care Research Unit
ED	Emergency Department
EMA	European Medicine Agency
EM	Emergency Medicine
EOT	End-of-Treatment
EPs	Emergency Physicians
EQ-5D- 5L	EQ-5D 5L Level Version
ESTI	Extremity Soft Tissue Infection
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPs	General Practitioners
hCG	human Chorionic Gonadotrophin
HEAnet	Irish Higher Education Authority Network
HPRA	Health Products Regulatory Authority
HRA-DI	Health Research Award Definitive Intervention
HRB	Health Research Board
HRQL	Health Related Quality-of-Life
HSE	Health Service Executive
IB	Investigators Brochure
ICER	Incremental Cost Effectiveness Ratios
ICH	International Conference on Harmonisation
ICTRN	Irish Clinical Trials Research Network
iKT	integrated Knowledge Translation
IMPs	Investigational Medicinal Products

ISF	Investigator Site File
ITT	Intention-To-Treat
I.V	Intravenous
KT	Knowledge Translation
MEMS®	Medication Event Monitoring System
mITT	modified Intention-To-Treat
MMUH	Mater Misericordiae University Hospital
MRSA	Methicillin-resistance Staphylococcus aureus
MUH	Mercy University Hospital
NCPE	National Centre for Pharmaco-Economics
PAP	Patient Advisory Panel
PI	Principal Investigator
PIL	Patient information leaflet
PLC	Project Life Cycle
PP	Per Protocol
PROM	Patient Report Outcome Measure
QALY	Quality-Adjusted Life-Year
QRAM	Quality and Regulatory Affairs Manager
QDS	Quater Die Sumendum (4 times daily)
RCEM	Royal College of Emergency Medicine
RCSI	Royal College of Surgeons
RCT	Randomised Clinical Trial
REC	Research Ethics Committee
SAE's	Severe Adverse Events
SAG	Scientific Advisory Group
SOP	Standard Operating Procedure
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SPSS	Statistical Package for Social Sciences
SSTI	Skin and Soft Tissue Infection

SUSAR	Serious Unexpected Suspected Adverse Reaction
TMC	Trial Management Committee
TOC	Test of Cure
UCC	University College Cork
UK	United Kingdom (UK)
US	United States

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5 ETHICS AND REGULATORY APPROVAL

5.1 INDEPENDENT ETHICS COMMITTEE APPROVAL

The study protocol and all its amendments, and the patient information sheet(s) were reviewed and approved by the appropriate independent ethics committees as detailed in table one below. A copy of the initial ethics approval can be found in *Appendix 1*

Table 1: Ethics committees

<table>
<tr><td>Centre name and number</td><td>
<table>
<tr><th>Site Name</th><th>Site ID</th></tr>
<tr><td>Beaumont Hospital</td><td>1000</td></tr>
<tr><td>Cork University Hospital</td><td>2000</td></tr>
<tr><td>Mater Misericordiae University</td><td>3000</td></tr>
<tr><td>Connolly Hospital</td><td>4000</td></tr>
<tr><td>Mercy University</td><td>5000</td></tr>
</table>
</td></tr>
<tr><td>Investigator</td><td>Site Principal Investigators

Beaumont Hospital, Dublin
Professor Abel Wakai Department of Emergency Medicine, Beaumont Hospital, Dublin 9.

Mater Misericordiae University Hospital, Dublin
Dr Adrian Moughty, Department of Emergency Medicine, Mater Misericordiae University Hospital, Eccles St, Dublin 7.

Connolly Hospital, Dublin
Mr Joseph McKeever, Department of Emergency Medicine, Connolly Hospital, Blanchardstown, Dublin 15.

Cork University Hospital, Cork
Dr Conor Deasy, Department of Emergency Medicine, Cork University Hospital, Wilton, Cork.

Mercy University Hospital, Cork
Dr Adrian Murphy, Department of Emergency Medicine, Mercy University Hospital, Greenville Place, Cork.

Contingency Sites Principal Investigators

Midlands Regional Hospital, Tullamore
Dr Robert Eager, Department of Emergency Medicine, Midlands</td></tr>
</table>

	Regional Hospital, Arden Road, Tullamore, Co.Offaly. *Our Lady of Lourdes Hospital, Drogheda, Co. Louth* Dr Niall O'Connor, Consultant in Emergency Medicine, Our Lady of Lourdes Hospital, Drogheda, Co Louth.	
Ethics committee	Clinical Research Ethics Committee of the Cork Teaching Hospital	
Chairman	Approval of initial application: Professor Michael G. Molloy Approval of amendment: Professor David Kerins	
Date of approval of the final protocol	23/09/2016	
Date of approval of amendment(s)	02-Nov-2017 17-Sep-2018 15-Oct-2018 07-Nov-2018 07-Jan-2020	

5.2 ETHICAL CONDUCT OF THE STUDY

The study was performed in accordance with the current version of the declaration of Helsinki (2013). The study was conducted in compliance with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP)

5.3 PATIENT INFORMATION AND CONSENT

All patients provided written informed consent to participate in the study prior to screening.

The patient information leaflet detailed the procedures involved in the study (aims, methodology, potential risks, and anticipated benefits) and the investigator explained these to each patient. The patient was then given adequate time to consider the information before signing and dating the informed consent form to indicate that they fully understood the information, and willingly volunteered to participate in the study. The patient was given a copy of the patient information leaflet and informed consent form for their information and a copy was filed in the patient medical records. The original copy of the informed consent form was filed in the investigator site file (ISF).

A sample of the patient information sheet and informed consent form can be found at A*ppendix 2*

5.4 REGULATORY APPROVAL

The study gained full regulatory approval from the Health Products Regulatory Agency (HPRA) on 07-Oct-2016 and was issued with the following CT reference number: 900/593/1 - Flucloxacillin. A copy of the initial HPRA approval can be found in A*ppendix 3.*

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Table 2 shows the key study personnel involved in the trial.

Table 2: key study personnel

Title	Name and affiliation
Chief Investigator	Professor Abel Wakai Department of Emergency Medicine, Beaumont Hospital, Dublin 9
Lead Investigator	Site Lead Investigators *Beaumont Hospital, Dublin* Professor Abel Wakai Department of Emergency Medicine, Beaumont Hospital, Dublin 9. *Mater Misericordiae University Hospital, Dublin* Dr Adrian Moughty, Department of Emergency Medicine, Mater Misericordiae University Hospital, Eccles St, Dublin 7. *Connolly Hospital, Dublin* Mr Joseph McKeever, Department of Emergency Medicine, Connolly Hospital, Blanchardstown, Dublin 15. *Cork University Hospital, Cork* Dr Conor Deasy, Department of Emergency Medicine, Cork University Hospital, Wilton, Cork. *Mercy University Hospital, Cork* Dr Adrian Murphy, Department of Emergency Medicine, Mercy University Hospital, Greenville Place, Cork. Contingency Sites Lead Investigators *Midlands Regional Hospital, Tullamore* Dr Robert Eager, Department of Emergency Medicine, Midlands Regional

	Hospital, Arden Road, Tullamore, Co.Offaly. *Our Lady of Lourdes Hospital, Drogheda, Co. Louth* Dr Niall O'Connor, Consultant in Emergency Medicine, Our Lady of Lourdes Hospital, Drogheda, Co Louth.
Sponsor	Royal College of Surgeons in Ireland (RCSI)
Project Manager	1. Ms Sinead Plunkett, RCSI, from 01/02/2016 to 04/12/2017. 2. Dr Donal Keogan, RCSI, from 05/02/2018 to 08/03/2019.
Medical Monitor	Dr Maurice Dowling, RCSI, from 25/10/2018
Chief Pharmacist	Dr John Hayden, RCSI
Statistician	Dr Fiona Boland, RCSI
Laboratory Assistant	Not applicable

7 INTRODUCTION

7.1 THERAPEUTIC AREA

Cellulitis, abscesses and wound infections most recently renamed as ABSSSI by the United States Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER) [1], are commonly encountered infections in clinical practice. In Ireland, cellulitis is the most common ABSSSI [3].

Cellulitis accounts for between 1.5 to 3% of ED attendances [3-5]. Hospital admissions for the treatment of cellulitis are second only to respiratory tract infection as the most common cause of inpatient antibiotic therapy in Europe [6]. Approximately 12 per 1,000 ED attendances in Ireland are due to cellulitis [3]. In 2009, 10,465 patients were admitted to Irish hospitals with cellulitis, of whom 9,716 were admitted through the ED [7]. In the UK, 87,749 people were admitted to hospital in 2010 for on average 7 days with cellulitis, at a cost of up to £254 million to the exchequer [8]. Hospital admissions for skin infections may incur significant healthcare cost [9,10] but have been shown to represent only 7% of the overall burden of cellulitis treated by emergency physicians and GPs [10]. It is important to note that most coding systems, including the ICD-9 system used in the US, do not differentiate between cellulitis or abscess. It is therefore likely that these figures represent heterogeneous ABSSSIs including cellulitis, abscesses and wound infections.

There is an obvious clinical equipoise between the use of oral flucloxacillin alone or combined with phenoxymethylpenicillin for the ED treatment of cellulitis as evidenced by current disparate prescribing practice and hospital guidelines. A Cochrane Review [11] that examined 25 RCTs of cellulitis therapy found no clearly superior, single treatment; the authors highlighted the need for higher-quality RCTs using clearer definitions of the disease and outcome measures. By using the most recently recommended guidelines from the FDA [1] and EMA [12], the planned research aims to fill this identified knowledge-gap.

Feasibility studies for the planned trial demonstrated that 45-50% of ED patients with cellulitis in Ireland are discharged on oral antibiotics [2, 13], which is consistent with findings in other jurisdictions [5]. Despite the significant healthcare and economic costs associated with ABSSSIs, there is a lack of scientific evidence concerning these conditions appropriate antibiotic treatment [11]. Although early and effective treatment of cellulitis reduces the risk of developing severe infections between 25 to 35 different antibiotic regimens are initially prescribed to treat cellulitis in EDs [4] and following hospital admission [14]. Additionally, "less severe" infections tend to be over-treated and severe infections under-treated, indicating unjustifiable levels of antibiotic misuse, insufficient knowledge of therapeutics and a lack of evidence to risk-stratify patients with cellulitis to different treatments [14]. In addition to increasing healthcare costs, inadequate antibiotic therapy in patients with complicated skin and soft tissue infection (SSTI) is associated with the development of antibiotic resistance [15], indirectly increasing length of hospital stay and leading to poorer patient outcomes [16].
The planned trial was likely to be definitive due to the current clinical equipoise between the use of flucloxacillin alone or combined with phenoxymethylpenicillin for the ED outpatient treatment of cellulitis, as evidenced by the disparate prescribing practices revealed by the feasibility studies for the planned project.

Penicillin, either as flucloxacillin and/or phenoxymethylpenicillin, is the standard antibiotic regimen for the treatment of cellulitis in Ireland and the UK [3, 17], and is also recommended by French [18] and Norwegian prescribing guidelines [19]. Clinicians, in both the UK and Ireland, commonly prescribe both antibiotics for the treatment of cellulitis [2, 13, 17, 20], with up to 65% of patients discharged from EDs prescribed the dual regimen [2]. In a feasibility study for the planned trial, one-third of patients with cellulitis discharged from the ED were prescribed flucloxacillin monotherapy, one-third were prescribed dual therapy (flucloxacillin and phenoxymethylpenicillin) and one-third were prescribed other antibiotics [13]. Meanwhile, local prescribing guidelines are contradictory in terms of recommending monotherapy or dual therapy. Several UK and Irish hospital prescribing guidelines, and at least one authoritative textbook [21] recommend the dual antibiotic regimen. In a large UK audit of a cellulitis clinic, all discharged patients received dual treatment [9].

The Foundation for the National Institutes of Health Biomarkers Consortium Project Team [22], and the FDA [1], have explicitly indicated that Patient Report Outcome Measures (PROM), or how a patient "feels and functions" are important, required by regulation, and should be measured at early and late time points. It is well recognised that RCTs of antibiotic therapy for cellulitis and other ABSSSIs to date have neglected this crucially important aspect of modern trial design, with no RCTs included in the recently published Cochrane review having assessed patient HRQL. In order to address this knowledge gap, the planned study aimed to measure HRQL using the EQ-5D- 5L instrument and validate a novel HRQL instrument [23]. Validation of the HRQL instrument may also inform future healthcare decisions about more costly interventions for cellulitis treatment. Also, since the economic impact for patients presenting to EDs with cellulitis in Ireland has never been studied, by performing a pharmacoeconomic analysis, we planned to provide useful insights regarding the economic impact of this common condition.

Research regarding antimicrobial resistance has been identified as a national priority for funding bodies in healthcare and biomedical science in Ireland [24]. Clinical trials that evaluate the important constituents of optimal drug regimens to treat infections provide an opportunity for innovative research in this field. The study design included a sub-study to evaluate adherence to therapy using an electronic monitoring system (MEMS®) and persistence to treatment within the trial. The purpose of this was to describe these parameters in the understudied area of short course outpatient antibiotic treatment as well as providing evidence for any adjustments in the analysis based on medication-taking behaviour. We planned to readily transfer the conclusions from the trial to daily clinical practice. We believed that the trial results could inform deliverable care pathways in the form of clinical practice guidelines (CPGs). CPGs are measurable, high-impact strategies to inform clinical practice, and are particularly useful in EDs that have high staff and patient throughput [32].

References:

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7.2 RATIONALE FOR THE STUDY

8 STUDY OBJECTIVES

Primary Objectives

To determine the non-inferiority of oral flucloxacillin alone (monotherapy) compared with a combination of oral flucloxacillin and phenoxymethylpenicillin (dual therapy) for the ED- directed outpatient treatment of cellulitis.

Secondary (Exploratory) Objective

1. To measure adherence and persistence of trial patients with outpatient antibiotic therapy measured by self-report and by counting the number of unused study medications at the end of treatment visit. In addition, to describe adherence and persistence in a sub-study using an electronic medication event monitoring system (MEMS®)
2. To perform a within-trial evaluation of the cost per QALY gained from the use of oral flucloxacillin compared with combination therapy over a one-month time horizon from the perspective of the health-care payer (direct costs). In a secondary analysis we planned to extend the perspective to consider costs related to the intervention falling on the patient and government.
3. To externally validate the ESTI-score, a HRQL questionnaire designed to quantify the impact of cellulitis on patient HRQL in clinical trials. Although investigator- determined clinical cure could be considered a composite of objective signs of cure and subjective patient experiences, the ESTI-score allows for quantification of these experiences and the effects of treatment.

9 STUDY DESIGN

9.1 OVERALL STUDY DESIGN AND PLAN

The planned trial was a multi-centre, active-controlled, double-blind, parallel-arm, non-inferiority randomised trial comparing oral flucloxacillin 500 mg QDS and placebo with oral 500 mg of flucloxacillin QDS and phenoxymethylpenicillin 500 mg QDS for the emergency department (ED)-directed outpatient treatment of cellulitis. The trial protocol items were consistent with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 checklist [1] and was published in a peer-review journal [2].

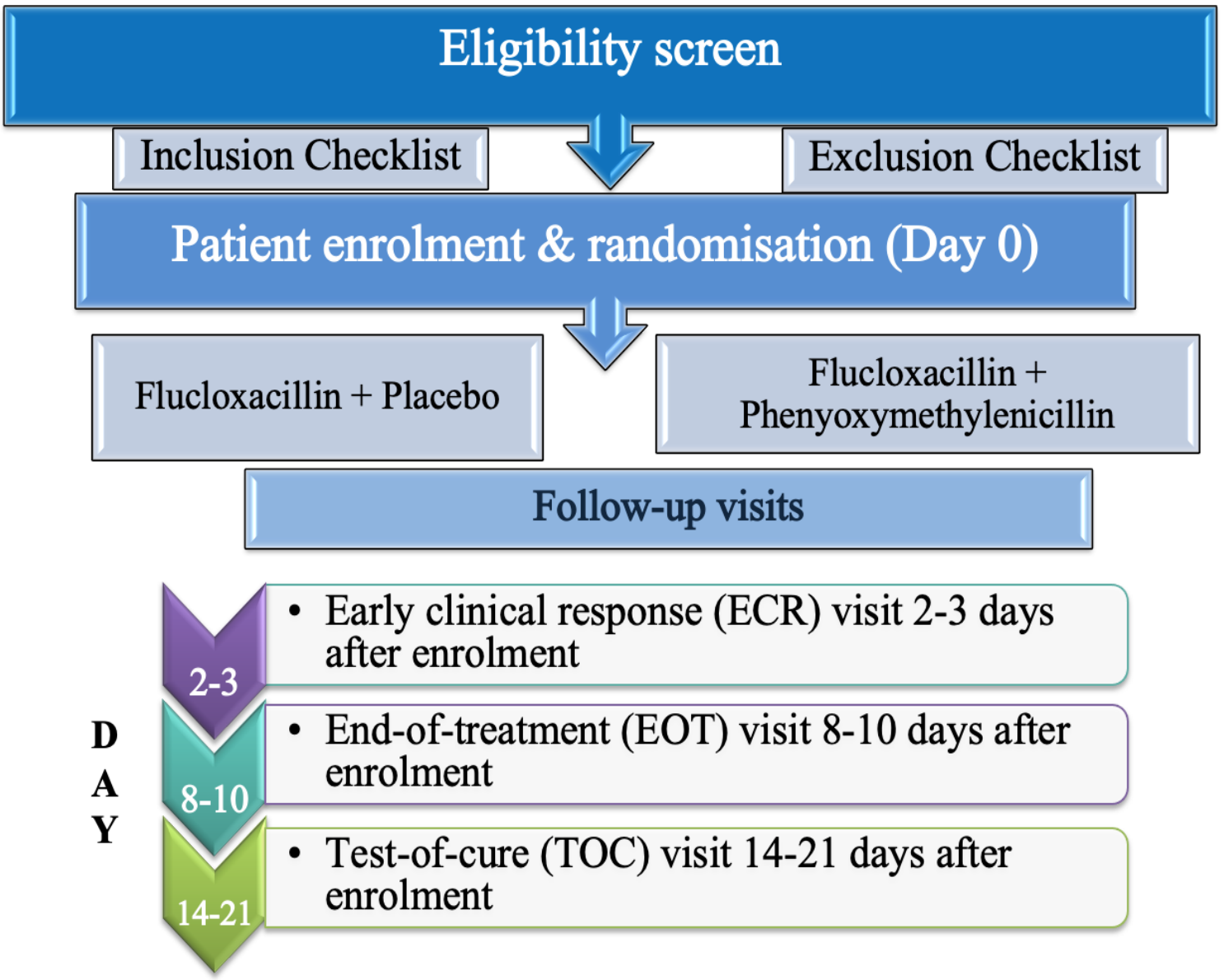
The trial consisted of a 7-day intervention period and a 2-week follow-up period. Measurements were undertaken at four specific time points: i) baseline; ii) day 2-3 after commencing treatment (early clinical response [ECR]); iii) 1-3 days after the end of treatment day (8-10 end-of-treatment [EOT]); iv) 7-14 days after the end of treatment (day 14-21, test-of-cure [TOC]).

The study design also included a sub-study, within the trial to evaluate patient adherence and persistence with therapy using an electronic monitoring system (MEMS®). The purpose of this was to describe these parameters in the understudied area of short course outpatient antibiotic treatment as well as to provide evidence for any adjustments in the analysis based on medication-taking behaviour.

References:

1. Schulz KF, Altman DG, Moher D, Grp C. CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomized Trials. Annals of Internal Medicine. 2010;152(11):726-W293.
2. Boland F, Quirke M, Gannon B, Plunkett S, Hayden J, McCourt J, O'Sullivan R, Eustace J, Deasy C, Wakai A. The Penicillin for the Emergency Department Outpatient treatment of CELLulitis (PEDOCELL) trial: update to the study protocol and detailed statistical analysis plan (SAP). *Trials* 2017 Aug 24;18(1):391. doi: 10.1186/s13063-017-2121-2.

STUDY TIMINGFigure 1 **Schematic diagram demonstrating study design**



STUDY LOCATION

9.2 DISCUSSION OF STUDY DESIGN

We aimed to perform a multi-centre non-inferiority randomised controlled trial (RCT) comparing flucloxacillin monotherapy's efficacy with combination flucloxacillin/phenoxymethylpenicillin for the outpatient treatment of cellulitis in the emergency department (ED) setting. Feasibility studies for the planned RCT revealed obvious clinical equipoise between the comparator interventions. The findings of a published Cochrane review further support this clinical equipoise. Feasibility studies for the RCT demonstrated ED patients and ED staff's willingness to participate in cellulitis research. The feasibility studies also provided estimates of the time needed to collect and analyse data for the planned RCT in the ED setting. We designed a trial that incorporated current recommendations by the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA), which measure patient-reported outcome measures (PROMs). The PROMs were measured using two instruments that have not previously been used in any antibiotic therapy trial for cellulitis. We measured medication adherence in the ED patient population with cellulitis using a novel method (Medication Event Monitoring System [MEMS®]).

9.3 SELECTION OF STUDY POPULATION

INCLUSION CRITERIA

Patients fulfilling the following criteria were eligible for inclusion in the study:

1. Clinically diagnosed cellulitis, wound infection & abscess affecting any body part, excluding the perineum, and having any two of the following signs:
    - Erythema
    - Warmth
    - Tenderness / Pain of affected area
    - Oedema / Induration
    - Regional lymphadenopathy
    - Purulent drainage
2. Cellulitis, wound infection & abscess deemed treatable with oral antibiotics on an outpatient basis.
3. Patients with cellulitis, wound infection & abscess who had no signs of systemic toxicity and have no uncontrolled co-morbidities.
4. Written informed consent obtained.
5. Sixteen years of age or older.
6. Fluency in written and spoken English.
7. Willing to return for study follow-up or to have the research nurse or clinical project coordinator visit them.
8. Willing to receive a telephone call from a study investigator.

EXCLUSION CRITERIA

Patients fulfilling the following criteria were excluded from participation in the study:

1. Penicillin allergy (self-reported or confirmed).
2. Any cellulitis wound infection & abscess that treating clinicians deemed treatable with intravenous (IV) antibiotics.
3. Patients that had a significant systemic upset such as acute confusion, tachycardia, tachypnoea, hypotension or had unstable co-morbidities that may interfere with a response to therapy or have a limb threatening infection due to vascular compromise.
4. Patients who had a severe life-threatening infection such as necrotizing fasciitis.
5. Any cellulitis wound infection & abscess of the perineal region.

6. Patients who had received more than 24 hours of effective antibiotics for the current episode of acute cellulitis, wound infection & abscess.
7. Any medical condition, based on clinical judgment that could interfere with the interpretation of the primary outcome measures (e.g. a chronic skin condition at the site of the cellulitis wound infection or abscess).
8. Immunodeficiency from primary or secondary causes (e.g. corticosteroids, chemotherapeutic agents).
9. Previous history of renal dysfunction or known chronic kidney disease under the care of a nephrologist.
10. Previous history of liver dysfunction defined as chronically deranged liver function tests elicited from the medical notes or history.
11. Suspected or confirmed septic arthritis.
12. Suspected or confirmed osteomyelitis.
13. Infection involving prosthetic material.
14. Pregnant or lactating women.
15. Patients with a previous history of flucloxacillin-associated jaundice/hepatic dysfunction
16. Patients with a previous history of methicillin-resistant staphylococcus aureus (MRSA) colonisation/infection.
17. Patients with lactose intolerance diagnosed by a medical professional.
18. Patients taking probenecid, neomycin, chloramphenicol, erythromycin , tetracyclines sulfinpyrazone, methotrexate, guar gum or an oral anticoagulant.

WITHDRAWAL OF PATIENTS FROM THERAPY OR ASSESSMENT

Patients were free to withdraw from the study at any time without giving a reason. Patients were advised that if they requested to withdraw from the study, at any time during the trial, then this would have no negative consequences on further care

9.4 TREATMENTS

TREATMENTS ADMINISTERED

This was a two-armed study. Patients were randomised to either flucloxacillin monotherapy or combination flucloxacillin with phenoxymethylpenicillin dual therapy.

DESCRIPTION OF INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

The investigational medicinal product (IMP) was Flucloxacillin 500mg capsules (Actavis PA1380/011/002).

EVIDENCE FOR COMPARATORS

The comparator was combination flucloxacillin with phenoxymethylpenicillin dual therapy using phenoyxymethylpenicillin 500mg capsules (two phenoxymethlypenicillin 250 mg tablets [Sandoz PL: 04520/0005]). Feasibility studies for the planned RCT revealed obvious clinical equipoise between the comparator interventions. The findings of a published Cochrane review further support this clinical equipoise.

BACKGROUND THERAPY

Penicillin, either as flucloxacillin and/or phenoxymethylpenicillin, is the standard antibiotic regimen for the treatment of cellulitis in Ireland and the UK [1, 2], and is also recommended by French [3] and Norwegian prescribing guidelines [4]. Clinicians, in both the UK and Ireland, commonly prescribe both antibiotics to treat cellulitis [2, 5, 6, 7], with up to 65% of patients discharged from EDs prescribed the dual regimen [8]. In a feasibility study for the PEDOCELL trial, one-third of patients with cellulitis discharged from the ED were prescribed flucloxacillin monotherapy, one-third were prescribed dual therapy (flucloxacillin and phenoxymethylpenicillin) and one-third were prescribed other antibiotics [6].

References:

1. Fulton R, Doherty L, Gill D, Harney AM, Harper C. CREST (Clinical Resource Efficiency Support Team) 2005. Crest Guidelines on the Management of Cellulitis in Adults. DHSS Northern Ireland, ISBN 1-903982-12-X.
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METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUPS

SELECTION OF DOSES IN THE STUDY

Group 1: One 500 mg capsule of flucloxacillin four times daily for 7 days and one 500 mg capsule of phenoxymethylpenicillin four times daily for 7 days.

Group 2: One 500 mg capsule of flucloxacillin four times daily for 7 days and one placebo capsule four times daily for 7 days.

PRIOR AND CONCOMITANT THERAPY

Patients were excluded from the trial if they had received more than 24 hours of effective antibiotics for the current episode of acute cellulitis, wound infection & abscess.

9.5 EFFICACY AND SAFETY VARIABLES

EFFICACY AND SAFETY MEASUREMENTS ASSESSED

1. Measurement of lesion surface area and early clinical response assessment (≥20% reduction in lesion surface area).
2. Clinical response assessment.
3. Measurement of HRQL measures (EQ-5D-5L, SF 12, ESTI-score).
4. Measurement of health resource use, using an adapted version of the CSRI.
5. Adverse events.

Table 3 Schedule of assessments and procedures

Study Procedures	Baseline	ECR Day 2-3	EOT Day 8-10	TOC Day 14-21	Unscheduled Visits
Inclusion/exclusion criteria (1)	X				
Informed consent (2)	X				
Consent to MEMS® cap sub-study	X				
Demographics	X				
Medical history*	X				
Concomitant medication	X	X	X	X	X
Physical examination****	X				
Lesion size measurement	X	X	X	X	X
Urinary HCG	X				
EQ-5D-5L & SF 12 measurement,	X	X	X	X	X
ESTI assessment	X	X	X	X	X

Study Procedures	Baseline	ECR Day 2-3	EOT Day 8-10	TOC Day 14-21	Unscheduled Visits
HRQL Questionnaire	x	X	X	X	X
Randomisation	X				
Dispense study medications & instructions for use	X				
Adverse event assessment	X	X	X	X	X
Early clinical response		X			
Investigator determined clinical response			X	X	X
Adherence (pill count, self-report)	X		X		
Mems® cap assessment			X		
Return of used & unused study medication			X		
Primary outcome assessment				X	

1. Eligibility screen: Inclusion and exclusion criteria evaluated by direct interview with potential study participant by study investigator (emergency physician(s),).
2. Appropriate written informed consent obtained on all study participants in accordance with approved standard operating procedures. Informed consent was obtained from study participants by a trained emergency physician with at least 2 years postgraduate experience in emergency medicine.

*Including smoking, alcohol history and risk factors

** If a patient was unable to return to the study site for the early response visit at day 2-3, then we planned to obtain follow-up information with a telephone call.

**** Physical Examination: of the body part affected by the cellulitis lesion.

DESCRIPTION OF STUDY ASSESSMENTS

Baseline Visit

Key baseline patient characteristics obtained at the baseline visit were recorded in the CRF, including patient demographics, relevant past medical and surgical history, and abnormalities noted on physical exam.

- ✓ Demographics included gender, date of birth, and racial/ethnic origin.
- ✓ Lesion size measurements.
- ✓ Medical history, including smoking, alcohol history and risk factors.
- ✓ Physical examination of the body part affected by the cellulitis lesion to the current infection, including medication allergies and reactions.
- ✓ Concomitant medications.
- ✓ Urinary hCG.
- ✓ Randomisation.
- ✓ Study medication administration.
- ✓ Measurement of HRQL measures (EQ-5D-5L, SF 12, ESTI-score).
- ✓ Measurement of health resource use, using an adapted version of the CSRI.
- ✓ Adherence interventions described above will be performed.
- ✓ Consent to MEMS® cap study (if eligible).
- ✓ MEMS® Cap administration and written instructions regarding the appropriate use of the MEMS® Cap were given to patients who are enrolled into the adherence sub-study.

ECR Visit (day 2-3 post-randomisation):

- ✓ Measurement of lesion surface area and early clinical response assessment (≥20% reduction in lesion surface area).
- ✓ Clinical response assessment.
- ✓ Measurement of HRQL measures (EQ-5D-5L, SF 12, ESTI-score).
- ✓ Measurement of health resource use, using an adapted version of the CSRI.
- ✓ Concomitant medications.
- ✓ Adverse events.

EOT VISIT (DAY 8-10 POST RANDOMISATION)

- ✓ Measurement of lesion size.
- ✓ Measurement of clinical response.
- ✓ Measurement of HRQL (EQ-5D-5L, SF 12, ESTI-score).
- ✓ Measurement of health resource use using an adapted version of the CSRI.
- ✓ Concomitant medications.

- ✓ Adverse events.
- ✓ Measures of adherence
    - Patient self-reported adherence. Prompting questions were asked by the study investigator as follows:

      Have you taken all of your antibiotic doses as prescribed?

      If not, how many times would you estimate you did not take your doses as prescribed? (Provide an estimated percentage of prescribed doses)

      Did you finish your antibiotic course?

      If not, when did you stop? (Day 0-7)
    - Pill count
    - MEMS® cap download (for patients enrolled in adherence sub-study)

7.4 TOC Visit – (Day 14 -21 post randomisation)

- ✓ Primary outcome assessment – clinical cure or failure.
- ✓ Lesion size measurement.
- ✓ Measurement of HRQL (EQ-5D-5L, SF 12 ESTI-score).
- ✓ Measurement of health resource use, using an adapted version of the CSRI.
- ✓ Concomitant medications.
- ✓ Adverse events.
- ✓ Investigator-determined clinical response.

7.2.3 Unscheduled Visit

- ✓ Measurement of lesion surface area and early clinical response assessment (≥20% reduction in lesion surface area).
- ✓ Clinical response assessment.
- ✓ Measurement of HRQL measures (EQ-5D-5L, SF 12, ESTI-score).
- ✓ Measurement of health resource use, using an adapted version of the CSRI.
- ✓ Measurement of medication adherence (patient reported adherence, pill count).
- ✓ Concomitant medications.
- ✓ Adverse events.

Concomitant Medication

The following patients were excluded:

1. Patients who had received more than 24 hours of effective antibiotics for the current episode of acute cellulitis, wound infection & abscess.
2. Patients taking probenecid, neomycin, chloramphenicol, erythromycin, tetracyclines sulfinpyrazone, methotrexate, guar gum or an oral anticoagulant.

Endpoint Assessments

There are no valid endpoint results because the study terminated after the recruitment of only four trial participants.

9.6 DATA QUALITY ASSURANCE

The Clinical Database Management System (CDMS) requirements for patient clinical and demographic data were covered by the development of a web-based database. Data was collected using a paper CRF at the patient bedside for enrolment and follow up procedure and subsequently entered manually into the CDMS by the Clinical Project Coordinator or research nurse or designee(s).

Data collection, source documents and CRFs

Source documents for this study included hospital medical records, procedure reports, laboratory results, health related questionnaires and other data collection forms approved by the sponsor as source data. Source documents were stored securely and were used to enter data on the CRFs. All data entered on the CRFs were legible. If an error was made, the error was crossed through with a single line in such a way that the original entry could still be read. The correct entry was then clearly inserted, and the alteration initialed and dated by the person making the change. We mandated that data reported on the CRF derived from source documents must be consistent with the source documents or the discrepancies must be explained.

We planned to remove the data and enter it manually at the individual recruitment sites, with PI, data monitors and system administration staff able to access data for their local site or all study sites if appropriate. The design, development and maintenance of the eCRF and database structure was controlled by a Clinical Informatics Manager. Site lead investigators were required to prepare and maintain adequate and accurate case histories, recording all observations and other data pertinent to the investigation on each subject and to retain.

Retention of essential documents

During the initiation visit of each study site, we planned to establish an ISF for that study site. The lead investigator or appropriate designee had the responsibility for maintaining the study documents in the ISF as specified in section 8 of the ICH GCP guidelines, and for the safe keeping of the ISF. We planned to store all relevant paper documents for 5 years, unless indicated otherwise by the sponsor.

Secure access

Access to the eCRF for data entry or query was by means of a secure connection to a web-based installation of a software package. This was hosted at the Irish Higher Education Authority network (HEAnet) secure hosting centre, with off-site backup and replicating facilities available. User access was by means of a unique, personal username and password. Changes to patient data were recorded in a system audit trail.

Database design process

The design of the eCRF and underlying database was based on the study protocol and data collection requirements. In close collaboration with the Chief Investigator, a tree-like, top-down structure was developed, dependencies and validation rules put in place, and individual data element definitions agreed. A prototype eCRF with minimum required data elements was developed and tested with the Chief Investigator until the final structure was in place and ready for live use.

Data entry

Data was collected from each site on a paper CRF and entered into the eCRF file by the Clinical Project Coordinator or research nurse, with validation rules, limited choice lists, range limits and dependencies as agreed with the Chief Investigator during the design phase. This ensured as far as possible that only valid data was recorded and minimised the amount of data cleaning required. The eCRF database solution could import from or export to other databases in standard formats and could merge data for analysis in tools such as SPSS.

9.7 STATISTICAL METHODS PLANNED IN THE PROTOCOL & DETERMINATION OF SAMPLE SIZE

STATISTICAL AND ANALYTICAL PLANS

A trial statistician blinded to the trial arm was to conduct data analysis and reporting. For the first stage of analysis, we planned to use descriptive statistics to describe recruited individuals compared to those eligible; and investigate the trial arms' comparability at baseline. We planned to assess non-inferiority using a 1-sided confidence interval on the difference of proportions between the trial arms for the primary outcome measure. If the upper limit of the CI was less than the non-inferiority threshold of 12.5%, we planned to infer non-inferiority. We planned to perform both intention-to-treat (ITT) and per-protocol analyses. ITT analyses include all patients randomised to a trial regardless of whether they actually satisfied entry requirements, received the assigned treatments, withdrew from the trial or adhered to the protocol. We planned to impute missing values, if possible, using a suitable imputation method. For a per-protocol analysis, we planned to include only patients who completed at least ≥75% of the doses provided during the first 48 hours of the treatment period and adhered to the protocol requirements. In a non-inferiority trial setting, it is suggested that a per-protocol analysis may be more appropriate since it is more likely to reflect actual differences between the two treatments. Also, ITT analysis may be interpreted as being too liberal in a non-inferiority trial and may bias toward making the two treatments appear similar. As a result, we planned to perform both an ITT and per-protocol analysis on the resulting data to assess non-inferiority of the placebo/flucloxacillin combination. In particular, to declare non-inferiority, we planned to exclude the non-inferiority margin in both the ITT and per-protocol analysis. We planned to conduct secondary analyses to investigate the effects of further adjustment for any variables displaying marked imbalance between the trial arms at baseline. We published a full

statistical analysis plan in a peer review journal before commencing trial participant recruitment and before undertaking any analysis [1]. We planned to report trial data in line with the Consolidated Standards of Reporting Trials (CONSORT) 2010 Statement [2].

References:

1. Schulz KF, Altman DG, Moher D, Grp C. CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomized Trials. Annals of Internal Medicine. 2010;152(11):726-W293.
2. Boland F, Quirke M, Gannon B, Plunkett S, Hayden J, McCourt J, O'Sullivan R, Eustace J, Deasy C, Wakai A. The Penicillin for the Emergency Department Outpatient treatment of CELLulitis (PEDOCELL) trial: update to the study protocol and detailed statistical analysis plan (SAP). *Trials* 2017 Aug 24;18(1):391. doi: 10.1186/s13063-017-2121-2.

DETERMINATION OF SAMPLE SIZE

We aimed to measure the non-inferiority of oral flucloxacillin and placebo compared to oral flucloxacillin and phenoxymethylpenicillin for the trial's primary and secondary outcomes. This was a non-inferiority trial as the trial's aim was to measure if the efficacy of placebo/flucloxacillin combination is not inferior to flucloxacillin/ phenoxymethylpenicillin combination therapy, as in this case the reduced antimicrobial exposure, the reduced cost of drug monotherapy and the greater convenience of a reduced pill burden, all support the preferred use of monotherapy.

The sample size per trial arm was calculated according to an assumed treatment success rate of 85% with oral flucloxacillin and phenoxymethylpenicillin, a non-inferiority threshold $\Delta = 12.5\%$ and $\alpha = 0.025$ (as this was a non-inferiority study). Sample sizes were calculated using SAS v9.3 (SAS Institute Inc., Cary, NC, USA). Given the preferred study power of 90% for non-inferiority trials and a clinical evaluability rate of 80%, it was estimated that a minimum sample size of 207 in each treatment group was required (n=414). We planned to assess non-inferiority using a one-sided confidence interval (CI) on the difference of proportions between the two groups. If the upper limit of the CI was less than the non-inferiority threshold of 12.5%, then we planned to infer non-inferiority.

Treatment success rate was implied from a multi-centre parallel RCT of cefditoren, cefuroxime and cefadroxil [28] in which clinical cure ranged from 83% to 88%. In a similar study of oral outpatient cefdinir versus cephalexin, the cure rates ranged from 89% for the clinically evaluable patient group, and 82-83% in the intention to treat (ITT) group [29]. To the best of our knowledge, there are no similar non-inferiority studies examining oral flucloxacillin as a comparator available for analysis [11]. There are few studies which assessed flucloxacillin treatment. To the best of our knowledge, no studies have examined percentage reduction in lesion size in outpatient RCTs of oral antibiotic treatment for cellulitis. The sample size for this study is therefore based on investigator-determined clinical response at the TOC visit.

References:

1. Bucko AD, Hunt BJ, Kidd SL, Hom R. Randomized, double-blind, multicenter comparison of oral cefditoren 200 or 400 mg BID with either cefuroxime 250 mg BID or cefadroxil 500 mg BID for the treatment of uncomplicated skin and skin-structure infections. Clin Ther 2002; 24(7):1134–47. PMID: 12182257
2. Giordano PA, Elston D, Akinlade BK, Weber K, Notario GF, Busman TA, et al. Cefdinir vs. cephalexin for mild to moderate uncomplicated skin and skin structure infections in adolescents and adults. Curr Med Res Opin. 2006; 22(12):2419-28.
3. Kilburn SA, Featherstone P, Higgins B, Brindle R. Interventions for cellulitis and erysipelas. Cochrane Database Syst Rev 2010; 16 (6): CD004299. PMID: 2055675711

9.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

A summary of the protocol amendments can be found in *Appendix 4.*

10 STUDY POPULATION

10.1 DISPOSITION OF PATIENTS

Recruitment

The TMC monitored recruitment. We planned to undertake regular TMC meetings between the TMC and Study Research Nurses and Clinical Project Coordinator to identify site-specific issues and tailor solutions for any recruitment problems. Trained members of the research team included an RCSI Research Nurse or Clinical Project Coordinator working from 0800-1700 hours, Monday to Friday, and covering recruitment and follow up in BH, CHB and the MMUH. We planned to employ a research nurse in the HRB Clinical Research Facility, University College Cork, for enrolment in CUH and the MUH.

We planned to support and encourage patient recruitment at site set-up meetings and at regular intervals throughout the trial's lifespan. Planned initiatives to enhance recruitment included increasing advertisement (e.g. brochures and posters for ED staff awareness and email reminders), and developing relationships with key clinical staff to identify potentially eligible trial participants. We planned to conduct training workshops at each site's ED medical staff changeover and at least monthly throughout the recruitment period.

We planned to put in place SOPs to guide study recruiters in each of the enrolling centres. The purpose of the SOPs was to ensure consistency in the recruitment procedure across the different sites and minimize the risk of enrolling patients with an alternative diagnosis to cellulitis.

We estimated that 8 suitable participants would be recruited from each study site per month from our feasibility studies. Our best estimate was that 60 patients should be enrolled by month 3, and 120 patients by month 6. We aimed to trigger contingency measures if we failed to reach 80% of our recruitment target by month 3 (48 patients).
The contingency measures included the following:

1. Emergency meeting to be arranged by TMC. Identification of site-specific issues and tailored solutions for recruitment problems to be discussed.
2. Increasing ED staff awareness of the RCT (e.g. through brochures, posters, email and website advertisement).
3. Conduct training workshops at each six-monthly staff changeover and 4-6 monthly throughout the recruitment period.
4. Increase the number of enrolling centres (i.e. start recruitment at contingency sites at Midlands Regional Hospital, Tullamore and OLOL, Drogheda).

Once a participant was enrolled, the study site was required to make every reasonable effort to follow the patient for the entire study period. It was projected that the rate of loss-to-follow-up on an annual basis would be at most 10%. We planned to devise an SOP for participant retention to attempt to minimize loss to follow up.

At the study inception stage, we planned to start recruitment in November 2016. However, due to delays in obtaining HPRA approval and delays in manufacturing the IMPs, the start of recruitment moved to February 2017. Delays in manufacturing the IMPs occurred due to unexpected increased costs by the contract manufacturer. Due to moving the start of recruitment to February 2017, we had to apply to the HRB to extend the project's finish date. Further delays occurred due to the HRB application process and due to the HPRA unexpectedly requesting analytical testing of the IMPs. These delays resulted in the start date for recruitment being moved to March 2018. However, further delays the anticipated national introduction of the European Union's new General Data Protection Regulation (EU) 2016/679 on the 25th May 2018 mandated a delay in starting trial participant recruitment that was supposed to begin in March 2018. The trial's patient information leaflet (PIL) and consent forms had to be amended to make them GDPR-compliant. The

amended documents were submitted to the REC that provided ethical approval for the study, the Cork Teaching Hospitals' Clinical Research Ethics Committee. Following submission of the GDPR-compliant documents to the Clinical Research Ethics Committee of the Cork Teaching Hospitals on the 31/07/2018, full approval for the study to commence patient recruitment was not obtained until the 22nd October 2018. These delays resulted in recruitment starting in January 2019

Screening

All emergency department patients with acute cellulitis underwent a study eligibility screen. The eligibility screen involved evaluation of the study's inclusion and exclusion criteria by direct interview with any patient with acute cellulitis by a study recruiter.

10.2 PROTOCOL DEVIATIONS

Table 4 gives details of protocol deviations observed during the study.

Table 4 Protocol deviations

Deviation	*Site: Beaumont*
Consent Procedures	0
Inclusion/Exclusion Criteria	0
Patient Compliance with IMP	0
Laboratory Assessments	0
Study Procedures	2
Serious Adverse Event Reporting	0

11 RESULTS

11.1 DATA SETS ANALYSED

No data analysis was performed because the study was terminated after the recruitment of only four trial participants.

11.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

No demographic data is presented because no data analysis was performed as the study was terminated after the recruitment of only four trial participants.

11.3 TABULATIONS OF PATIENT DATA

No data analysis was performed because the study was terminated after the recruitment of only four trial participants.

11.4 STATISTICAL/ANALYTICAL ISSUES HANDLING OF DROPOUTS OR MISSING DATA

No statistical analysis was performed because the study was terminated after the recruitment of only four trial participants.

We planned to perform both intention-to-treat (ITT) and per-protocol analyses. ITT analyses include all patients randomised to a trial regardless of whether they actually satisfied entry requirements, received the assigned treatments, withdrew from the trial or adhered to the protocol. We planned to impute missing values, if possible, using a suitable imputation method. For a per-protocol analysis, we planned to include only patients who completed at least ≥75% of the doses provided during the first 48 hours of the treatment period and adhered to the protocol requirements. In a non-inferiority trial setting, it is suggested that a per-protocol analysis may be more appropriate since it is more likely to reflect actual differences between the two treatments. Also, ITT analysis may be interpreted as being too liberal in a non-inferiority trial and may bias toward making the two treatments appear similar. As a result, we planned to perform both an ITT and per-protocol analysis on the resulting data to assess non-inferiority of the placebo/flucloxacillin combination. In particular, to declare non-inferiority, we planned to exclude the non-inferiority margin in both the ITT and per-protocol analysis.

12 SAFETY EVALUATION

There were no SAEs reported to the Sponsor during the trial

12.1 DEATHS

There was no deaths reported during the trial.

12.2 CLINICAL LABORATORY EVALUATION

12.3 VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY

Vital signs and pertinent physical findings were evaluated at each study visit and abnormal findings recorded as adverse events where appropriate.

13 DISCUSSION AND OVERALL CONCLUSIONS

Trial participant recruitment started in January 2019. Only four trial participants were recruited. The project was terminated on the 9th April 2020 after six months when it was impossible to recruit more trial participants consistently. The trial was closed for the following reasons:

1. An inability to recruit a full-time research nurse at the Dublin study sites.
2. A failure to recruit a project manager.
3. Suspension of patient recruitment due to the ongoing coronavirus pandemic that made achieving the recruitment target impossible during the project's funded period.

14 FIGURES, GRAPHS AND TABLES

Figure, Table, Graph	**Title**
Figure 1	Schematic Diagram demonstrating study design
Table 1	Ethics committees
Table 2	Key study personnel
Table 3	Schedule of assessments and procedures
Table 4	Protocol Deviations
Table 5	Randomisation and Allocation of Study Drug

15 APPENDICES

Appendix 1-Initial Ethics Committee Approval
Appendix 2-Patient Information Leaflet and Consent Form
Appendix 3-Initial HPRA Approval
Appendix 4-Summary of changes to protocol (Version 1- Version 5)

16.1.1 Randomisation and Allocation of Study Drug

Table 5

Patient Study ID Number	Randomisation Date	Allocation
11001	4/2/2019	Penicillin V
11002	11/2/2019	Placebo
12001	25/2/2019	Penicillin V
11003	28/1/2020	Placebo

16.1.2 Audit Certificate

Not applicable

16.1.3 Statistical Analysis Plan

Described in the report

16.1.4 Laboratory quality assurance

Not applicable.

16.1.5 Publications based on the study

1. Maher S, Walsh SJ, Takyi J, **Wakai A**, Brayden D, Hayden J. Effect of over-encapsulation on the disintegration and dissolution of licensed formulations for blinding in randomised controlled trials. *J Pharm Sci* 2019;108(3):1227-1235. PMID: 30385287
2. Boland F, Quirke M, Gannon B, Plunkett S, Hayden J, McCourt J, O'Sullivan R, Eustace J, Deasy C, **Wakai A**. The Penicillin for the Emergency Department Outpatient treatment of CELLulitis (PEDOCELL) trial: update to the study protocol and detailed statistical analysis plan (SAP). *Trials* 2017 Aug 24;18(1):391. doi: 10.1186/s13063-017-2121-2

16.1.6 Publications referenced in the report

Where there are relevant publications, they are referenced at the end of each section of the report.

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