Full title: DEXACELL: DEXAmethasone as an adjunctive therapy for the management of CELLulitis - a randomised controlled trial in urgent secondary care

Short title: The DEXACELL trial

PROTOCOL

Version 3.0, 30th September 2024

IRAS number:	1009877
ISRCTN:	<to be assigned and inserted>
Funder's reference:	NIHR153216

This protocol has regard for the HRA guidance.

i. SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature:	Date (dd/mm/yyyy):
Name (please print):	
Position:	

Chief Investigator:

Signature:	Date (dd/mm/yyyy):
Name: (please print):	

Senior Trial Statistician:

Signature:	Date (dd/mm/yyyy):
Name: (please print):	

ii. PROTOCOL AMENDMENT HISTORY

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
N/A	1.0	N/A	N/A	N/A first version for initial submissions
N/A	2.0	N/A	Katie Joyce Edward Carlton	Updates made between pharmacy assurance submissions and IRAS submissions: • Defining the term 'clinician', who can be PI, and who can confirm eligibility. • Moving the collection of ethnicity data pre-consent. • Clarification that eligibility will be captured in medical notes. • Correction to typo in minimisation criteria in section 7.5
N/A	3.0	<To be inserted>	Katie Joyce	Updates made in response to REC feedback: • Update to give vouchers to all as an inconvenience payment. • Clarification that watching information video alone is not sufficient prior to consent (PIS must be given).

iii. KEY TRIAL CONTACTS

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i. LIST OF CONTENTS

ii. LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
AUC	Area Under the Curve
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
ED	Emergency Department
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
MHRA	Medicines and Healthcare products Regulatory Agency
NHS R&D	National Health Service Research & Development
NSAID	Non-Steroidal Anti-Inflammatory Drug
PI	Principal Investigator
PIS	Participant Information Sheet
QALY	Quality Adjusted Life Year
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

iii. TRIAL SUMMARY

Trial Title	A pragmatic, multi-centre, double-blind, placebo-controlled, randomised, parallel group, phase 3 superiority trial with cost-effectiveness analysis of adjunctive DEXAmethasone in adults with CELLulitis	
Internal ref. no. (or short title)	The DEXACELL Trial	
Clinical Phase	Phase 3	
Trial Design	A pragmatic, multi-centre, double-blind, placebo-controlled, randomised, parallel group superiority trial, with internal pilot and parallel health economic evaluation.	
Trial Participants	Adult patients (16 years old and over) with a clinical diagnosis of cellulitis at any body site except the orbit.	
Planned Sample Size	450	
Treatment duration	24 hours	
Follow up duration	90 days	
Planned Trial Period	36 months	
	Objectives	**Outcome Measures**
Primary	To establish if the addition of dexamethasone to treat patients with cellulitis reduces total pain reported over the first three days (post-randomisation) compared to a control (placebo)**.**	Total pain experienced over the first 3 days, calculated using the standardized area under the curve (AUC) approach from seven individual pain scores captured at baseline and approximately 12-hour intervals using a numerical rating scale (NRS; 0-10).
Secondary	See Table 1 in Section 3.3.2.	See Table 1 in Section 3.3.2.
Investigational Medicinal Product(s)	Dexamethasone	
Formulation, Dose, Route of Administration	Two 8mg doses of dexamethasone (or matched placebo) taken ~24 hours apart. Each dose is made up of 2 x 4mg tablets of dexamethasone over-encapsulated into two separate capsules for blinding purposes with matched placebo capsules.	

iv. FUNDING AND SUPPORT IN KIND

This trial is funded by the NIHR Health Technology Assessment Programme (NIHR153216). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

The trial was developed with support from the UK Dermatology Clinical Trials Network (UK DCTN). The UK DCTN is grateful to the British Association of Dermatologists and the University of Nottingham for financial support of the Network.

v. ROLE OF TRIAL SPONSOR AND FUNDER

Sponsor role

North Bristol NHS Trust is Sponsor for the DEXACELL trial. The Sponsor has input into the design of the trial and the drafting of this protocol but overall responsibility for the design lies with the Chief Investigator. The Sponsor is responsible for authorising the initial submission to the Medicines and Healthcare products Regulatory Agency (MHRA), Research Ethics Committee (REC) and Health Research Authority (HRA) and any subsequent amendments. The Sponsor will ensure appropriate agreements and indemnity arrangements are in place, overseeing the conduct of the trial and ensuring it adheres to the principles of Good Clinical Practice (GCP) and the UK Policy Framework for Health and Social Care Research. The Sponsor will oversee archiving at the end of the trial. The Sponsor is not responsible for and has no involvement in the data analysis or interpretation, or for writing manuscripts.

Funder role

The NIHR as funder are responsible for providing funds to cover the agreed research costs. The funder is not responsible for and has no involvement in data analysis or interpretation, or for writing manuscripts.

Clinical Trials Unit role

Exeter Clinical Trials Unit (ExeCTU), University of Exeter, is the Clinical Trials Unit responsible for the day-to-day management of the trial. Responsibilities of ExeCTU, the Sponsor and Chief Investigator are defined in detail in a separate task allocation document. ExeCTU will be closed on bank holidays and University of Exeter closure days; only emergency trial support will be available at these times.

vi. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Trial Steering Committee

The Trial Steering Committee (TSC) will be composed of an independent chairperson with expert knowledge in the subject area, an independent statistician, Patient and Public Involvement (PPI) representative(s) and at least one other independent professional member. The Chief Investigator and co-lead will join the TSC as non-independent members. Observers will be invited to attend TSC meetings but will not be voting members (e.g. trial manager(s), trial statistician(s), health economist(s), Sponsor representative, Funder representative).

The role of the TSC is to monitor and supervise the progress of the trial. The TSC chair and/or TSC committee will have reviewed the final protocol prior to submission to MHRA/HRA/REC and the TSC independent statistician will approve the Statistical Analysis Plan (SAP) prior to final database lock.

The TSC will meet prior to recruitment commencing and approximately 6-monthly thereafter. Further details of the roles and responsibilities of the TSC are documented in the TSC charter.

Data Monitoring Committee

The Data Monitoring Committee (DMC) will be composed of a minimum of three independent professional members, including a statistician. The Chief Investigator, co-lead, senior statistician, trial statistician and trial manager will be invited to attend the open sessions of DMC meetings but will not be voting members. The senior statistician will be unblinded throughout the trial and the trial statistician will remain blinded until the completion of the primary statistical analysis. Only the unblinded statistician can be invited to the closed section of DMC meetings and will prepare/review unblinded sections of the DMC report.

The DMC will monitor accumulating trial data, including safety, and make recommendations to the TSC as to whether there are any ethical or safety issues that may necessitate a modification to the protocol or early closure of the trial. Further details of the roles and responsibilities of the DMC are documented in the DMC charter.

Trial Management Group

The Trial Management Group (TMG) will be composed of the Chief Investigator, co-lead, trial co-applicants, trial statisticians, PPI lead, at least one lay representative, the trial manager(s), data manager(s) and a Sponsor's representative. The TMG are responsible for writing the protocol, statistical analysis plan and participant-facing materials, obtaining relevant approvals from an NHS REC, the MHRA and the HRA, coordinating with NHS Trusts to set up sites and ensuring the trial is conducted according to the principles of GCP and the UK Policy Framework for Health and Social Care. The TMG will meet regularly (approximately every two months) to manage the trial, monitor safety, key performance indicators and discuss and resolve emerging issues. Members of the TMG will analyse the data, interpret the analyses, write reports to the funder and write and submit manuscripts to peer-reviewed journals. A 'core' group of TMG members may meet more frequently and liaise by email to discuss the day-to-day running of the trial; this will include the Chief Investigator, co-lead, the trial manager(s), statistician(s), health economist(s) plus other members of the wider TMG, as relevant for the topic at hand.

PPI group

An overarching Patient Advisory Group (PAG), led by the PPI lead, will have reviewed patient-facing materials prior to submission for ethical review and will have input into any revisions to patient-facing materials throughout the trial. This group will meet regularly throughout the trial.

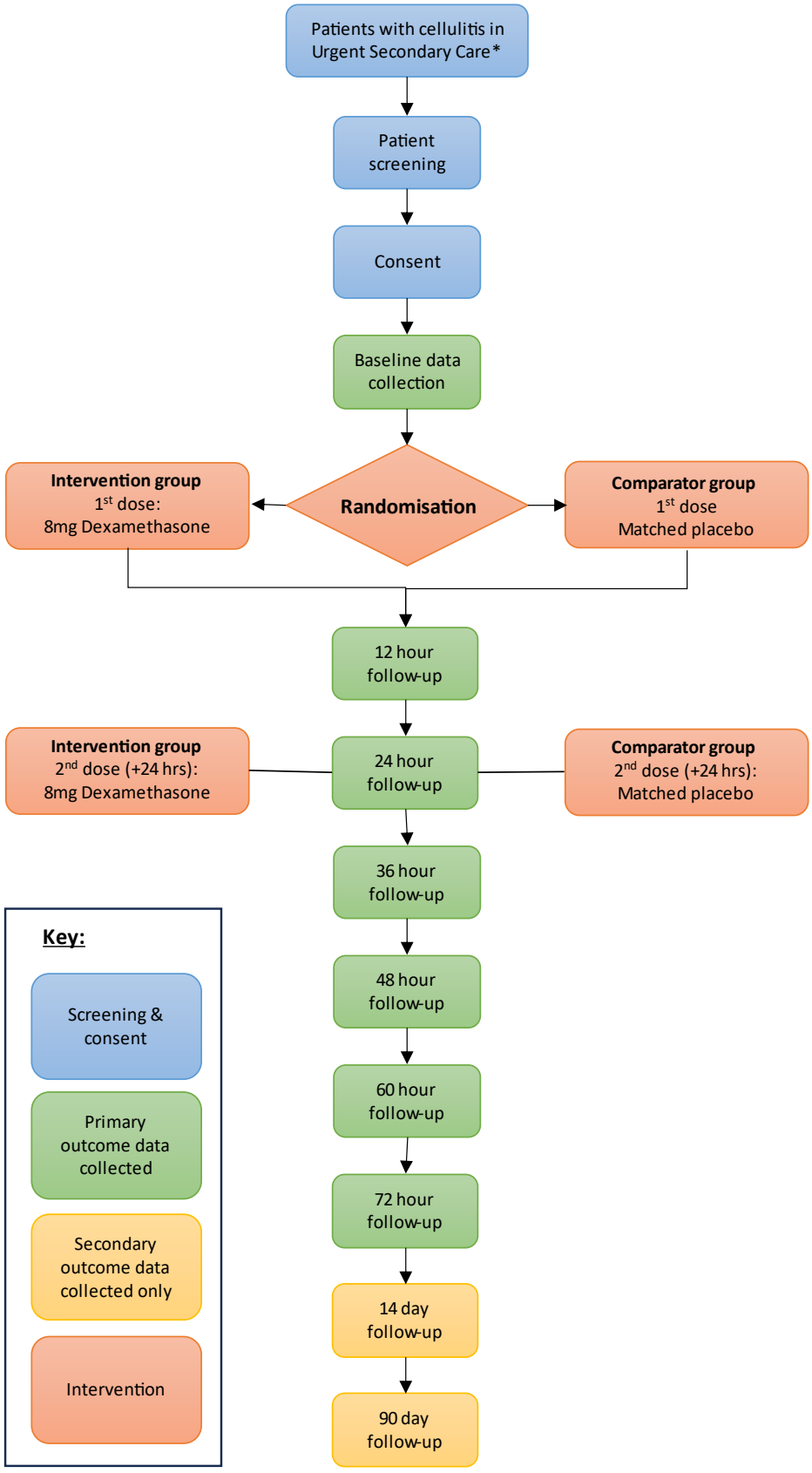
As intravenous drug users are an underserved population and commonly experience skin infection, this will be supplemented through ongoing engagement activities with Bristol Drugs Project (BDP) and relevant keyworkers. BDP have been invited to have a representative sit on the TMG and/or the PAG throughout the trial.

vii. KEY WORDS

Cellulitis; emergency; dexamethasone; corticosteroids; pain; infection

viii. TRIAL FLOW CHART

Figure 1: Participant pathway.



**Emergency Departments, Ambulatory Care Units, Same Day Emergency Care*

1. BACKGROUND

Cellulitis is a very common bacterial skin infection. It has a major impact, causing pain, swelling, and reduced ability to perform normal activities of daily living. It accounts for over 300,000 presentations to Emergency Departments (ED) each year in England alone (2019 figures), with 50% of patients subsequently admitted to hospital.[1] Patients with cellulitis account for 3% of all adult hospital admissions and are estimated to occupy 1% of NHS hospital beds in England and Wales.[2] Management of cellulitis is described in NICE guidance NG141, and includes antibiotic therapy, analgesia, and advice to seek further healthcare consultation if symptoms are worsening or not improved at 48-72 hours.[3] Ongoing symptoms lead to repeat consultation in around 1 in 5 patients, with the literature describing pain, despite analgesia use, as the major reason for reattendance at hospital or to another healthcare provider.[4–7] Although antibiotics are highly effective at killing bacteria, they have no direct effect on inflammation. Consequently, it is common for pain and swelling to progress in the first few days of antibiotic treatment.[5,6,8,9] One in five patients re-present to hospital or primary care. Antibiotic courses are often extended or switched to intravenous therapy; both options have been shown to have no benefit and can cause harm to patients, at increased cost, and contribute to antibiotic resistance.[7,9–11] There is therefore an unmet need to try and improve early response in cellulitis, by modulating the host immune response.

Review of evidence for steroids as a potential therapeutic option

Corticosteroids ("steroids") are anti-inflammatory agents, used successfully to treat numerous other acute infections[12–17] yet are not currently recommended by NICE for treatment of cellulitis.[3] They have a wide range of effects that dampen down the immune response and improve short term symptoms in infection.[18] For example, in a Cochrane review of randomised trials of adjunctive steroids in sore throat, the use of steroids reduced symptoms and had limited adverse effects.[14] Recent randomised trials in various surgical settings have shown a single dose of corticosteroids at the time of surgery reduces post-operative pain.[19,20]

Two randomised trials of steroids for acute cellulitis are known to have taken place, one of which is unpublished. The first trial randomised 112 hospitalised cellulitis patients in Denmark to steroids (30mg prednisolone once daily for 2 days, then reducing over a week) or placebo, alongside antibiotics.[21] The primary outcome was time to clinical cure, defined as lack of fever and lack of 'blush', which was significantly quicker in the prednisolone arm compared to placebo (10.0 vs 14.6 days, $p<0.01$). Clinical cure occurred rapidly in the prednisolone arm, with divergence of survival curves by 48 hours. Importantly, long-term (1-year) follow-up identified no evidence of increased cellulitis recurrence or other steroid-related adverse outcomes.[22] In the second (unpublished) trial (NCT01671423), a single dose of 60mg prednisolone was compared to placebo (n=25).[23] Correspondence from the Chief Investigator reported a greater (not statistically significant) reduction in pain at 48 hours with steroids vs placebo: mean change from baseline 39.9 (SD 27.9, n = 14) vs 30.5 (SD 9.8, n = 11) points on 0-100 Visual Analogue Scale (VAS).

Two additional trials have been identified that have assessed the role of non-steroidal anti-inflammatory drugs (NSAIDs) in addition to usual care for patients with cellulitis. NSAIDs are likely to have a similar mechanism of action to steroids. Davis et al randomised 51 ED patients to ibuprofen, 400mg three times a day for 5 days, or placebo.[24] A higher rate of clinical improvement at 48 hours was observed with ibuprofen (80% vs 65%). Dall et al used a non-random sequential trial of ibuprofen 400mg 4 times a day vs usual care for 5 days. Regression of inflammation was observed in a higher proportion of those who received ibuprofen compared to those who did not (83% vs 10%). In other

skin and soft tissue infections, evidence favours a beneficial effect of steroids on pain. In particular, in orbital cellulitis (managed differently due to the risk of visual loss), a small randomised trial (n = 21) showed a reduction in pain with the addition of steroids, with an 8 point mean difference (SD 21) in pain (once rescaled between 0-100) at 48 hours after starting steroids.[25] A randomised trial of corticosteroids in paediatric orbital cellulitis is planned in Australia (ANZCTR ref: ACTRN12622000808741).

The above evidence was summarised in a 2020 Cochrane review on interventions for cellulitis[26] that concluded that further trials are needed before adoption of steroids as standard practice. In agreement with this, Infectious Diseases Society of America (IDSA) guidance recommends a randomised controlled trial (RCT) of anti-inflammatory therapy.[27]

1.1. Proposal for a randomised trial and participants

There is clear equipoise around the potential benefit of corticosteroids in treating cellulitis. With no current consensus, two major guidance bodies (Cochrane and IDSA) are calling for randomised trials to investigate whether steroids might improve outcomes. As such, a randomised trial of steroids to reduce the burden of symptoms and onward consequences of cellulitis is warranted. This trial is focused on adult participants who present to emergency and urgent care with cellulitis, as this population is at higher risk of treatment failure than those who present to primary care, and the severity of disease is generally higher.

2. RATIONALE

Research question: Is the addition of oral dexamethasone to usual care in patients who present to urgent and emergency care with cellulitis effective and cost-effective in terms of reducing pain, improving quality of life, and reducing further antimicrobial usage and healthcare utilisation?

2.1. Justification of importance

As cellulitis is very common (around 3% of all hospital admissions, > 300,000 presentations to emergency departments (ED) each year), even a small reduction in patient symptoms or downstream healthcare costs is likely to be beneficial and cost-effective. If steroids reduce pain and symptoms as much as in other acute infections, this could lead to large reductions in morbidity across the population and likely lead to reduced subsequent antimicrobial prescriptions and healthcare costs. Extensive Patient and Public Involvement (PPI) work during the development of this trial identified pain as a key issue in patients with cellulitis, and a recent priority setting partnership in cellulitis confirmed our outcomes as key issues for patients.[28]

2.2. Potential benefits of steroids

As outlined above, steroids have been shown to be effective in numerous other infective conditions, with meaningful and clinically relevant effect sizes. A review of the literature (described in section 0), identified reductions in pain that were clinically significant, with shorter time periods until full recovery and large reductions in pain within the first few days.

2.3. Choice of placebo design

This trial proposed is a placebo-controlled trial. The choice of placebo control is because the primary outcome is participant-reported pain, which would be at great risk of bias in an open label design. The

use of a placebo control is further justified because all participants will receive standard care for cellulitis in line with local policies including clinical assessment, antibiotics and analgesia, hospital admission if deemed required by the treating clinical team, together with advice on management of concomitant conditions (e.g. diabetes) and advice on expected symptom duration in line with NICE guidance (NG141). In addition to this usual care, patients will also receive either the dexamethasone or placebo.

2.4. Assessment and management of risk

Cellulitis is commonly treated in hospital emergency departments and other urgent care settings and is generally more severe than when patients present in primary care.

The intervention group for this trial will be prescribed 2 x 8mg doses of dexamethasone to be taken orally 24 hours apart (+/- 6 hours). The comparator group will take 2 x matched placebo doses. Each 8mg dose of dexamethasone will be made up of 2 x 4mg tablets over encapsulated into two capsules, for blinding purposes.

A detailed risk assessment has been carried out by the Sponsor and will be maintained and updated throughout the trial. This trial has been characterised as Type B (somewhat higher than the risk of standard medical care) as the IMP (dexamethasone) has marketing authorisation but the DEXACELL trial will use the IMP outside of these specifications.

Extensive experience of short-course steroids in infection have not identified major safety concerns[14,29] and patients with contraindications to dexamethasone will not be eligible to participate in the trial. Dexamethasone is already indicated for several conditions, including short term local treatment of inflammation, suppression of inflammatory and allergic disorders, croup (a respiratory viral condition in infants), treatment of COVID-19 requiring supplemental oxygen, and a variety of other conditions.[30] The dosage being used in this trial is much lower than dosages recommended for some conditions, e.g. in idiopathic thrombocytopenic purpura 40mg doses are recommended daily for up to 4 days and in some cases of acute cerebral oedema doses of up to 64mg per day are given for days to weeks. Comparing with other infectious diseases, in this trial a total dose of 16mg will be given; when compared to 400mg recommended in adjunctive therapy for meningitis this is a 25 fold difference.[31]

Information about possible benefits and risks of participation will be described in the Participant Information Sheet (PIS).

2.4.0. Potential risks

Known drug reactions and interaction with other therapies

The main risks to the participants are potential side effects of the study drug. A full list of known adverse effects of dexamethasone is detailed in the Summary of Product Characteristics (SmPC).

The adverse effect profile of steroids is well documented, although most data relate to chronic use (>2 weeks) of steroids, with less randomised trial data on harms of short-term steroid use. The short-term adverse effects are hyperglycaemia (particularly in people with diabetes), gastrointestinal (GI) toxicity leading very rarely to bleeding, and psychosis, which is extremely rare.[32]

A Cochrane review of randomised trials of short-term steroid use in pharyngitis[14] did not identify increased rates of these or other adverse events compared to placebo. In the RECOVERY trial for patients with COVID-19, participants were randomised to dexamethasone (6mg once daily for ten

days) or usual care.[13] Despite 2,104 patients randomised to dexamethasone only 4 serious adverse events (2 hyperglycaemia, 1 GI bleed, 1 psychosis) were reported. Importantly, 25% of all recruits to the RECOVERY trial had diabetes, suggesting that significant and clinically important hyperglycaemia is a rare event even in patients with diabetes. In three recent placebo controlled randomised trials in surgery (n > 1,600) using similar or larger doses (8-24mg) than this trial, there was no increase in adverse events to those assigned steroids.[19,20]

However, a proportion of potential participants for this trial may have risk factors for these adverse events of steroids that warrant further consideration and risk assessment. These are described below and the local PI/CI (or appropriately qualified delegate) will assess these risks on recruitment. Mitigation approaches are described in each section.

Gastrointestinal Bleeding

GI bleeding is expected to be very rare in our trial population but can be serious. Some potential participants are likely to be at increased risk of GI bleeding, particularly those of older age, with peptic ulcer disease or those taking NSAIDs, either long-term or for acute pain due to their cellulitis.

There is no contraindication or warning in the SmPC for dexamethasone concurrent to NSAID usage. In some studies, co-prescription of steroids and NSAIDS has been associated with increased rates of GI bleeding. However, this was with long-term steroid usage and absolute rates were very low (3.19-7.74 per 1000 patient years for GI bleeding-related hospitalisation). NICE recommends prescription of a protein pump inhibitor when co-prescribing NSAIDs and long-term steroids for rheumatoid arthritis and recommends an assessment of the risk of GI bleeding with long-term steroid use.[33] This is not applicable in this trial, given the short-term use of dexamethasone.

A 2021 RCT (DEX-2-TKA) provides useful evidence on the safety of the short-term combination of NSAIDs and steroids.[20] The mean age of participants was 69 years, 20% had recent NSAID use, and >80% had comorbidities. Importantly, all participants received ibuprofen regularly at 400mg four times a day alongside dexamethasone/placebo. No increase in adverse events was noted in the dexamethasone arms, compared with placebo, with all participants followed up at 90 days. Prophylaxis with proton pump inhibitors was not mandated and was at the discretion of the treating physician. No GI bleeds were reported, with one participant reporting “GI upset”. This trial data suggests the absolute risk of GI bleeding is very low and does not support an increased risk in patients with short-term use of dexamethasone. However, potentially eligible participants for this trial may have other risk factors for GI bleeding (e.g. older age, peptic ulcer disease).

To mitigate this risk, despite the very low absolute risk given the very short course of dexamethasone, sites are provided with a working instruction on assessing the risk of GI bleeding in patients. Clinicians are advised to consider prescribing a proton pump inhibitor if felt to be clinically indicated, based on patient risk factors and recent NSAID usage. Proton pump inhibitor prescription will be recorded, and GI bleeds reported as a Serious Adverse Event (SAE). Additionally, patients with known active gastric or duodenal ulceration will not be eligible to participate.

Hyperglycaemia in diabetes

Hyperglycaemia is a known side effect of dexamethasone. In the context of diabetes, dexamethasone can produce prolonged hyperglycaemia, requiring insulin or other medications to control it. As cellulitis is common in patients with diabetes, a substantial proportion of our trial participants are anticipated to have diabetes and it would not be appropriate to exclude them from the trial. In all patients with diabetes who develop infection, or other illnesses, the requirement for monitoring of blood sugars increases and patients on insulin may require more (or less) insulin. The absolute risk of severe

hyperglycaemia with dexamethasone use appears low from recent trial data; (2/2104 participants in the RECOVERY trial assigned dexamethasone reported hyperglycaemia; diabetes prevalence 25%, and 0/323 reported hyperglycaemia in DEX-2-TKA; diabetes prevalence 10%).

Given the seriousness (and potential for under-reporting in previous trials) of this risk, site-specific training and working instructions will be provided to sites covering hyperglycaemia, sick day rules, and advice on diabetes management for all participants with diabetes.

To mitigate these risks further participants with diabetes will be provided with additional patient information sheets prior to consent. These incorporate Diabetes UK guidance on sick day rules and how to manage high sugar levels. Site-specific information on who to contact in case of concern, are included. Episodes of severe hyperglycaemia will be recorded as SAEs see section 9.

Psychosis

Psychosis is a rare but recognised complication of steroid treatment, although it is very rarely seen with short term courses and is recognised to be dose related and related to total course length,[34–36] with incidence likely to be very rare given the total dose in this study (16mg dexamethasone) over 24 hours. For example, in one study, rates of psychosis were ~16 times higher in those receiving 80mg prednisolone than those receiving <40mg of prednisolone a day.[36] In the RECOVERY study, the total dose of steroid was ~5 times higher (6mg IV OD for 10 days, equivalent total oral dose ~80mg[37]) than will be used in this trial and only a single case of psychosis was observed among 2,104 patients assigned dexamethasone. In two recent surgical trials (n = 323[20] and n = 674[38] randomised to dexamethasone at higher doses than those being prescribed in this trial), not a single patient was reported to have developed psychosis.

As per the 2007 MHRA drug safety update on prescribing systemic corticosteroids, information on this risk is provided in the patient information sheet.

2.4.1. Potential benefits

Participants enrolled in this trial have the potential to reduce the risk of pain and other cellulitis symptoms, and the potential to reduce future unscheduled healthcare visits and further antimicrobial usage for cellulitis. The other main benefit is to potentially improve care for other patients in the future.

3. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1. Primary objective

To establish if the addition of dexamethasone to treat patients with cellulitis reduces total pain reported over the first three days (post-randomisation) compared to a control (placebo)**.**

3.2. Secondary objectives

To determine whether the addition of dexamethasone to treat patients with cellulitis when compared to a control (placebo):

a) Improves quality of life and other patient reported outcomes,
b) Reduces subsequent antimicrobial prescribing, analgesia usage and healthcare utilisation
c) Is cost-effective.

3.3. Outcome measures/endpoints

3.3.0. Primary endpoint/outcome

The primary outcome for this trial is total pain experienced over the first 3 days after randomisation. Seven individual pain scores will be captured using a numerical rating scale (NRS; 0-10) and used to calculate the standardised (scaled between 0 and 100) area under the curve (AUC) over the period.

The first (baseline) pain score will be collected in person pre-randomisation as part of a participant questionnaire pack. The remaining 6 pain scores will be collected post-randomisation, at approximately 12-hour intervals. The post-randomisation scores will be collected remotely via a survey sent via SMS message. Text messages will be sent at around 8am and 8pm to ensure participants recruited overnight (e.g. at 3am) are not receiving text messages during the night, as recommended by PPI input. The first follow-up text message will be sent/received at the first available follow-up timepoint (~8am or ~8pm) after the time of randomisation; the subsequent 5 follow-up texts will be received every 12 hours thereafter. If they feel able to, participants will be encouraged to complete the first follow-up survey even if it is received close to their baseline data collection (e.g. if they are randomised at 7am and receive first follow-up request at 8am). The actual time of response will be recorded and statistical modelling (described in data analysis section below) will be used to calculate total pain over the first 3 days.

If the participant cannot complete the surveys on a mobile phone, a telephone follow-up option may be offered depending on staff capacity. Participants admitted to hospital will be offered in-person visits by a member of the study team for data collection where possible or they can continue to provide pain scores remotely if preferred.

3.3.1. Secondary endpoints/outcomes

1. Health-related quality of life, measured by EQ-5D-5L at Day 3, Day 14 and Day 90 post-randomisation
2. Patient Global Impression of Improvement (PGI-I) measured daily for first 3 days and at Day 14 post-randomisation
3. Analgesia usage (number and type of analgesia taken over first 3 days) post-randomisation
4. Antibiotic usage (route, type, and post-randomisation length of course) up to Day 14 post-randomisation
5. (Re)admissions to hospital by Day 14 post-randomisation
6. Complications of dexamethasone use by Day 14 post-randomisation
7. Unscheduled healthcare usage until Day 14 post-randomisation
8. Health, social care and broader societal resource use, measured by a resource use questionnaire based on the Modular Resource Use core module (ModRUM) tailored to the study population, to Day 90 post-randomisation
9. Recurrence of cellulitis by Day 90 post-randomisation
10. Serious and/or potentially related adverse events by Day 90 post-randomisation
11. Pain experienced at Day 14 post-randomisation

3.3.2. Table of endpoints/outcomes

See Table 1 for a summary of the objectives and outcome measures.

Table 1: Table of endpoint/outcomes.

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure
<u>Primary Objective</u>		
To establish if the addition of dexamethasone to treat patients with cellulitis reduces total pain reported over the first three days.	Total pain experienced over the first 3 days post-randomisation, calculated using the standardized area under the curve (AUC) approach from seven individual pain scores. First is captured at baseline and then 6 scores captured post randomisation at approximately 12-hour intervals using a numerical rating scale (NRS; 0-10), starting at the next available 8am or 8pm timepoint.	Baseline T1* T2* T3* T4* T5* T6*
<u>Secondary Objectives</u>		
To determine whether the addition of dexamethasone to treat patients with cellulitis:		
Improves quality of life and other patient reported outcomes.	Health-related quality of life, measured by EQ-5D-5L up to day 90 post-randomisation	Day 3 Day 14 Day 90
	Pain experienced at day 14 post-randomisation, measured using a numerical rating scale (NRS; 0-10)	Day 14
	Patient Global Impression of Improvement (PGI-I) up to day 14 post-randomisation	T2* T4* T6* Day 14
Reduces subsequent antimicrobial prescribing, analgesia usage and healthcare utilisation.	Number and type of analgesia taken up to day 3 post-randomisation	Day 14
	Antibiotic usage (route, type, and post-randomisation length of course) up to day 14 post-randomisation	Day 14
	Unscheduled healthcare usage up to day 14 post-randomisation	Day 14
	(Re)admissions to hospital by Day 14 post-randomisation	Day 14
	Recurrence of cellulitis up to day 90 post-randomisation	Day 90
	Serious and/or potentially related adverse events up to day 90 post-randomisation	Day 14 Day 90

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure
	Complications of dexamethasone use by Day 14 post-randomisation	Day 14
Is cost-effective.	Health, social care and broader societal resource use, measured by a resource use questionnaire based on the Modular Resource Use core module (ModRUM) tailored to the study population, to Day 90 post-randomisation	Baseline Day 90

** The first follow-up text message (T1) will be received at the first available follow-up timepoint (~8am or ~8pm) after randomisation, the subsequent 5 follow-up texts (T2-T6) will be sent every 12 hours thereafter.*

4. TRIAL DESIGN

A pragmatic, multi-centre, double-blind, placebo-controlled, randomised, parallel group superiority trial, with internal pilot and parallel health economic evaluation in hospitals in the UK.

4.1. Internal Pilot

Judgement of the success of the internal pilot (after first 6 months of participant recruitment) will focus on the opening of 10 sites, recruitment rate and completeness of pain scores to calculate the primary outcome. Given the seasonality of cellulitis[1] (and hence reduced recruitment rate predicted in initial months) and allowing for staggered site opening, the progression criteria for mean recruits/site month are green: ≥2; amber: 1.4-1.9; red: <1.4. Other progression criteria are shown in Table 2.

Table 2: Proposed progression criteria to be assessed after first six months of participant recruitment.

	Green	Amber	Red
Number of sites open to recruitment	10	6 to 9	<6
Number of participants recruited	≥70	50-69	<50
Mean recruitment rate/site/month*	≥2	1.4-1.9	<1.4
% of participants with primary outcome (pain AUC)	≥85	75 to 84	<75

**Calculated over months a site is open to recruitment. Note: due to seasonality of cellulitis, with planned recruitment opening in September 2024, the mean/site/month is lower than is expected over summer months (mean of 4 recruits/site/month), leading to total recruitment period of ~17 months.*

In close consultation with the DMC, TSC, Sponsor and funder, the following actions will be taken in response to progress at the end of the pilot phase as measured against the progression criteria:

- **Green:** The trial will proceed. Refinements to enhance recruitment, adherence and retention will be implemented by the trial team.
- **Amber:** The trial team will discuss modifications to improve recruitment and adherence. The trial will continue if effective modifications to research processes can be agreed with the TSC and funder and made, with regular reviews.

- **Red:** The trial team will discuss any mitigating circumstances with the TSC and the funder. If the trial does not prove feasible, a closure plan will be agreed.

4.2. Main Trial

On progressing to the main trial period, sites will continue to be opened as required based on the internal pilot phase. Building on the internal pilot phase, it is anticipated that over a total of 15 sites, an average of 2.6 participants/site/month will need to be recruited (4/site/month in the summer period; 2/site/month in other months) to reach the overall recruitment target. Therefore the aim is to open a minimum of 15 sites to recruitment.

5. TRIAL SETTING

Participants will be recruited from hospital sites across England and Wales (and potentially Scotland). Each site must have an emergency department or urgent care service. All sites will treat and manage continued care for trial participants. Each site will have a research team, with a local Principal Investigator (PI) and research nurses/Allied Health Professionals (AHPs). The Principal Investigator may be a registered doctor or an appropriately qualified, registered and experienced prescribing clinician. The term 'clinician' has been used throughout this protocol to refer to the myriad of healthcare professionals that treat patients with cellulitis independently within urgent secondary care. The Principal Investigator must be a registered prescriber and have suitable clinical experience. The Sponsor will be responsible for approving any nominated Principal Investigators that are not registered doctors, ensuring they have an appropriate level of experience and expertise to lead the site team. A list of participating sites will be maintained by the trial manager and can be found within the Trial Master File (TMF).

6. PARTICIPANT ELIGIBILITY CRITERIA

6.1. Inclusion criteria

- Aged 16 years old or over
- A current clinical diagnosis of cellulitis at any body site except the orbit (periorbital/orbital cellulitis)
- Able to provide informed consent

People of child-bearing* potential must be willing to:

- Use an effective method of contraception** (and must agree to continue 3 months after the last dose of the IMP)
- Inform the trial team if pregnancy occurs during trial participation

** Potential participants are considered not of child-bearing potential if they are surgically sterile (i.e. they have undergone a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or they are postmenopausal (no menses for 12 months without an alternative medical cause).*

*** Highly effective contraception is defined as one of the following: combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable); intrauterine device(IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; vasectomised*

partner; practising true sexual abstinence (when this is in line with the preferred and usual lifestyle of the individual).

6.2. Exclusion criteria

Participants may not enter trial if ANY of the following apply:

- Orbital or periorbital cellulitis, surgical site infection, or planned surgical management (e.g abscess) as managed under a different clinical pathway
- Allergy to dexamethasone
- Contraindication to dexamethasone due to concurrent medication (e.g. cobicistat)
- Has known current invasive fungal infection**
- Has known current gastric or duodenal ulceration
- Already on corticosteroids
- Unable to take oral medication
- Lack of capacity
- Inability to complete follow-up procedures
- Prisoner*

People of child-bearing potential only:

- Pregnant***, breastfeeding, or planning to conceive in next 3 months

**This does not exclude patients in police custody, though consideration should be given to whether they are able complete the trial follow-up procedures.*

*** This includes only invasive infections such as pulmonary aspergillosis and does NOT include cutaneous infections such as athlete's foot, vaginal thrush, etc.*

****Must have a negative pregnancy test no more than 7 days prior to initiation of treatment.*

6.3. Inclusivity

Recruiting sites will be selected with an aim to cover underserved geographical areas to ensure we recruit diverse and disadvantaged populations, with a focus on areas of social deprivation. Changes in skin tone are not included in the inclusion criteria or outcome measures as this is a recognised issue with previous cellulitis studies and was raised by the Patient Advisory Group (PAG), other stakeholders, and the UK DCTN in relation to the potential biasing effect on both recruitment and collection of outcomes.

Other potential recruitment issues may arise in relation to language. During site selection and the internal pilot phase languages spoken by potential recruits will be recorded, including when language was a barrier to recruitment and/or participation and whether standard NHS translation services were used. Translation of key documents and the addition of subtitles to the video PIS will subsequently be carried out in key languages, where required.

Patients without capacity will not be eligible for this trial. This decision was made after extensive discussion with our PAG and the trial team. Given the primary outcome is self-reported pain, it is unlikely that patients lacking capacity to provide informed consent would be able to reliably provide primary outcome data. In discussion with the PAG, the use of Abbey pain scales[39], or similar, was considered as these are designed for patients with dementia. However, it would be too challenging to synthesise these differing primary outcomes and provide a meaningful statistical estimate of the

interventions effect. In addition, there is significant concern about the validity of the Abbey pain scores.[40]

6.4. Co-enrolment policy

Participants will be permitted to take part in other clinical trials including interventional or non-interventional studies (e.g. Clinical Trials of an Investigational Medicinal Products (CTIMPs), non-CTIMPs, observational studies) as long as the burden placed on the participant is reasonable and the other trial protocol permits this. This is to be agreed with the CI on a trial-by-trial basis ensuring that both studies' outcomes will not be compromised by the co-enrolment.

7. TRIAL PROCEDURES

7.1. Recruitment

Identification of potential participants will be locally led, as the provision of urgent care differs across sites. Recruitment processes will be performed by appropriately trained and delegated members of the research team (e.g. clinicians, research nurses). Recruitment out of normal research working hours will be facilitated through targeted training of clinicians (onsite 24/7) at participating sites. The NIHR Associate Principal Investigator Scheme will also be utilised to support recruitment.

Research delivery teams will identify those diagnosed with cellulitis who are potentially eligible (16 years or over with identified cellulitis at any body site except the orbit or periorbital area). Final eligibility must be confirmed prior to consent by the PI or an appropriately qualified and delegated clinician. This will be captured in the medical notes and documented in the eCRF. As noted in Section 5 (Trial Setting), the term 'clinician' has been used in this protocol to refer to the myriad of healthcare professionals that treat patients with cellulitis independently within urgent secondary care . All staff delegated to confirm eligibility must be a registered prescriber with appropriate clinical experience.

Potential participants will be given a Participant Information Sheet (PIS) describing the trial, which will have a brief PIS summary on the first pages. Potential participants will also be offered the opportunity to watch a participant information video describing the trial. Potential participants with diabetes will be given an additional information sheet describing the risks associated with taking steroids when diabetic and how this can be managed.

Due to the emergency/urgent care setting and the relatively acute nature of the condition and intervention, it is not felt practical to mandate potential participants have a specific amount of time to consider their participation in the trial. However, it is imperative that all potential participants be given sufficient time (as determined by the potential participant themselves) for trial information to be considered and for questions to be asked.

7.2. Payment

There will be no 'research only' visits, therefore participant payments for travel expenses are not included. However, to acknowledge the time taken to participate in the trial, and as responses to the SMS surveys are charged at standard network rates, all participants will be offered a supermarket voucher or equivalent (£20 per participant) for participating. This is optional and participants can decline the offer.

Intravenous drug users

Intravenous drug users are both underserved by trial research and have high rates of skin infection.[41] Funding is therefore available for each site to support the recruitment of this population; this funding is to cover any additional staff time that may be taken to support these patients. As services differ across the country, this funding will be paid directly to sites per IV drug user recruited with flexibility on how it is used (e.g. it could fund a dedicated drug user support service team, or additional staffing time from the core research team if no dedicated service is available).

7.3. Screening

Screening will be performed by dedicated research teams at each site based on the clinical presentation. A screening log eCRF will be completed for all potentially eligible adult patients (16 years or over with identified cellulitis at any body site except the orbit). Eligibility will be confirmed by the PI or an appropriately qualified and delegated clinician as described in section 7.1.

Screening logs will record non-identifiable general patient demographic data (including age, ethnicity and sex) so the patient population can be described. Eligibility, reasons for ineligibility, details of approach for consent, or details of declined consent will also be recorded where applicable. Participants' first language and use of any translation services will be recorded to identify any need for translations of participant materials.

Personal identifiable data will not be recorded on screening logs, instead a unique Participant number will be assigned.

To confirm eligibility of people of child-bearing potential, a negative pregnancy test (taken as part of routine care) will be required no more than 7 days prior to initiation of treatment.

Potentially eligible patients will undergo a capacity assessment from a suitably trained staff member. Patients without capacity will not be eligible for consent and this will be recorded on the screening log.

Eligibility should be confirmed by the PI or delegated clinician, this will be captured in the medical notes and documented in the eCRF. Only after eligibility is confirmed, will the patient be approached for their consent to take part in the trial (see consent section 7.4).

7.4. Consent

Informed consent will be sought from each eligible and interested patient by an appropriately trained and delegated member of the research team before enrolment into the trial. Consent can be obtained face to face either in writing on a paper consent form or electronically using a purpose designed electronic database (REDCap Academic).

Whether completed electronically or on paper, the consent form will be signed by the patient and countersigned by the staff member receiving consent. If a participant has capacity to verbally consent but cannot physically complete the consent form (e.g. due to cellulitis affecting the arm), a witness can sign the form on their behalf. The witness can be anyone who is independent from the trial, for example another member of staff. The witness must initial the statement boxes with their own initials after witnessing the participant's verbal consent to each statement and then sign their own name in the witness box of the consent form. If possible, the participant should be encouraged to 'mark' the form in the best way they can.

As part of the consent process participants can optionally consent to receive trial newsletters and/or the trial results and their allocation at the end of the trial. Participants' permission will be sought to use the trial data beyond the end of the study and optional consent for longer term follow-up, via linkage to routinely collected clinical data.

Sites should record key details of the informed consent process in the patient's medical record. Patients are not required to provide reasons if they choose not to participate, but if reasons are given, then they should also be documented in their notes and the screening log.

A copy of the consent form should be provided to the participant (by email or physical copy as preferred). Copies should also be added to the medical notes, stored in the ISF (or a file note to their location) and for paper consent forms only - an unredacted copy will be uploaded to REDCap by the site team, for monitoring by ExeCTU

After consent, participants will be given a paper diary/aide-memoire to record data required for the Day 14 & Day 90 follow-up calls (e.g. analgesia usage (type and frequency) for the first 3 days after randomisation). These will not be collected back in and are only to be used as a prompt for the follow-up calls.

7.5. Baseline data collection

Baseline assessment will be completed in person. Baseline assessment will include:

Questionnaire (participant completed): Participants will complete a baseline questionnaire pack containing the patient reported outcome measures listed below.

- EQ-5D-5L
- Health, social care and broader resource use (resource use questionnaire tailored for the population)

eCRF (staff completed):

- Contact details and contact preferences
- Demographics (including age, sex at birth, ethnicity, date of birth, self-reported gender, postcode for index of multiple deprivation)
- NHS number (or equivalent)
- Anthropometrics (height & weight for BMI (patient reported measurements will be accepted))
- Current pain score (NRS; 0-10)
- Current and recent (last 3 days) analgesia (including NSAID)
- Current and recent antimicrobial therapy for this episode of cellulitis (including length and route of administration)
- Current use of intravenous "street" drugs
- Clinical comorbidities (including diabetes, peripheral vascular disease, chronic venous insufficiency and morbid obesity; defined as a BMI of 40 and above)
- Other risk factors for steroid adverse events (including recent or previous gastric ulcers and proton-pump-inhibitor usage)
- Routine baseline observations (to calculate Eron and NEWS2[43])
- Cellulitis details, including:
    - Cellulitis severity will be captured by the Eron classification[44]
    - Cellulitis anatomical location
    - Timing of cellulitis onset

    - Other clinical details of cellulitis
- Clinical frailty scale

GP Practice contact details

GP Practice contact details will be collected/checked on the medical notes by the site in order to send out the GP letter, but will not be collected on the eCRF or returned to ExeCTU.

Minimum baseline data, pre-randomisation

Of the data listed above, a minimum baseline dataset must be collected prior to randomisation, this includes; inclusion and exclusion criteria, confirmation of eligibility, confirmation of consent, baseline pain score, mobile phone number and the minimisation criteria (diabetes status, severity of cellulitis and prior antimicrobial therapy for this current episode of cellulitis).

All other baseline data will ideally be collected before randomisation, but if not, immediately after randomisation and prior to giving the IMP.

7.6. Randomisation

Once collection of the minimum baseline data is complete, participants will be randomised on a 1:1 basis to either dexamethasone or placebo.

Participants will be randomised into the trial by a delegated member of the site team using an online randomisation service.

ONLINE ACCESS FOR 24-HOUR RANDOMISATION

Further information on how to randomise can be found in the separate 'Randomisation' work instruction contained in the Investigator Site File.

In any case where technical issues prevent the site team from accessing the online randomisation service, ExeCTU staff will be available within office hours to randomise on behalf of a delegated member of the site team. No back-up will be available out of office hours. Details for this procedure will be outlined in the 'Randomisation' work instruction.

Allocation will be stratified by recruiting site and then participants allocated using a minimisation algorithm with random element, to aid balance between the two study groups on the following factors:

1. Prior antimicrobial therapy for this current episode of cellulitis (yes/no)
2. Diabetes status, defined by a known diagnosis of either type 1 or type 2 diabetes mellitus (yes/no)
3. Severity of Cellulitis (Eron Class 1 vs all other classes)

Once the online randomisation process is complete, the system will indicate to the user a blinded pack ID which should be dispensed to the participant, it will not indicate whether the participant has been allocated to receive IMP or placebo.

The online randomisation system will automatically send an email to ExeCTU and the site team confirming the randomisation has taken place and the pack ID allocated. Site staff will note in the medical records that the patient has been enrolled into the trial. Site staff will then complete and send

the approved letter to the participant's GP (e.g. via post or secure email) informing the GP that their patient has entered the trial.

7.7. Blinding

This trial will be double-blinded and therefore neither clinicians nor participants will know which treatment has been allocated. This will be achieved by the IMP manufacturer over-encapsulating, packaging, and labelling the IMP and placebo doses to look identical. The IMP/placebo packs will be labelled with blinded pack IDs and the randomisation system will automatically assign a pack ID to be dispensed to the participant after randomisation is complete. Only the senior (unblinded) statistician, the IMP manufacturer and the developers of the randomisation system will have access to the master list which will indicate which pack IDs relate to placebo packs and which relate to dexamethasone packs.

The trial statistician(s) undertaking analyses will be blinded until the primary statistical analysis of the primary outcome is complete. Where possible, the research teams at the trials centre and sites will remain blinded.

7.7.0. Emergency Unblinding

A trial-specific procedure is in place for emergency unblinding although with both the short-term intervention period and low risk of serious adverse events it is anticipated that the need for unblinding will be minimal. Emergency unblinding will be available 24/7 via a dedicated and automated phoneline. Further details will be provided in a separate unblinding work instruction.

If the person requiring the unblinding is a member of the investigating team, then a formal request to the PI or other delegated member of the team will be made who will then call the phoneline to trigger the unblinding.

Although the safety of the trial participants must always take priority, maintenance of the blinding is crucial to the integrity of the trial. Unblinding is strongly discouraged and should only occur for medical or safety reasons. Investigators should only break the blind when information about the participant's trial treatment is clearly necessary and will alter the appropriate medical management of the participant.

An assessment to unblind should be made in consultation with the clinical and research teams wherever possible. The treating clinician has the ultimate decision and right to unblind the participant.

ACCESS FOR 24-HOUR UNBLINDING

Further information on how to unblind can be found in a separate 'Unblinding' work instruction in the Investigator Site File.

Each time an unblinding occurs, an email alert will be sent to ExeCTU and the site team, informing them that the unblinding has happened (this email will not reveal the allocation). A member of the site team should document the details of the unblinding and reasons for it on the 'Unblinding' eCRF, in the investigator site file and in the medical notes.

Following an emergency unblinding the participant should be treated according to the treating clinician's assessment.

Trial committees, where required within their charters, will also be notified of any unblinding.

7.8. Trial assessments

The timing of trial assessments is shown in Table 3.

Table 3: Data collection and schedule of assessments

Assessment / event	**Baseline (in person)**	**Early follow up (text message survey†)**						**Late follow up (telephone)**	
	Recruitment (time 0)	**T1‡**	**T2‡**	**T3‡**	**T4‡**	**T5‡**	**T6‡**	**14 days (±2)^**	**90 days (±7)^**
Eligibility screen	X								
Consent	X								
Randomisation	X								
Study drug dispensed*	X								
Intervention compliance data	X			X					
Demographics	X								
Anthropometry	X								
Contact details	X								
Contact preferences	X								
Comorbidities	X								
Cellulitis details	X								
Risk factors for steroid adverse events	X								
Frailty score (Rockwood[45])	X								
Current pain (NRS, 0-10)	X	X	X	X	X	X	X	X	
PGI-I			X		X		X	X	
EQ-5D-5L	X						X	X	X
Analgesia usage	X							X	
Antibiotic usage	X							X	
Complications potentially related to dexamethasone								X	
(Re)admission to hospital								X	

Assessment / event	Baseline (in person)	Early follow up (text message survey†)						Late follow up (telephone)	
	Recruitment (time 0)	T1‡	T2‡	T3‡	T4‡	T5‡	T6‡	14 days (±2)^	90 days (±7)^
Unscheduled healthcare usage								X	
Health, social care, broader societal resource use	X								X
Recurrence of cellulitis									X
Adverse event review								X	X

The first dose of study drug will be given **after baseline assessments and randomisation have been performed, the second dose will be taken ~24 hours later*.

†*SMS survey is default option with options for face-to-face for inpatients or telephone call for outpatients if unable to complete SMS survey.*

‡ *The first follow-up text message (T1) will be received at the first available follow-up timepoint (~8am or ~8pm) after randomisation, the subsequent 5 follow-up texts (T2-T6) will be received every 12 hours thereafter.*

^*The anchor point (Day 0) is the date of randomisation.*

7.9. Follow-up assessments

All participants will be followed-up to 90 days after randomisation. The timing and frequency of research assessments is shown in Table 3.

Follow-up assessment in this trial will occur remotely for participants discharged after initial assessment and recruitment (the majority, estimated to be 80% of all participants).

Remote assessment in the first three days post randomisation will be via text message surveys. All participants will receive a text message twice a day (at 8am and 8pm) asking them to complete a survey to collect key outcomes. A similar (text message based follow-up) approach is being utilised in the recently funded HTA trial in primary care cellulitis (COAT, NIHR134867). For participants unable to complete on a mobile phone, a telephone follow-up option may be offered depending on staff capacity. Participants admitted to hospital will be offered in-person visits by a member of the study team for data collection where possible or they can continue to provide pain scores remotely if preferred. This flexibility is to ensure the pragmatic running of the trial and encourage weekend recruitment/follow-up in sites which may not have research staff capacity at weekends.

At Day 14 (±2 days) post-randomisation, all participants will receive a phone call from a delegated member of the site team to record their analgesia usage over the first 3 days and antimicrobial usage up to the Day 14 call (as noted on participants' paper aide-memoire), current pain score (NRS), impression of improvement (PGI-I), unscheduled healthcare usage, health-related quality of life (EQ-5D-5L), adverse events, complications related to steroids and any hospital (re)admissions. Participants will receive a reminder text 2 days before their follow-up phone call is due; site teams will attempt to telephone them up to a maximum of 3 times.

At Day 90 (± 7 days) post-randomisation, all participants will receive a further phone call to capture cellulitis recurrence, any adverse events, to complete the EQ-5D-5L and provide information regarding their health, social care and broader societal resource use to enable the cost-effectiveness analysis. Participants will receive a reminder text 7 days before their follow-up phone call is due; site teams will attempt to telephone them up to a maximum of 3 times.

Loss to follow-up is not expected to be high as the duration of follow-up and the intervention period are short.

7.10. Withdrawal and change in participation status

Participants are free to discontinue from some or all aspects of the trial at any time if they wish to do so without having to give a reason and without detriment to their ongoing care. In addition, a participant may be withdrawn from any aspect of the study at the request of a healthcare professional if they feel it is within the best interest of the patient. In accordance with regulatory guidance, data that have already been collected will continue to be retained and used in the analysis.

Participants will be able to flexibly change their participation in the study by selectively ceasing any or all of the following aspects:

- Their allocated treatment
- Remote follow-up
- Passive data collection from medical records where relevant (except where required for reporting of serious adverse events)

Participants who withdraw consent for trial treatment prior to randomisation will be fully withdrawn from the study and no further data will be collected. These participants will not count towards the recruitment target.

A decision by a randomised participant that they no longer wish to continue receiving study treatment should not be considered a withdrawal of consent for follow-up or passive data collection from medical records unless the participant explicitly requests this.

PeRSEVERE principles will be followed for participants who cease to engage with the study (See: https://perseverepriciples.org/). If a participant becomes uncontactable and stops engaging with the study, passive data collection will continue where available from the medical notes (e.g. (re)admissions at Day 14) unless the participant expressly indicates they wish to withdraw. If a participant is not engaging with the study at a particular follow-up timepoint, attempts will still be made to contact them at the next timepoint unless they expressly indicate they wish to withdraw (e.g. if they don't answer their phone at the Day 14 timepoint, attempts should still be made to complete the Day 90 follow-up call).

If it becomes apparent that a participant has lost capacity and is unable to complete a follow-up timepoint (e.g. delirium at Day 14), this will be recorded in the eCRF but they will not be withdrawn from any aspect of the trial unless a personal consultee requests this. Their original consent will remain legally valid and unless withdrawn by a consultee they should be contacted again at the next follow-up timepoint and a new assessment of capacity carried out.

All participants who change their participation status, or cease engaging with the study, will still have the option to receive information about the trial, including newsletters and end of trial results unless they opt not to receive them.

The details and reason for change in participation status will be recorded in the participant's 'Change in Participation' eCRF and medical notes.

7.11. End of trial

The trial will end for a participant after their 90-day follow-up assessment. The end of the trial as a whole will be after the last 90 day follow up is complete, all data queries have been resolved, the database locked and the analyses completed. A declaration of end of study form will be submitted to the MHRA and NHS REC that awarded the favourable opinion within 90 days of the end of study.

If the study is terminated early, the study will end on the date the Sponsor formally declares the study terminated in writing. The MHRA and NHS REC will be notified of early termination within 15 days of the Sponsor deciding to end the study.

8. TRIAL TREATMENTS

All participants will receive usual care for cellulitis including clinical assessment, antibiotics and analgesia in line with local policies, hospital admission if deemed required by the treating clinical team, together with advice on management of concomitant conditions (e.g. diabetes) and advice on expected symptom duration in line with NICE guidance (NG141).[3]

In addition to usual care, trial participants will be randomised on a 1:1 ratio to receive either:

- Dexamethasone 8mg orally on recruitment, then dexamethasone 8mg orally ~24 hours later.

OR

- Matched placebo capsules on recruitment, then matched placebo capsules ~24 hours later.

8.1. Name and description of investigational medicinal product(s)

Dexamethasone (CAS 50-02-2) is the investigational medical product in this trial. Dexamethasone is a glucocorticoid (steroid) that is widely used for several indications. Glucocorticoids have a wide range of activities including modifying immune responses and altering body-wide homeostatic responses. Dexamethasone can be given orally, intravenously, intramuscularly or in a variety of topical forms. In this trial the oral form of dexamethasone is being used.

8.1.0. Rationale for choice of dexamethasone as study drug and dose

Dexamethasone was chosen as a) it has the most glucocorticoid activity of all commonly used oral steroids and is therefore the most anti-inflammatory;[46] and b) there is significant recent clinical experience of dexamethasone in both clinical trials and practice e.g. RECOVERY trial[13]. As this trial has a patient reported primary outcome, placebo control should reduce bias. This trial therefore uses matched placebo for the control group.

The dose (8mg), route (oral), and course of dexamethasone chosen (2 doses) was based on expert opinion and published trial data suggesting additional benefit of a second dose at ~24 hours in a trial of dexamethasone with a primary outcome of pain [20]. Given the half-life of dexamethasone, it is expected that the selected dose/course will continue to have an effect on swelling and pain over the next 24-48 hours.

8.2. Regulatory status of the drug

Dexamethasone has marketing authorisation in the United Kingdom.

The IMP is being processed for this trial (for blinding purposes) in the following ways; deblistering and over encapsulation with backfill before repackaging into HDPE bottles, labelled as per MHRA annex 13 labelling requirements. Piramal Healthcare UK Limited will complete these activities, as sub-contracted by the IMP supplier for this trial, MODEPHARMA Ltd.

8.3. Product Characteristics

For details of product characteristics refer to the provided Summary of Product Characteristics (SmPC).

8.4. Drug storage and supply

Full details can be found in the pharmacy manual. The dexamethasone and placebo will be provided directly to sites by the contracted IMP supplier. It will be delivered to sites in batches with the first delivery prior to site greenlighting. Deliveries will be receipted by the pharmacy department at sites and recorded as received on a study specific IMP management database. Stock of the study drug (and placebo) packs may be stored away from pharmacy (e.g. in an emergency department) if required and approved locally. This should be risk assessed at site level and appropriate storage conditions must be ensured as detailed in the pharmacy manual. Access should be limited to authorised members of the study team.

A drug accountability record will be maintained and updated by delegated site staff for all IMP packs provided and dispensed. The delegated persons at the sites will keep records of the receipt, dispensing, returns, quarantine or destruction of trial medication. The blinded pack IDs will be used to identify the packs on the accountability logs. A file note should be included in the Pharmacy Site File (PSF) directing to the location of these records. At the end of the trial, the drug accountability record should not be destroyed without Sponsor authorisation.

All data regarding the trial medication must be recorded either on forms provided by ExeCTU or on local accountability forms authorised by ExeCTU.

8.5. Preparation and labelling of Investigational Medicinal Product

Preparation and labelling of the IMP will be completed by the contracted IMP supplier in accordance with Annex 13 of Good Manufacturing Practice (GMP) guidelines. Full details can be found in the pharmacy manual.

For blinding purposes, the active drug will be over-encapsulated. The participant will take two capsules per dose each capsule containing 1 x 4mg tablet of dexamethasone and backfill. Placebo capsules will be manufactured to match in appearance and will not contain any active ingredients. The capsules used may include bovine gelatin and are HALAL certified.

The active tablets have the following excipients; Maize starch, microcrystalline cellulose, lactose monohydrate, highly dispersed silicon dioxide, magnesium stearate. All capsules will contain a backfill made of one of these excipients.

Active and placebo capsules will be packaged into HDPE containers (4 capsules per container) with tamper-evident seals. All containers will be labelled with unique pack IDs.

8.6. Dosage schedules

Participants will be administered one dose of 8mg of dexamethasone (2 x 4mg capsules) or matched placebo in hospital as soon as possible after randomisation. If the site team would prefer to delay the administration of the first dose for any reason, randomisation should be delayed where possible until a time where the first dose can be administered soon after randomisation.

If the participant is discharged before 24 hours from the first dose has passed, they will be given the second dose of 8mg dexamethasone or matched placebo to take home with clear instructions to take it ~24 hours after the first dose. Participants will be encouraged to take their second dose as close to the 24-hour timepoint as possible, within a window of 6 hours before to 6 hours after the 24-hour timepoint.

For participants that are hospitalised, they will be administered the first dose as usual, and the second dose prescribed on the drug chart (or electronic equivalent) for 24 hours later. The storage and management of the product between doses will be in line with the local NHS trust policies.

8.7. Dosage modifications

No modification of trial dosage is permitted in the study.

8.8. Known drug reactions and interaction with other therapies

A full list of known adverse effects of dexamethasone is detailed in the latest Summary of Product Characteristics (SmPC). Please see the risk section 2.4 for more information.

8.9. Concomitant medication

Dexamethasone has some direct interactions with medications although the major reason it will be contraindicated is due to its known effects in patients with certain medical comorbidities, described fully in the risk section 2.4.

A list of medications that interact with dexamethasone are available at the British National Formulary (BNF) (https://bnf.nice.org.uk/interactions/dexamethasone/). Dexamethasone does not affect any kind of contraception.

The major concomitant medication that the BNF identifies as a potential interaction is NSAIDs, leading to a potential increased risk of gastric bleeding. The use of NSAIDs will be allowed when participating in this trial. Please see detail described in the risk section 2.4.

The SmPC for dexamethasone lists a precaution for use of live vaccines during treatment with dexamethasone due to the risk of viral infection. In line with national immunisation policies (the Green Book, Chapter 6[47]), live vaccines should only be avoided when the duration of steroid is greater than one week. Therefore, no exclusion is necessary in this trial for those who have recently received a live vaccine, and live vaccines can be received as normal during participation in the trial, if deemed appropriate/necessary.

8.10. Trial restrictions

Women of childbearing potential are required to use adequate contraception for the duration of their participation in the trial (3 months from randomisation), as defined in the eligibility criteria section 6. Breastfeeding mothers and pregnant people are not eligible to participate in this trial.

8.11. Assessment of compliance with treatment

As only two doses of the drug are being taken 24 hours apart, adherence is expected to be high. Sites will record when the first dose is taken on the eCRF. Participants will be asked to confirm whether they have taken their second dose via their 3rd SMS survey (T3).

9. PHARMACOVIGILANCE

9.1. Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in the SmPC. It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative aetiology that would explain the event.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death. • Is life-threatening; an event in which the participant was at risk of death at the time of the event. This does not refer to an event which hypothetically might have caused death if it were more severe. • Requires inpatient hospitalisation or prolongation of existing hospitalisation. • Results in persistent or significant disability/incapacity. • Consists of a congenital anomaly or birth defect. Other ‘important medical events’ may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. **In this trial the following conditions will always be reported as serious adverse events:** • Gastrointestinal bleeds • Psychosis • Severe hyperglycaemia (defined for this trial as ketoacidosis, hyperglycaemic hyperosmolar state or hyperglycaemia requiring new use of insulin)
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to the trial treatment, based on the information provided.

Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information.

Severity classifications

Mild event	An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
Moderate event	An event that is sufficiently discomforting to interfere with normal everyday activities.
Severe event	An event that prevents normal everyday activities.

9.2. Expected adverse events associated with the study drug

The reference safety information (RSI) for this study is section 4.8 of the supplied pharmacovigilance reference copy of the dexamethasone SmPC.

9.3. Recording and reporting adverse events

The safety reporting period will begin at the time of randomisation up to the 90-day follow-up timepoint. The recording and reporting requirements are summarised in the safety reporting flowchart in appendix 1.

Only serious or related adverse events (AR/SAE/SAR/SUSAR) need to be recorded in the eCRF, from the time of randomisation up to the 90-day follow-up timepoint. All adverse events should be recorded in the participant's medical notes.

All adverse events will be assessed for seriousness, severity and relatedness to the study drug as per the definitions in section 9.1 above. These assessments should be carried out by the site PI, or delegated medic and recorded in the medical notes (and eCRF where serious or related).

Important: please note that psychosis, gastrointestinal bleeds and severe hyperglycaemia should always be classified as serious in this trial. Severe hyperglycaemia is defined for this trial as ketoacidosis, hyperglycaemic hyperosmolar state or hyperglycaemia requiring new use of insulin.

As this is a blinded trial, adverse events should be evaluated on the assumption that the participant was allocated the active drug i.e. dexamethasone. The blind should only be broken where knowing the allocation is clearly necessary and will alter the appropriate medical management of the patient. If unblinding is necessary, please refer to the Emergency Unblinding section of the protocol (7.7.0) and the 'Unblinding' working instruction.

9.4. Recording and reporting of SAEs, SARs AND SUSARs

The recording and reporting requirements are summarised in the safety reporting flowchart in appendix 1.

All serious adverse events (whether related or not) should be reported to ExeCTU **within 24 hours** of the event being assessed as serious by completing the '**SAE' eCRF in REDCap.** All SAE eCRFs must

be reviewed and signed off by a Principal Investigator (PI) or delegated medic within REDCap. In the event of a death the 'Notification of Death' eCRF should also be completed in REDCap.

Information not available at the time of the initial report (e.g. test results) must be added to the SAE eCRF by the site team as soon as it becomes available.

ExeCTU will receive an automated email notification to alert them to a new SAE eCRF or when a change is made to an SAE eCRF. For events occurring up to Day 14 (post-randomisation) ExeCTU will onward report all SAEs to the Sponsor within 24 hours of becoming aware of the event. For events occurring from Day 15 to Day 90, ExeCTU will onward report SUSARs to the Sponsor within 24 hours of becoming aware but all other SAEs reported from Day 15 onward will be reviewed by the sponsor in bulk (e.g. as listed in TMG reports).

9.4.1. Reviewing serious adverse events

The CI or designated representative will review all reported SAEs to assess relatedness, and where related, assess expectedness to the IMP against the RSI. The CI will not downgrade a PI's assessment of relatedness, however they may upgrade a PI's assessment of relatedness (i.e. from unrelated to related).

Sites should respond as soon as possible to requests for further information by the CI or designated representative required for the final assessment of the SAE.

In the event of a SUSAR, the Sponsor or ExeCTU will take responsibility for unblinding prior to submission of the SUSAR to the MHRA and the REC. Investigators will only receive information on the results of the unblinding if it is judged necessary for the safety of the participant.

9.4.2. Ongoing events

Some SAEs/SARs/SUSARs may be ongoing at the time of initial reporting.

It is the PI or delegated clinician's responsibility to ensure that that all participants with ongoing SAEs/SARs/SUSARs are followed up until the final outcome is reached or until the Sponsor and CI agree that no further follow-up is required.

There is no mandatory requirement regarding the frequency which follow-up reports should be submitted. All follow-up information should be entered into the eCRF as soon as possible after the PI or designated representative becomes aware of an update. As a minimum, a report should be submitted when the event resolves/ends.

Ongoing SAEs/SARs/SUSARs at the end of the trial will be followed up by the participant's GP and/or the routine clinical care team until discharge.

9.4.3. Notification of deaths

Irrespective of whether the death is related to the intervention or if it is unrelated, all deaths occurring during the safety reporting period must be reported to ExeCTU and the Sponsor **within 24 hours** of the PI or research team becoming aware of the event. This will be reported by completing an 'SAE' eCRF in REDCap. The 'Notification of Death' eCRF should also be completed in REDCap.

9.4.4. Expedited reporting of SUSARs

If a SUSAR is reported by a site, the Sponsor will coordinate onward reporting to the REC and the MHRA (within **7 calendar days** of receipt of the initial report for fatal/life-threatening events or **15 calendar days** of receipt of the initial report for non-fatal/non life-threatening events)

All other recruiting sites will be informed of the SUSAR by ExeCTU.

9.5. Responsibilities

The CI is responsible for oversight of the safety of participants in the trial, including an ongoing review of the risk/benefit. They will review SAEs causality using their medical judgement and review all SARs for expectedness using the RSI in a timely manner.

The CI (or delegate) will assign Medical Dictionary for Regulatory Activities (MedDRA) coding to all reportable safety events.

9.6. Pregnancy reporting

In the event of a pregnancy being reported by a female participant, this must be reported using an ExeCTU 'Pregnancy' eCRF within 24 hours of learning of its occurrence. Pregnancies from randomisation until Day 14 should be reported. If the pregnancy is not known until after this time frame, it should still be reported if conception was during this period. As dexamethasone is not known to have harmful effects on male fertility/health of children conceived by males taking dexamethasone, pregnancies in partners of male participants will not be reported.

If a pregnancy is reported during the intervention period, the participant should be withdrawn from the intervention and instructed not to take any further doses of the study drug, however, they can continue to complete follow-up. If pregnancy is reported after the intervention period they should continue with follow-up as planned unless the participant requests otherwise. No additional follow-up is required for participants who become pregnant during the trial.

Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE.

9.7. Overdose

As per the SmPC for dexamethasone, reports of acute toxicity and/or deaths following overdose with glucocorticoids are rare.

Overdoses are not anticipated as participants will be given only two pre-measured doses of the IMP (or matched placebo). As per the risk section 2.4, the dexamethasone SmPC recommends dosages which are much higher than the total dosage of 16mg of dexamethasone (2 x 8mg doses) that will be dispensed to intervention participants in this trial.

9.8. Reporting urgent safety measures

The Sponsor, CI, co-lead, PI, DMC and/or TSC may take appropriate urgent safety measures (USM) in order to protect the participants of a clinical trial against any immediate hazard to their health or safety.

If a PI implements a USM at site they must inform the CI immediately (see contact details in key trial contacts section and copy ExeCTU; DEXACELL@exeter.ac.uk). If time permits it, the investigator

should discuss any proposed actions with the CI prior to implementation. A record of all discussions, decisions, actions etc must be recorded in the Investigator Site File.

The CI will inform the Sponsor within 24 hours to discuss the hazard and any actions taken (prior to implementation if time allows). USMs identified shall take immediate effect and the CI or Sponsor will telephone the REC and MHRA ideally within 24 hours (no later than 3 days) to discuss the event with a medical assessor. The CI, Sponsor (or delegate) will further notify the REC and MHRA in writing within 3 days from the date the measures were taken.

If the CI and the Sponsor consider the USM to affect all participants, ExeCTU will inform all PIs of the USM under the CIs oversight.

9.9. The type and duration of the follow-up of participants after adverse reactions

If a participant has an adverse reaction (AR) whilst in hospital they will be monitored until a resolution or stabilisation is reached.

9.10. Development safety update reports

A DSUR will be provided to the MHRA and REC by ExeCTU at the end of each reporting year. The CI (or designated representative) in collaboration with ExeCTU will prepare all relevant information for the DSUR. The sponsor will review the DSUR prior to submission and the CI will review the clinical sections and provide final sign off prior to submission.

10. STATISTICS AND DATA ANALYSIS

10.1. Sample size calculation

Participants will be randomised on a 1:1 basis to receive dexamethasone plus usual care or placebo plus usual care. The required sample size has been calculated based on detecting a between-group difference in total pain, from baseline over the first 3 days post-randomisation, of 10 points, based on a standardised area-under-the-curve approach (on a scale of 0-100), with pain NRS collected twice-daily.

The minimum clinically important difference (MCID) in pain is 10 points, based on previously reported emergency care literature.[48] The conservative SD estimate (30 points) is based on previous cellulitis trials reporting pain at single time points, reviewed in a recent meta-analysis.[49] Based on these assumptions, the target standardised effect size is 0.33. This estimate of the pooled SD will be reviewed, blinded, at the end of the internal pilot phase.

191 participants in each allocated group with primary outcome data will give 90% power to detect the MCID of 10 points, assuming a standard deviation (SD) of 30 points, at the two-sided 5% statistical significance level. The recruitment target is 450 participants (225 per allocated group), allowing for up to 15% of participants not returning any pain score 24 hours after the baseline score.

Planned recruitment rate

It is estimated (using NHS Digital hospital episode statistics data and multi-site audits) that in summer months, on average 50 people will present to each site each month and ~50% will be eligible to take part. It is estimated ~50% of eligible patients will be approached, of whom ~35% will be randomised,

giving mean recruitment rate/site/month of ~4 participants once recruitment processes are fully established. However, as incidence rates of cellulitis vary by season (higher rates in the summer months) lower recruitment rates of ~2/site/month are anticipated during the non-summer months. Our projected recruitment period therefore allows for both seasonality and staggered site opening.

10.2. Statistical analysis plan

A detailed statistical analysis plan (SAP) will be written, following published guidelines,[50] approved by the TSC and made publicly available before the follow-up period concludes. Any amendments will be discussed with the TMG and TSC, and documented with date and details of the amendment.

Results will be reported following the CONSORT statement and relevant extensions (Patient Reported Outcomes; Pragmatic Trials).[51,52]

Throughout the analysis, emphasis will be placed on estimation rather than hypothesis testing. Where hypothesis tests are carried out, these will be at the 5% two-sided level for primary and secondary outcomes.

10.2.0. Summary of baseline data and flow of patients

Participants' baseline characteristics will be summarised descriptively overall and by allocated treatment group. There will be no formal between-group testing of baseline data.

Means with standard deviations and ranges will be reported for the continuous variables: baseline pain (NRS, 0-10), age, BMI, NEWS2 Score, clinical frailty scale, index of multiple deprivation, time since cellulitis onset, unless the distributions appear to be skewed in which case medians and interquartile ranges will be reported instead. Percentages and numbers will be reported by category for the categorical variables sex (male/female), ethnicity, self-reported gender, severity of cellulitis (using Eron classification), location of cellulitis (leg/other location), antimicrobial therapy for this episode of cellulitis prior to attending urgent and emergency care (yes/ no), diabetes status (yes/no), current use of intravenous "street" drugs (yes/no), current and recent analgesia including NSAID (yes/no), clinical comorbidities (including peripheral vascular disease, chronic venous insufficiency and morbid obesity), risk factors for steroid adverse events and other clinical details of cellulitis.

Loss to follow-up after randomisation will be reported separately for each group with regards to these variables.

A CONSORT flow diagram will be produced to illustrate the flow of participants through the trial. Specifically, the number of participants approached, eligible, consented and recruited, and assessed at baseline, 3, 14 and 90 days will be illustrated, along with the number of participants withdrawn or loss to follow-up between each data collection time point. The reasons for ineligibility and withdrawal will also be presented.

10.2.1. Primary outcome analysis

General principles for primary analysis of primary outcome

An area under the curve (AUC) approach will be used to capture the primary outcome, total pain experienced over the first 3 days, including baseline. The AUC will be calculated using the trapezoidal rule, by rescaling the numerical rating pain scores (0-10) at each time point to a 0-100 scale , to give a standardised AUC on a scale of 0-100. Participants will be included in the primary intention-to-treat analysis if they contribute at least 2 out of a possible 7 pain scores, with the second pain score being

at least 24 hours after the baseline pain score. Missing pain scores will be imputed using linear interpolation, if scores are available either side of the missing pain score. If final scores are missing, then scores will be imputed using last observation carried forward, a conservative approach.

The primary outcome (pain AUC) will be analysed using a mixed effects linear regression (intention-to-treat) model, adjusting for age, sex, baseline pain, severity of cellulitis, antimicrobial therapy for this episode of cellulitis prior to attending urgent and emergency care, diabetes status and severity of cellulitis (Eron Stage1 vs all other stages) as fixed effects and recruitment site as a random effect to account for potential between-site heterogeneity. From the model, the adjusted difference in means for the pain AUC between the dexamethasone and placebo group will be reported with 95% confidence interval. The unadjusted between-group difference in means with 95% confidence interval will also be reported.

Estimands framework for primary outcome

The primary estimand of interest is the effect of the addition of dexamethasone to usual care compared to placebo and usual care, which will be addressed by the proposed intention to treat analysis, with a treatment policy strategy applied to intercurrent events, which is a conservative approach. The key intercurrent event of seeking additional healthcare input has been identified.

Any secondary estimands will be defined clearly and a priori in the SAP.

Approach to handling missing data for primary outcome

Missing pain scores will be imputed using linear interpolation, if scores are available either side of the missing pain score. If final scores are missing, then scores will be imputed using last observation carried forward, a conservative approach. Different approaches for dealing with missing scores may be considered in a sensitivity analysis, which will be detailed in the SAP.

Sensitivity analysis for primary outcome

Sensitivity analysis will be undertaken to check the robustness of the primary analyses to assumptions, in particular with regards to the imputation methods used for missing pain scores in the first 3 days. Multiple imputation using chained equations may be considered. Imputation algorithms will include allocated treatment group, baseline score, centre, minimisation variables and age, sex and baseline characteristics that are predictive of missingness.

If imbalances are noted between the trial groups in other baseline characteristics and thought to be predictive of outcome, then as part of a sensitivity analysis, the analysis will be repeated adjusting for these characteristics in addition to those already listed.

10.2.2. Secondary outcome analysis

General principles for secondary outcomes

If the necessary data assumptions are met, a mixed effects linear regression model will be fitted for the secondary outcomes of PGI-I and pain at 14 days. A mixed effects repeated measures model will be fitted for PGI-I recorded at days 1,2, and 3. In the case of model assumptions not being met, alternative modelling approaches will be considered, depending upon the distribution of the outcomes, such as a mixed effects ordinal logistic models or dichotomising the categories for a logistic regression. Alternative modelling approaches to be considered will be detailed further in the SAP.

Mixed effects logistic models (if the number of observed events allow) will be fitted for the dichotomous secondary outcomes; additional antibiotic use post-randomisation to Day 14, (re)admission to hospital by Day 14, any unscheduled health care use until Day 14 and recurrence of cellulitis by Day 90. All models will adjust for the same factors as with the primary analysis of the primary outcome.

For the continuous secondary outcomes with mixed effects linear models fitted, adjusted differences in means between the dexamethasone and placebo group will be reported with 95% confidence intervals. For outcomes analysed using mixed effects logistic regression models, adjusted odds ratios will be reported with 95% confidence intervals. The unadjusted difference in means and odds ratios with 95% confidence interval will also be reported to aid future meta-analysis.

A descriptive analysis will report, by allocated group, on compliance, the amount and type of analgesia taken over the first 3 days, and on the route, type and length of post-randomisation antibiotics prescribed and hospital (re)admission related to dexamethasone use and complications related to dexamethasone use (all until Day 14).

Estimands framework for secondary outcomes

For all secondary outcomes, the same estimands as with the primary outcome will apply (see section 10.2.1).

Approach for handing missing data for secondary outcomes

As with the primary outcome, multiple imputation may be considered, using the methods described for the primary outcome for missing secondary outcomes (see section 10.2.1).

Sensitivity analysis for secondary outcomes

Similarly, as described for the primary outcome, multiple imputation maybe considered, and in the case where imbalances in a characteristic are noted in the treatment groups, the analysis maybe repeated adjusting for that characteristic (see section 10.2.1).

Adverse Events Analysis

SAE's will be reported descriptively by whether or not the first dose was taken, rather than as intention to treat.

10.2.3. Subgroup analyses

Although the trial is not powered for subgroup analysis, a small number of pre-specified exploratory analyses will be undertaken on the primary outcome for subgroups of particular interest: cellulitis location (lower limb vs other), and NSAID usage at time of randomisation (user vs non-user). These analyses will be carried out by refitting the mixed effects linear regression model described for the primary outcome primary analysis (see section 10.3.2) with the addition of an interaction between the primary outcome and the subgroup of interest. Minimum numbers required to perform these analyses will be pre-specified in the SAP.

10.3. Interim analysis and criteria for the premature termination of the trial

No interim analyses are planned for the trial.

The trial may be terminated early on the recommendation of DMC or funder. The TSC will make the final decision to terminate or continue the trial.

10.4. Participant population

The primary analysis population will include all those who were randomised to the trial, including those who were randomised to dexamethasone group, but did not receive it (Intention to Treat). Participants also need to contribute at least 2 out of a possible 7 pain scores, with the second pain score being at least 24 hours after the baseline pain score to be included.

10.5. Other statistical considerations

Any changes made to the SAP will be documented, including details of when the change was made (e.g. prior to data export) and whether the trial statistician was blinded to allocated group at the time of change.

11. ECONOMIC EVALUATION

A full within-trial cost-effectiveness analysis (CEA) will be conducted to estimate the incremental cost-effectiveness of the dexamethasone intervention as compared to placebo.

Resources and costs of providing oral dexamethasone will be established. Participant health, social care and broader societal resource use will be captured at baseline, Day 14 and Day 90 using self-report resource use questionnaires. These are based on the ModRUM core module[53,54] but tailored to the study population, as informed by the PAG and trial team.[55] Nationally-recognised UK health and social care unit costs will be applied to the resource use data.[56]

QALYs will be estimated using EQ-5D-5L data collected at baseline and to Day 90 follow-up. The 'cross-walk' algorithm will be used to provide QALY weights from the EQ-5D-3L UK general population valuation survey, in accordance with the current 'position statement' of the National Institute of Health and Care Excellence (NICE).[57,58] Descriptive statistics will summarise costs and QALYs by the dexamethasone and placebo groups. Mixed effects linear regression models will be undertaken to test for differences in costs and QALYs. In line with the SAP, these models will adjust for age, sex, baseline pain, severity of cellulitis, antimicrobial therapy for this episode of cellulitis prior to attending urgent and emergency care (yes/no) and diabetes status as fixed effects and recruitment site as a random effect to account for potential between-site heterogeneity. In addition, the cost regression model will adjust for baseline costs, and the QALY model for baseline EQ-5D-5L values. The CEA will synthesise cost and outcome data to present incremental cost-effectiveness ratios for: i) the trial primary outcome, in the form of cost of total pain prevented over 3 days post-randomisation, and for ii) the policy relevant economic endpoint, cost per quality-adjusted life-year (QALY) at Day 90 follow-up.

Sampling uncertainty will be accounted for in the analysis, and the pattern and potential mechanisms of missing data will be explored in considering multiple imputation. Cost-effectiveness acceptability curves will be presented as appropriate using the net-benefit approach. These will show the probability that the dexamethasone intervention is cost-effective (as compared to placebo) over a range of cost-per-QALY thresholds (e.g. the £20,000 and £30,000 thresholds considered by NICE[59]). The CEA will initially be undertaken from a primary perspective of the NHS and Personal Social Services, with

broader societal perspectives considered in sensitivity analyses, informed by input from the PAG. A Health Economics Data Analysis Plan will be developed which will be fully concordant with the SAP, and the internationally-recognised CHEERs guidelines for reporting CEA studies.[60]

12. DATA MANAGEMENT

12.1. Data collection tools and source document identification

The local research team will use the REDCap application provided by Exeter CTU to record participant data in accordance with the protocol, this electronic data capture system (EDC) will be the CRF. Direct data entry is preferred but in circumstances where there is difficulty accessing the internet or necessary IT equipment, paper source data worksheets may be required with subsequent data entry by the local research team.

The electronic randomisation and IMP management system is provided by Centre for Healthcare Randomised Trials (CHaRT; University of Aberdeen). IMP orders, receipt confirmation and individual pack statuses will be recorded directly in this system to ensure only available and non-expired drugs are able to be allocated by the system during randomisation. Sites will maintain locals IMP accountability logs for the purposes of monitoring and inspection (full details in pharmacy manual). Data required for randomisation will be entered into REDCap directly. When the user confirms they are ready to randomise the necessary data will be piped into the CHaRT system which will automatically randomise, and the allocated pack ID will be piped back in to REDCap for the user to check (see section 15.5 for further details on data transfer between REDCap and CHaRT).

Sites will be required to answer data queries raised by ExeCTU in a timely manner within the study database.

12.2. Source Data

At screening and baseline, the primary data source will be the medical notes. Where information is collected on the eCRFs (or source data worksheets, where required) and not previously recorded in the medical notes, the eCRFs and worksheets will be source data.

Participant questionnaires will be completed for patient reported outcome measures in the following ways at each timepoint:

- Baseline - completed by the participant on paper and transcribed into the study database by the study team.
- T1-T6 - completed electronically by participant via SMS survey, or completed electronically by site staff on REDCap when conducting in person/telephone follow-up.
- Day 14 & Day 90 - completed electronically by site staff on REDCap when conducting a follow-up telephone call with the participant.

If there are technical difficulties at T1-T6, Day 14 or Day 90, source data worksheets (paper questionnaires) can be used by the site team and the data transcribed into the database.

If completed electronically the trial database will form the source data, otherwise the paper questionnaire will form the source data.

The source data for the randomised allocation and the pack ID(s) allocated to the participant will be in the CHaRT randomisation system.

Medical case notes containing source data or other trial-related information should be identified by a label (or equivalent for electronic notes, where feasible), e.g. “Keep until at least dd/mm/yyyy” where the date given is at least ten years after the end of the trial.

12.3. Data handling and record keeping

A Data Management Plan (DMP) will be created for the trial and will be updated throughout the trial as appropriate. Work instructions will be provided to the site teams on record keeping and data entry processes. Electronic systems will be validated, tested and documented before starting recruitment.

Mobile phone numbers will be shared with our SMS service provider in order to send the follow-up texts (see section 12.4 for more details). If routine data linkage is added to the trial, this will be outlined in an amendment or a new ethics application by the trial team. In this case NHS number and date of birth may be shared with NHS Digital for the purpose of linkage (this would only be completed for participants who gave consent for this on the main trial consent form). No other information capable of identifying participants will be made available in any form to those outside the trial.

Any source data worksheets, paper questionnaires, paper consent forms and trial specific documents held by the site teams will be stored securely with access restricted and limited to delegated research staff. If these are not stored in the ISF, a note to file will be placed in the ISF to indicate their location. Any source data recorded on paper questionnaires or source data worksheets will be transcribed into the eCRF.

Please see the data protection section (15.5) for details on the electronic data capture system and how identifiable data will be stored.

12.4. Access to Data

Participants will be asked to consent to representatives of the Sponsor, the University of Exeter, University of Bristol, University of Cardiff or regulatory agencies (e.g. MHRA) accessing their data that is relevant to their participation in the trial.

Access to the data held at participating sites will be restricted to those who have a relevant purpose to access the data. Access will be granted to authorised representatives from the North Bristol NHS Trust as Sponsor, as well as representatives from University of Exeter and regulatory agencies e.g. MHRA, for the purposes of auditing, monitoring and inspection of the trial.

Data entered into the study database (including unredacted uploads of paper consent forms and electronic consent forms) may be accessed by authorised members of the trial team at participating sites, ExeCTU and regulatory authorities (e.g. MHRA) and collaborating organisations. Access to the database will be controlled by password protected individual user accounts. Staff will have access restricted by site, functionality and data that are appropriate for their location and role in the trial.

Participants will also be asked to consent to data being shared with the following third-party providers:

- Centre for Healthcare Randomised Trials (CHaRT, University of Aberdeen) will provide the randomisation and IMP management system. CHaRT will not receive any identifiable information but will receive the participant’s trial ID and eligibility/minimisation criteria that are required for the randomisation. This system will also store the randomisation and IMP allocation data and a record of IMP pack statuses. Similarly to REDCap, access to CHaRT’s system will be restricted to password protected user accounts restricted by site, functionality and data appropriate to the user’s role.

- The SMS text messaging service provider will receive the participant's telephone number and the wording for the follow-up text messages. Their text messaging data centre is located in the United States. Participants will respond to follow-up text messages either by direct SMS reply which the service provider will automatically feedback into REDCap, or by a personalised survey link included in the message which would feed directly into REDCap. No other identifiable information will be shared with the SMS service provider. By linking directly into REDCap, REDCap will be used to store logs and records of communications with participants and the SMS service provider will delete their logs and not hold data after it has been fed back into REDCap.
- The IMP manufacturer will not receive or hold any participant data.

The above third parties will not be able to log into the study database.

12.5. Archiving

ExeCTU will support sites to prepare trial records for archiving in accordance with the Data Management Plan. The Sponsor is responsible for arranging appropriate archiving of the Trial Master File and EDC system data on conclusion of the trial.

Essential documentation will be archived by each participating site as per local procedures, including the Investigator Site File, consent forms (including copies of electronic consent forms, where relevant) and any source data worksheets. The site must notify ExeCTU and the Sponsor of their archiving arrangements and the Sponsor must be granted access to the archived documents/data upon request.

The essential documentation will be archived for a minimum of 10 years after the end of the trial. After 10 years, all personal identifiable data will be securely destroyed upon authorisation from the Sponsor. The anonymised dataset will be stored indefinitely for the purposes of future ethically approved research.

13. MONITORING, AUDIT & INSPECTION

A detailed monitoring plan will be agreed by the CI, ExeCTU and the Sponsor based on the trial risk assessment. Both will be reviewed periodically throughout the trial and updated as necessary (e.g. after amendments to the protocol).

Monitoring will be led by ExeCTU and will be conducted remotely, centrally and potentially on-site as required. This will include monitoring of unredacted consent forms and paper consent forms will be uploaded (unredacted) to the trial database for this purpose. Extra on-site monitoring may be conducted if triggered according to pre-defined criteria in the monitoring plan, or if concerns are raised by an individual with knowledge of the trial.

Sites will be expected to cooperate with monitoring procedures through timely provision of copies of requested documents and completion of self-audit checks where required. In the case of on-site monitoring visits, sites will be expected to provide space for the monitor(s) to work on the Trust premises and provide access to all documents requested in the notification of monitoring visit letter. The PI or delegated member of the trial team must be available during on-site monitoring visits. The ExeCTU will provide sites with sufficient notice to prepare for a monitoring visit.

The Sponsor and/or regulatory authorities may audit or inspect the trial, including on-site visits at any time during the trial. All trial related documents will be made available on request for monitoring and audit by the Sponsor or regulatory authorities.

The DMC will review data completeness, quality and accumulating safety data at agreed intervals throughout the trial.

14. PUBLIC AND PATIENT INVOLVEMENT

This trial was developed with members of the North Bristol Infection Science Patient Advisory Group (PAG). The study team have also worked with people who use intravenous drugs who commonly suffer with cellulitis, and with patients with skin of colour where cellulitis may be less obvious. This has helped to design an inclusive trial to ensure our research is relevant to these important groups.

An overarching Patient Advisory Group (PAG) led by the Sponsor's PPI lead will advise on study processes throughout the trial. This may include inputting into patient-facing materials throughout the trial, co-producing the dissemination materials to be shared with participants and the public once the trial results are available and advising on the participant pathway and any potential recruitment barriers. We will encourage diversity within our PPI representatives and will invite participants for the PAG on a national level. Representatives from the Bristol Drugs Project will be invited to sit on our advisory group.

At the end of the trial, interested participants will be invited to help us develop participant focused trial literature with our PAG, which will be released on social media and our trial website.

A patient representative is a co-applicant and sits on the TMG. Two independent lay members sit on the TSC.

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1. Research Ethics Committee (REC) review & reports

The research will be performed subject to a favourable opinion from an NHS REC, HRA and MHRA, with subsequent appropriate local R&D departments Capacity & Capability Approval for each participating site prior to starting the trial at the site.

Ethics review of the protocol and other trial related essential documents (e.g. PIS and consent form) will be carried out by a UK NHS REC. Any subsequent amendments to these documents will be submitted to the REC, HRA and MHRA for approval prior to implementation. Amendments to the trial documents will also be submitted to the sites for information or approval as required, including confirmation of continued capacity and capability. The Chief Investigator or delegate will work with sites to put the necessary arrangements in place to implement the amendment.

Annual progress reports will be submitted to the REC that issued favourable opinion and the MHRA annually until the trial is declared ended.

The REC will be notified of the end of the trial. If the trial is ended prematurely, this will be notified to the REC that approved the trial. A final report will be submitted to the REC after the end of the trial.

15.2. Peer review

The proposal for this trial has been peer-reviewed through the NIHR peer-review process, which includes independent expert and lay reviewers.

15.3. Regulatory Compliance

Dexamethasone is classed as an IMP and the trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA as well as favourable REC opinion. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

Before any site can enrol participants into the trial, the Sponsor, Chief Investigator or delegate will ensure that appropriate approvals from regulatory authorities and the participating organisation are in place.

For any amendment to the trial, the Chief Investigator or delegate, in agreement with the Sponsor will submit information to the appropriate body in order for them to issue approval for the amendment.

15.4. Protocol compliance

Non compliances are defined as follows:

- **Deviation:** A change or departure from the approved trial protocol, other key trial documents, GCP and/or applicable regulatory requirements that is **not likely** to affect the safety and rights of a participant or the reliability and robustness of the data generated in the clinical trial.
- **Violation:** Failure to comply with the approved trial protocol, other key trial documents, GCP and/or regulatory requirements which has the **potential** to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical trial.
- **Serious Breach:** A non-compliance that is **likely** to affect to a significant degree the safety or physical or mental integrity or rights of the trial participants, or the scientific value of the trial.

Study personnel will be provided with a 'Non-compliances' work instruction for guidance in the event that they become aware of a deviation, violation or suspected serious breach.

Non compliances may be identified through routine or triggered monitoring, inspection by the regulatory authorities, by chance or by direct report to ExeCTU and/or the Sponsor by a member of the study team or other party.

Non-compliances will be reported on a 'Non-Compliance Report' form on REDCap, which will be reviewed by ExeCTU on receipt. All reports of violations/suspected serious breaches will be forwarded by ExeCTU to the Sponsor within 24 hours of ExeCTU becoming aware of the event. The Sponsor will determine whether the event constitutes a serious breach and will manage onward reporting to the REC and MHRA, as required.

ExeCTU and the Sponsor will work with study and site personnel to identify the cause of any non-compliances and put in place steps to mitigate them, as appropriate.

Non-compliances will be reviewed regularly by the CI and the TMG. Recurrent deviations will be discussed with the TMG and TSC, as appropriate.

If a non-compliance is also associated with an event which meets the criteria of an SAE or SUSAR this should also be reported in accordance with the pharmacovigilance section 9 of the protocol.

15.5. Data protection and patient confidentiality

Data will be collected and retained in accordance with the UK General Data Protection Regulation (UK GDPR), in conjunction with the Data Protection Act (DPA) 2018 and ICH GCP E6 R2 with regards to the

collection, storage, processing, destruction and disclosure of personal information. Trial data will be reported anonymously so that it will not be possible to identify any individual taking part in the trial.

Each participant will be assigned a unique participant ID number. Personal identifiable data and contact details will be collected and stored in the study database as required for the research (e.g. to send follow-up or trial results). Fields which contain participant identifiers will sit on separate eCRFs to the rest of the data and will be restricted so that only authorised users can access the identifiable data. Uploaded unredacted paper consent forms and the unredacted eConsent forms will also be access restricted to authorised users of the database. Personal data will only be used for reasons relevant to the research as outlined in the participant information sheets and will be stored for 10 years after the end of the study before being destroyed.

Data will be managed by Exeter Clinical Trials Unit following UK General Data Protection Regulation. Access to the EDC system (REDCap Academic) web interface will be over Hyper Text Transfer Protocol Secure (HTTPS) / Transport Layer Security (TLS) version 1.2 as a minimum and it will be ensured that web traffic to and from the REDCap server is encrypted. REDCap Academic will be hosted within University of Exeter Amazon Webservices (AWS) account. All data will be securely stored in AWS data centres in the UK. Amazon Relational Database Service (RDS) will be encrypted. Amazon RDS encrypted database instances use the industry standard AES-256 encryption algorithm to encrypt the data on the server that hosts the Amazon RDS database instances. The AWS global infrastructure is designed and managed according to security best practices as well as a variety of security compliance standards. AWS provides on-demand access to security and compliance reports and select online agreements through AWS Artefact. Standards include ISO 27001 and ISO 9001.

The management of randomisation data at CHaRT adheres to the UK General Data Protection Regulation (GDPR), ensuring compliance with robust data protection measures. CHaRT employs secure data transmission protocols, utilizing HTTPS/TLS 1.2 connections with industry-standard encryption algorithms to safeguard sensitive information during transfer. Data is securely stored in Aberdeen data centres, with off-site backups stored at Robert Gordon University. Access to data is strictly controlled through authentication mechanisms, ensuring only authorised users can access endpoints within the infrastructure. CHaRT conducts regular security audits and vulnerability assessments to identify and mitigate potential risks to data security. Additionally, all data transfers are logged to maintain a comprehensive record of activity. By implementing these measures, CHaRT ensures the secure management and transfer of randomisation data, maintaining the integrity and confidentiality of sensitive information in accordance with GDPR requirements.

Only Principal Investigators or their authorised delegates who are suitably qualified and trained will access the patients' medical notes to gather the required information for the trial. Investigators will hold substantive or honorary contracts with the NHS Trust at which the patient is recruited and will therefore be bound by a duty of confidentiality.

Data collected at sites on paper such as consent forms (including any printed copies of eConsent forms) will be stored securely and archived at site. Any electronic copies of the eConsent form (downloaded from REDCap) held at sites will be stored and archived in accordance with local policy and access restricted to authorised members of the research team.

The data controller for the study is the Sponsor, North Bristol NHS Trust.

15.6. Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

The Chief Investigator and co-lead do not have any competing interests. Members of the TSC and DMC will complete conflict of interest forms declaring any competing interests; these will be filed in the TMF. PIs will be provided with a PI declaration form as part of the model non-commercial agreement in which competing interests will be identified.

15.7. Indemnity

This is an NHS-Sponsored research trial. For NHS Sponsored research if there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm.

15.8. Amendments

Any amendments to the trial documents must be approved by the Sponsor prior to submission to the HRA/REC/MHRA. The Sponsor will decide if an amendment is substantial or non-substantial following HRA guidance.

All substantial amendments and relevant non-substantial amendments will be discussed by the TMG and with the PAG if appropriate. The Chief Investigator will be responsible for the final decision on making an amendment to the protocol. The approval of the TSC chairperson will be sought for substantial amendments to the protocol in advance of submitting them to the REC/MHRA/HRA, and if necessary, a meeting of the TSC will be convened to discuss the amendment. The funder representative will be notified of relevant substantial amendments in advance of submission, and a full list of all substantial and non-substantial amendments will be provided as part of regular funder reports.

All amendments will be submitted to the NHS REC that issued a favourable opinion (if appropriate), the HRA and/or the MHRA following the appropriate amendment process in place at the time of submission. Amendments will be communicated by ExeCTU to R&D departments, PIs and research teams at participating sites as soon as possible upon receipt of approval to do so from the HRA. The CI or delegate will inform the trial registry of changes to the study.

The protocol version history will be recorded on the protocol.

15.9. Post trial care

Participation will end for a participant after the 90-day follow-up. After this point, patient participants will continue to receive standard NHS care with no special arrangements made in relation to the trial.

15.10. Access to the final trial dataset

Anonymised research data and outputs will be stored in an open research repository hosted by one of the collaborating organisations (Sponsor, University of Exeter and/or University of Bristol) to facilitate open access to, and the impact of, our research. The details will be outlined in the data management plan. All future research proposals must obtain the appropriate ethical and regulatory approvals.

16. DISSEMINATION POLICY

16.1. Dissemination policy

The findings will be disseminated by usual academic channels, i.e. the trial team aim to present findings at international meetings, as well as by peer-reviewed publications (including a full report to the NIHR Health Technology Assessment programme) and through patient organisations and newsletters to patients, where available. The results will be communicated to Royal College of Emergency Medicine, Society for Acute Medicine, NICE and NHS England to inform national guidelines.

Our patient groups will guide us how to inform patients of the results, using social and traditional media. The results will be posted on the publicly available registry (ISRCTN).

On recruitment, all participants will be invited to be updated on the trial progress and findings. A trial website and social media accounts will be maintained to share updates on recruitment, results, and general trial information.

16.2. Authorship eligibility guidelines and any intended use of professional writers

Authorship on relevant publications will be offered in line with The International Committee of Medical Journal Editors guidance. This will include contributors to trial development (e.g. grant funding, protocol development), running the trial (e.g. recruiting patients, being a lead investigator for sites) and other aspects of trial design/analysis (e.g. statistical and methodological work).

The trial team do not plan to engage the use of professional writers for this study.

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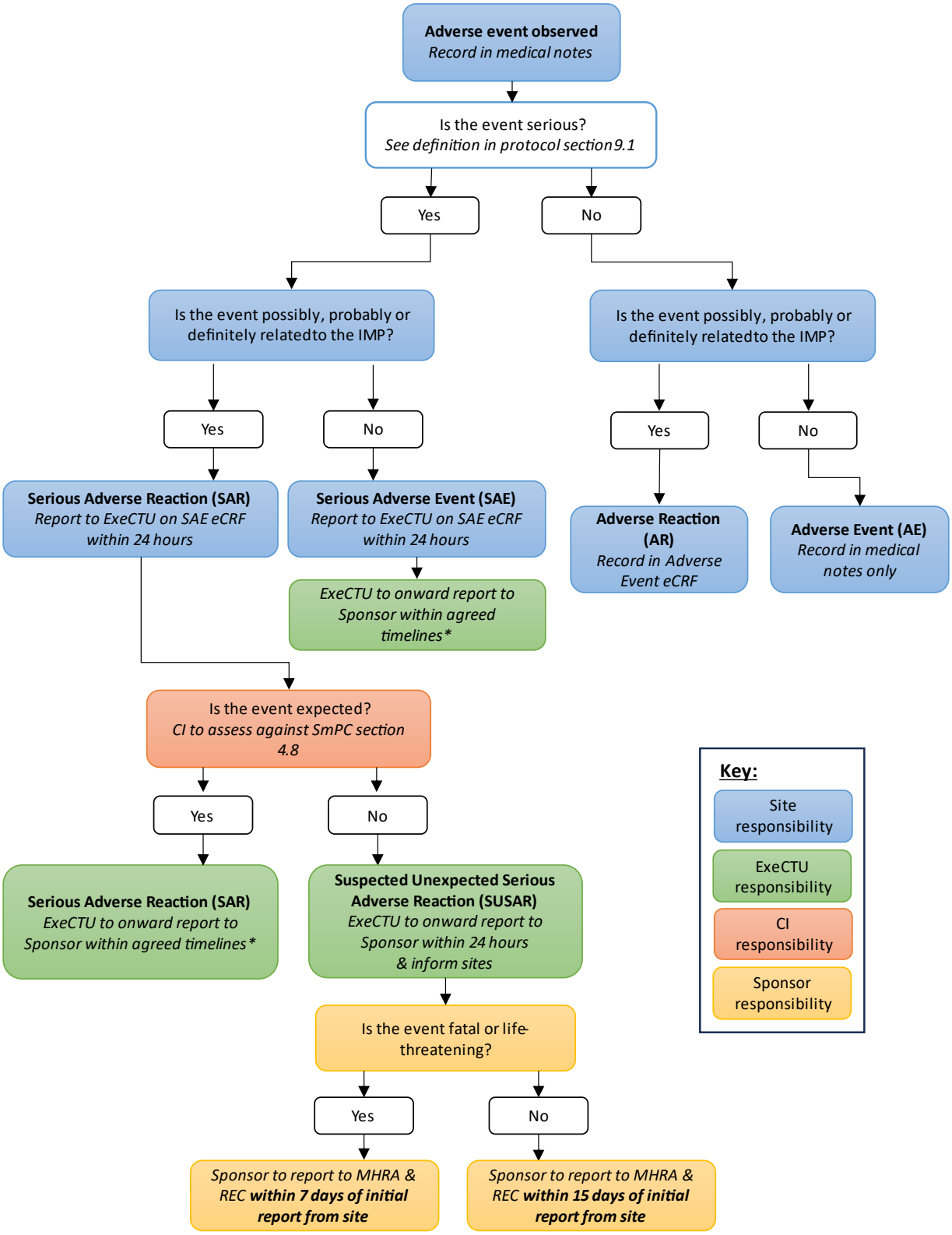
APPENDICIES
Appendix 1- Safety Reporting Flow Chart



**From randomisation to Day 14 ExeCTU will report SAEs and SARs on to Sponsor within 24 hours of becoming aware. From Day 15 onwards SAEs and SARs will be reported to the Sponsor in batches at agreed intervals.*