

EXamining antibiotiCs for ulcerated skIn cancer Surgical Excision

PROTOCOL

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Co-Chief Investigators agree to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the relevant trial regulations, GCP guidelines, and CTR's SOPs.

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 from the trial as planned in this protocol will be explained.

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General Information This protocol describes the EXCISE clinical trial and provides information about the procedures for entering participants into the trial. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other patients. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial. Problems relating to the trial should be referred, in the first instance, to CTR.

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The EXCISE trial is being coordinated by the Centre for Trials Research (CTR) Cardiff University, a United Kingdom Clinical Research Collaboration (UKCRC) registered trials unit.

This protocol has been developed by the EXCISE Trial Management Group (TMG).

For **all queries** please contact the EXCISE team through the main trial email address. Any clinical queries will be directed through the Trial Manager to either the Chief Investigator or a Co-Investigators.

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Randomisations:

Randomisation
Locations should provide a delegation log to the CTR EXCISE team during trial set up and update the log as required. Location staff delegated to patient enrolment and/or data entry duties will be granted access to the trial database for enrolment and data entry. A link to the randomisation system will be sent upon location activation along with a database User guide. See section 9.5.2 for more details.

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EXCISE-CTR@cardiff.ac.uk **All clinical queries will be directed to the most appropriate clinical person.**

Serious Adverse Events (SAE):

SAE reporting
Where the adverse event meets one of the serious categories, an SAE form should be completed by the responsible clinician and submitted to Centre for Trials Research Safety Team within 24 hours of becoming aware of the event (See section 14 for more details). **Contact details: CTR-Safety@Cardiff.ac.uk**

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Glossary of abbreviations

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CAVUHB	Cardiff and Vale University Health Board
CDC	Centers for Disease Control and Prevention
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trials Authorisation
CTCAE	NCI Common Terminology Criteria for Adverse Events
CTIMP	Clinical Trial of Investigational Medicinal Product
CTR	Centre for Trials Research
CTU	Clinical Trials Unit
CU	Cardiff University
DSUR	Development Safety Update Report
EHR	Electronic Health Records
eMC	electronic medicines compendium
GCP	Good Clinical Practice
GDPR	General Data Protection Regulations
GMP	Good Manufacturing Practice
GP	General Practitioner
HCP	Health Care Professional
HE	Health Economics
HTA	Health Technology Assessment
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention- To- Treat
MA	Marketing authorisation
MHRA	Medicine and Healthcare products Regulatory Agency

NICE	National Institute for Clinical Excellence
NIMP	Non-Investigational Medicinal Product
PAG	Patient Advisory Group
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality control
QL (QoL)	Quality of Life
QP	Qualified Person
QR	Qualitative Researcher
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary Product Characteristics
SOP	Standard Operating Procedure
SSI	Surgical Site Infection
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
WHQ	Wound Healing Questionnaire

1 Amendment History

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment No. *(specify substantial/non-substantial)*	**Protocol version no.**	**Date issued**	**Summary of changes made since previous version**
AM 2 (Non-Substantial)	V1.1	20.10.2025	Minor amendment comprising of clerical changes and removal of typographic errors. Additionally, it is clarified that the SOPs of the CTR will be followed instead of CAVUHB. Further information was added to those able to collect informed consent. Bristol stool chart, removed as an assessment in table 2. Added information to the analysis section.
AM 4 (Non-Substantial)	V1.2	22.01.2026	The protocol has been amended to clarify that the follow-up period and the SAE reporting period commence from the day of surgery rather than from randomisation. This amendment allows sites to randomise participants in advance of the day of surgery where required.
M5 (Modification of an important detail)	V1.3	12.08.2026	Clarified eligibility criteria and statistical analysis for participants undergoing excision of multiple lesions, including eligibility requirements and handling in the main analysis. Clarified optional long-term follow-up arrangements for Northern Ireland, including data sharing expectations, references to the Mental Capacity Act (Northern Ireland) 2016, and inclusion of H&C numbers alongside NHS and CHI identifiers. Administrative updates made to reflect changes to trial personnel and new clinical trial regulation terminology.

2 Synopsis

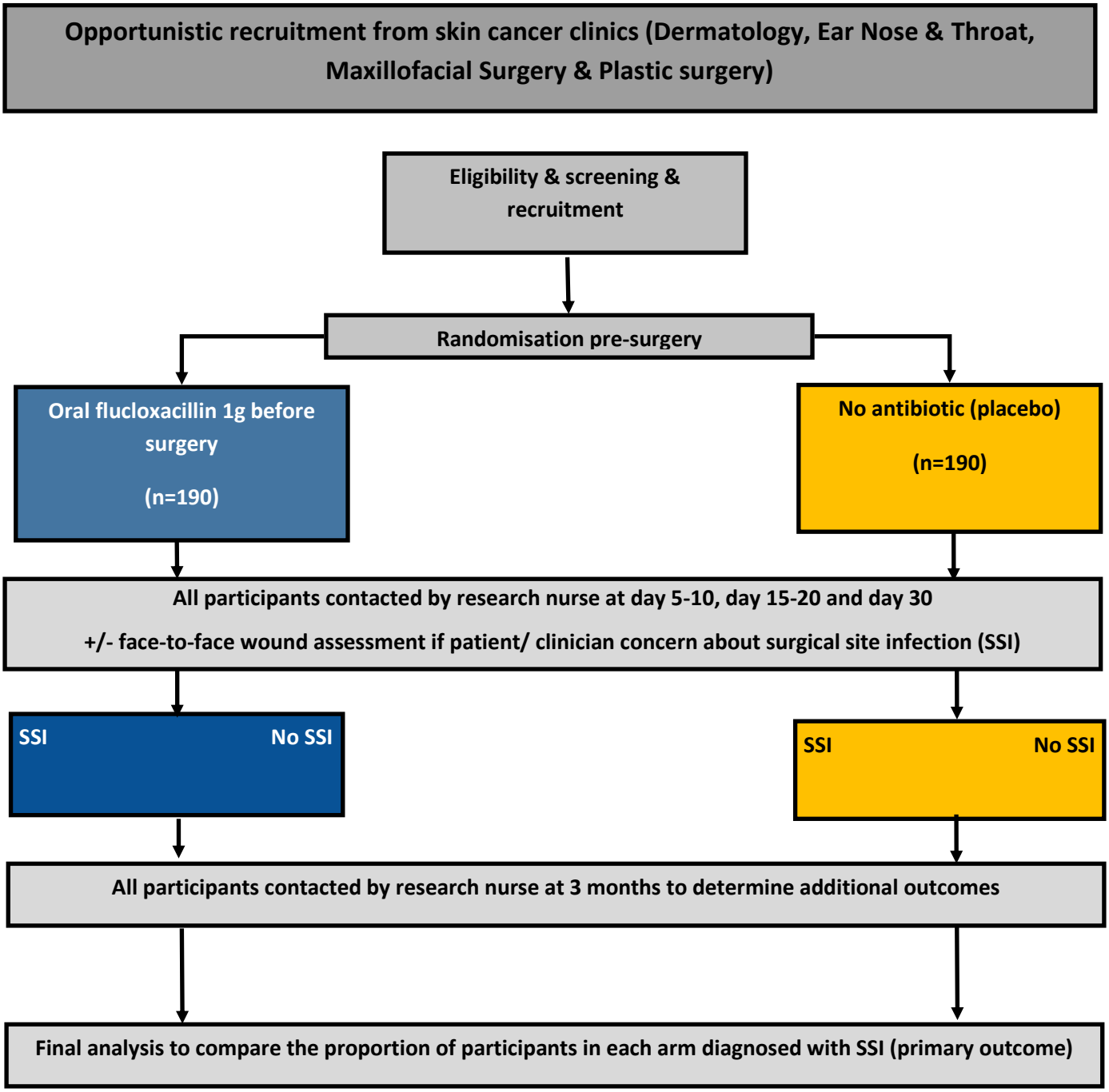
Short title	EXamining antibiotics for ulCerated skIn cancer Surgical Excision
Acronym	EXCISE
Internal ref. no.	1612
Clinical phase	IV
Funder and ref.	National Institute for Health and Care Research NIHR160872
Trial design	Randomised, double-blind, superiority placebo-controlled trial (with internal pilot).
Trial participants	Adult patients undergoing surgical excision of ulcerated skin cancer in UK NHS hospitals
Planned sample size	380
Planned number of locations	10-15
Inclusion criteria	1. Adult patients (≥ 16) with a clinically ulcerated suspected skin cancer (at any body site) listed for excision under local anaesthetic with planned wound closure by any secondary care speciality.* 2. First time in the EXCISE trial. 3. Ability to provide informed consent (by participant or through a participant's personal legal representative). *Where multiple lesions are to be excised, at least one lesion must meet the above inclusion criteria
Exclusion criteria	1. Clinical evidence of skin cancer infection at baseline using CDC criteria.* 2. Skin tumour removal planned with curettage, Mohs micrographic surgery/ margin-controlled excision or shave excision.* 3. Wound left for delayed reconstruction or secondary intention healing or closed with dermal substitute.* 4. Concurrent oral antibiotic treatment (<24 hours after last dose). 5. Documented poor renal function (creatinine clearance < 10ml/min). 6. Previous allergic reaction to penicillin. *Where multiple lesions are to be excised, all lesions must NOT meet the above exclusion criteria
Treatment duration	Single 1g dose (500mg x 2) of pre-operative oral flucloxacillin or placebo
Follow-up duration	3 months (primary outcome 30 days)
Planned trial period	1st January 2025 – 31st December 2027
Primary objective	To investigate the efficacy of a single pre-operative 1g dose of oral flucloxacillin in preventing SSI within 30 days in adults undergoing surgical excision of an ulcerated skin cancer under local anaesthetic with planned wound closure.
Secondary objectives	To assess the adverse events of a single dose of oral flucloxacillin. To investigate antibiotic resistance in infected wounds. To evaluate the cost effectiveness of oral flucloxacillin versus no antibiotic treatment.

	To evaluate participants' and clinicians' views on oral antibiotics in preventing wound infection. To investigate the feasibility of 'Selfi-wound' photos. To validate the WHQ for SSI assessment in skin surgery.
Tertiary/Exploratory objectives	To explore patient wound burden.
Primary outcomes	To compare the proportion of participants in the oral flucloxacillin group with the no antibiotic (placebo) group diagnosed with Surgical Site Infection within 30 days post-surgery.
Secondary outcomes	1) The number of participants with adverse events within 30 days of surgery using the Medical Dictionary for Regulatory Activities. 2) Antibiotic resistance to clinically relevant antibiotics will be evaluated in isolates from participants' wounds at diagnosis of SSI and after 7 days if no response to treatment. 3) Health-related QoL measured by EQ-5D-5L questionnaires at baseline (face-to-face), 30 days and 3 months. 4) Time to return to normal activity/work at 30 days and 3 months. 5) Resource use (related to wound complications including SSI) and cost of hospital visits/stays - at 30 days and 3 months. 6) Qualitative process evaluation assessing implementation and acceptability of oral antibiotics including facilitators and barriers. 7) Feasibility of 'Selfi-wound' photos as measured by the number of participants who were able to successfully take and transmit an image of their wound images via the online system. 8) Validation of WHQ remote use for SSI assessment via SWAT.
Tertiary/Exploratory outcomes	Explore participant wound burden.
Investigational medicinal products	Flucloxacillin or placebo
Form	Capsule
Dose	1g (2 x 500mg)
Route	Oral

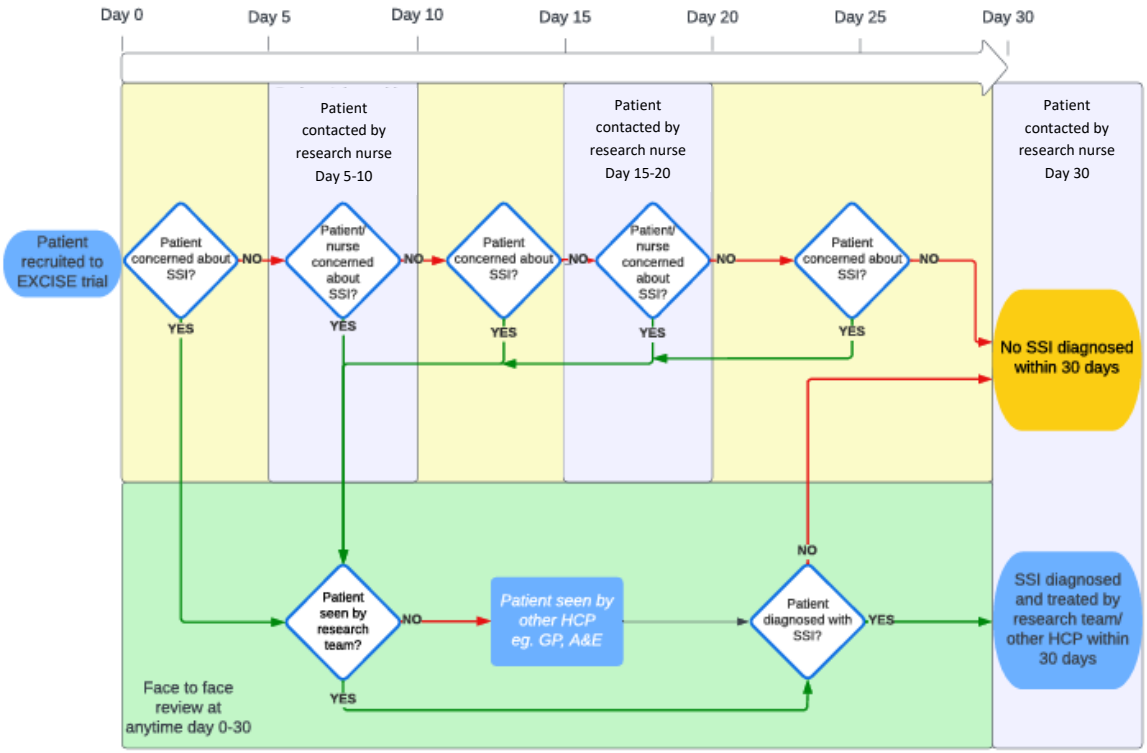
3 Trial summary & schema

3.1 Trial schema

EXCISE trial flow chart—2 arm design



3.2 Participant flow diagram



3.3 Trial lay summary

Skin cancer is the most common type of cancer. Every year in the UK, around 200,000 people have their skin cancer removed surgically. Some people develop skin cancers that break through the skin surface causing a wound on the skin (called an ulcerated skin cancer) which are six times more likely to develop a wound infection after surgery. Doctors often prescribe antibiotics at the time of surgery to prevent wound infections, but we do not know whether antibiotics reduce the risk of getting an infection. Using more antibiotics than is needed may lead to patients having unnecessary side effects and lead to the bacteria causing the infection becoming resistant to antibiotics, which then work less well in the future.

We want to know whether antibiotics should be prescribed to patients at the time of surgically removing their ulcerated skin cancer to reduce their risk of wound infection. Participants will be given a one-off dose of antibiotic or no antibiotic (dummy pill called placebo). We will see how many in each group develop wound infections. This will help us to decide whether antibiotics should be given to patients before skin surgery.

We asked UK doctors who remove skin cancers (through an online survey) if they prescribe antibiotics, and if so, what they give and for how long. 50% said they routinely prescribe antibiotics, while 50% never prescribe antibiotics. We also carried out a study which found that a third of patients developed a wound infection after removal of their ulcerated skin cancer.

We will recruit 380 people with ulcerated skin cancers from UK NHS hospitals. Before surgery, participants will be randomly allocated by a computer to have a one-off dose of a common antibiotic or no antibiotics (placebo). Everyone will receive the same wound care advice that they normally get as part of their NHS treatment. Participants will be asked to contact us if they are worried about their wound, they will receive a photo booklet to help identify potential infections. We will contact everyone between day 5-10, 15-20 and 30 days after surgery to ask about their wound, signs of infection and side effects. Participants will be seen in hospital if a wound infection is suspected, all will receive additional treatment if required. We will also ask how long it took to return to normal activity and the impact on daily life at 30 days and 3 months after surgery. At the end of the trial, we will know how many participants developed a wound infection and whether taking antibiotic tablets before surgery reduces the risk of wound infection.

Two members of the public are part of our core team, also forming part of a wider patient advisory group. We talked to patients with experience of skin cancer surgery and with the Centre for Evidence Based Dermatology Patient Panel. Their views have informed the trial design, and all agreed that the trial is relevant to patient needs. Our partners will work with us throughout the trial and help to disseminate the results.

We will continue to engage with Clinician Stakeholders. Findings will be presented at conferences, published in free to access journals and on social media. Results will be shared with participants who took part, the national press, skin cancer and infection prevention charities, skin surgery guideline and policy writers and through the UK Dermatology Clinical Trials Network.

4 Background

Skin cancer (including basal cell cancer and cutaneous squamous cell cancer - known collectively as keratinocyte cancer – and melanoma) is the most common cancer in the UK with a lifetime incidence of 1 in 4 for men and 1 in 6 for women (1,2). Surgical excision is the gold standard treatment, and it is estimated that over 200,000 surgical excisions are carried out in UK dermatology services alone each year (3). Wound healing following skin surgery may be complicated by Surgical Site Infection (SSI). Local audits, and the wider global literature, suggest that overall incidence of SSI following skin surgery is 1-27% (4,5). SSI causes patient morbidity; requiring treatment with oral or intravenous antibiotics, repeated consultations in primary or secondary care to assess resolution, delayed wound healing, repeated surgical procedures, and poor cosmetic scar outcome, together with increased costs to individuals and the healthcare system (6,7). Patient representatives shared their experiences in two small group discussions and told us that their experience of SSI was 'as debilitating and, in some cases, more painful than the surgery itself.' The estimated cost of managing SSI in other surgical specialties is over £10,000 per patient and the use of antibiotic prophylaxis at the time of surgery has been shown to be cost-effective (8). Skin cancers are commonly ulcerated (Ulceration will be defined as the absence of an intact epidermis (≥3mm) overlying a major portion of the tumour which

is based on the American Joint Committee on Cancer definition of ulceration of primary melanoma (9). Our prospective, multicentre evaluation of UK patients (n=249) undergoing excision of suspected skin cancers, found that one third were clinically ulcerated (10). A systematic review of risk factors for SSI following skin surgery identified one prospective study of moderate quality which found that ulceration of the lesion was a risk factor for SSI (OR, 3.15; 95% CI, 1.8-5.7; P = .008) (4,11). This may be due to loss of the dermis, bacterial colonisation, inflammation and subsequent difficulty in obtaining a sterile field; thus, excision of ulcerated skin cancers could be considered 'contaminated' rather than 'clean' surgery (12).

There is no UK nor European guidance for prescribing antibiotics before or after skin surgery. NICE recommends a single dose of intravenous antibiotic prophylaxis before contaminated surgery (12); however skin surgery is usually performed with local anaesthetic, and therefore intravenous access is not routinely obtained. Excision of ulcerated skin cancers in the UK is mostly undertaken by dermatologists, but also performed by Plastic and Reconstructive, Ear, Nose and Throat (ENT) and Oral Maxillofacial (OMF) surgeons (13,14). Our multi-specialty survey (n=129) conducted in 2021 reported that peri-operative antibiotics were 'always'/ 'often'/ 'sometimes' prescribed for excision of ulcerated skin cancers by 49% of respondents and 'rarely' / 'never' by 51% demonstrating clinical equipoise (15). A multi-specialty, retrospective evaluation of suture use and complications after excisional skin surgery conducted in the UK, Ireland, Australia, and New Zealand reported 44/139 participants with ulcerated lesions were prescribed oral/ intravenous antibiotics including flucloxacillin, co-amoxiclav, erythromycin, doxycycline, amoxicillin, cephalexin and clarithromycin: 17/139 participants were prescribed oral flucloxacillin 250mg 500mg four-times daily for 7 days with 6% retrospectively reported to have SSI; 7/139 participants were prescribed a single dose of intravenous flucloxacillin with 1/7 (14%) retrospectively reported to have SSI. However, data were retrospectively recorded from the case notes and the SSI criteria were undefined (13). A national audit of keratinocyte cancer excisions by UK plastic surgeons in 2020 reported: 598/2607 (23%) recorded as 'ulcerated' (undefined) with 123/598 (21%) prescribed antibiotics (route, type, course length not recorded) (14). SSIs were reported in 20/598 (3.3%), but this was not a primary outcome, nor a mandatory data point and so likely to be an underestimate. Of those reported to have an SSI 11/20 were not prescribed antibiotics, 4/20 were prescribed antibiotics postoperatively and 4/20 were prescribed antibiotics pre-operatively. These data show that antibiotics are being widely and variably prescribed for ulcerated skin cancer surgery without strong evidence of effectiveness.

Therefore, given the current lack of evidence and variation in practice, this trial is needed to provide clear evidence for appropriate antibiotic use in this setting. Whilst there is variability in antibiotic prescribing for ulcerated skin cancer surgery, our Clinician Stakeholders told us that they most wanted to know whether a single pre-operative dose is effective in reducing the risk of SSI. To address this evidence gap, this double-blinded, superiority randomised control trial (RCT), will evaluate the clinical and cost effectiveness of a single

pre-operative dose of oral flucloxacillin to reduce SSI rates following excision of ulcerated skin cancers compared to no antibiotic treatment. We will assess SSI using the Centers for Disease Prevention and Control (CDC) criteria (16) which are widely used to diagnose SSI including by the UK Health Security Agency (HSA) for SSI surveillance (17).

Review of existing evidence

A recent systematic review (18) of efficacy of antibiotics in preventing SSI after skin surgery identified three RCTs which investigated a single dose of pre-operative 2g oral cephalexin (19,20) or 2g intravenous cefazolin (21) in reducing SSI after skin surgery. The studies demonstrated an overall benefit from the antibiotic in reducing the likelihood of postoperative infection (OR 0.35), with reported rates of infection 7%, 21% and 36% in the placebo groups and 5%, 6% and 9% in the antibiotic groups (18). Ulceration was not documented in two studies; however, Dreher *et al* (21) reported that 68/208 (33%) skin cancers were ulcerated with 12/35 (34%) developing SSI in the no antibiotic group compared to 3/33 (9%) in the group given a single dose of 2g intravenous cefazolin; relative risk ratio 0.61 (number needed to treat = 4.8). Our 2018 systematic review of efficacy of antibiotics in reducing SSI following ulcerated skin cancer excision identified one low-quality RCT (22). The authors reported that 1/37 participants developed 'purulent wounds' in the oral antibiotic group (cephalexin 500mg for 2 days prior to surgery) compared with 0/37 in the mupirocin group and 5/23 in the cetrimide-chlorhexidine cream group (23). An updated search of PubMed, Embase, Cochrane Library database, ISRCTN Registry, ClinicalTrials.gov and the International Clinical Trials Registry Platform (last search 27/11/23), identified two recruiting trials.

A single-centre US trial (NCT04580472) is investigating the effectiveness of a single dose of preoperative oral cephalexin in reducing SSI in patients undergoing repair with skin flap or graft (or wedge resection) on the nose or ear, and in patients undergoing Mohs surgery with closure or partial closure or surgical excision on the lower extremity below the knee. The trial team have confirmed that they are including both ulcerated [defined as 'clinical ulceration (obvious crust)'] and non-ulcerated skin cancers (personal communication).

A single centre, open label Japanese trial (ISRCTN ID: JPRN-jRCT1031220718) is investigating the effect of post-operative oral cefaclor, prescribed 3 times daily for 3 days, versus no antibiotic on SSI assessed at 7 days after skin surgery (primary outcome). A multi-centre Australian trial (ACTRN12624000076572) is investigating the efficacy of two interventions (oral clindamycin pre-and post-operatively; and pre-operative chlorhexidine wash and nasal mupirocin) in reducing SSI in people undergoing flap or graft procedures for treatment of skin cancer below the knee (doi: 10.31128/AJGP-06-23-6881).

We undertook a prospective, observational feasibility study of patients undergoing excision of an ulcerated skin cancer (March 2019-March 2020) competitively funded by the UK Dermatology Clinical Trials Network (UK DCTN) (24). The primary outcome was SSI within 30 days as determined by the Wound Healing

Questionnaire (WHQ) which was developed as part of an NIHR workstream and validated for assessment of SSI in closed primary wounds after hospital discharge (25,26). In total, 148 participants were recruited: 77.1 years (12.3); 12% prescribed peri-operative antibiotics with the following histological diagnoses: basal cell cancer 81/148 (56%), cutaneous squamous cell cancer 46/148 (32%), melanoma 3 (2%), other 16/148 (11%), missing data 2/148. These data suggest that cutaneous squamous cell cancer is overrepresented in our study population (32%) compared to 23% of overall skin cancer diagnoses in the UK (27). Primary outcome data were available for 116 (78%) participants of whom 35 (30%) were defined as having SSI using the WHQ (with a cut-off score of 8) and 41% (with a cut-off score of 6). Whilst the WHQ has not been validated in patients undergoing skin surgery, these data are comparable to previously reported SSI rates following excision of ulcerated skin cancers: 34% in the RCT reported by Dreher et al., and 33% in a single-centre UK cohort study (n=68) (21,28).

Limitations of the existing evidence

Oral flucloxacillin is commonly prescribed in the UK for patients undergoing excision of an ulcerated skin cancer with the aim of preventing SSI; however, there is no RCT investigating the benefits and harms of oral flucloxacillin in this setting. Two RCTs have investigated the use of pre-operative oral cephalexin prior to excision of skin cancers (ulceration was not detailed) in Australia (19,20); however, oral cephalexin can promote resistance development and more importantly is linked to gut decolonisation and associated *C. difficile* infection. One RCT reported the use of pre-operative intravenous cefazolin prior to excision of ulcerated skin cancers (not primary outcome) in Brazil (21); however, intravenous access is not routinely obtained for skin surgery.

4.1 Rationale

Health/care need*:* Confirming appropriate antibiotic prescribing practices and reducing inappropriate prescriptions has been identified by patients, carers and healthcare professionals (HCPs) as a top priority, after being deemed priority number 5 of the James Lind Alliance (JLA) priority setting partnership (PSP) on healthcare associated infections (29). Determining the best methods of reducing SSI was also listed in the top 16 JLA PSP on skin cancer surgery completed in 2022 with 643 respondents to the initial survey (62% from people with experience of skin cancer) (30). Antibiotic stewardship programmes are prevalent in most UK hospitals and aim to limit use of broad-spectrum antibiotics and promote more appropriate use of antibiotics in all clinical scenarios without harm to the patient. Inadequate or inappropriate antibiotic use may lead to increased risk of SSI which adversely affects patients' psychological and physical health and brings a financial burden to patients, carers and healthcare organisations (6). The lack of robust evidence to support antibiotic therapy recommendations has resulted in inappropriate use of antibiotics, which can lead to unwanted side

effects for patients and contributes to development of antimicrobial resistance (AMR). Tackling AMR is an urgent national and global priority. This trial is timely as it aligns with the Department of Health and Social Care's recently launched UK five-year national action plan "Tackling antimicrobial resistance 2019–2024", whose objectives are for optimising the use of antimicrobials in humans and embraced by the NIHR (31) and responds to research recommendations from NICE guidance for antimicrobial stewardship (32).

Sustained interest and intent*:* UK incidence rates for keratinocyte cancer and melanoma have increased by 169% and 140% respectively between 1993-1995 and 2016-2018 (1,2). Antibiotic prescribing associated with skin surgery is also increasing (10,15,33). Addressing the limited evidence base for the use of antibiotics for skin surgery is needed to standardise clinical practice and national policy.

Capacity to generate new knowledge*:* This trial will provide a clear answer to a precise research question to ascertain if oral flucloxacillin prevents SSI assessed by CDC criteria (16). And if so, the magnitude of benefit of flucloxacillin use for SSI prevention following ulcerated skin cancer surgery and the relationship between adverse events. SSI data following skin surgery are not routinely collected as patients are discharged home and often not followed up by the operating team. Other surgical specialties have developed tools to facilitate remote diagnosis/ triage of SSI using telemedicine (34) including the WHQ (25,26). We plan to validate the WHQ in patients undergoing skin surgery in a Study Within a Trial (SWAT) (35). In our feasibility study, we asked participants to complete the WHQ via post/ email (24) and we found it to be an acceptable and low-cost self-reporting measure. 'What are the best ways to measure outcomes after skin cancer surgery?' was listed within the top 10 research priorities in the recent JLA PSP on skin cancer surgery (30). Therefore, the SWAT evaluation will generate further data for the use of the WHQ in the future in audit and research for remotely monitoring SSI following skin surgery. Wound swabs will be collected from all participants who develop SSI and attend their recruiting centre and will be repeated seven days later if the SSI does not respond to treatment (based on CDC criteria). All swabs will be sent to a central microbiology laboratory at Public Health Wales for antimicrobial resistance analysis. This will establish the most common bacterial pathogens associated with the site of infection and will determine their susceptibility/resistance to clinically relevant antibiotics. This additional work will provide information for recommendations for appropriate targeted antibiotic treatment and national policy.

Hypothesis*:* This trial will assess the clinical and cost effectiveness of a 1g dose (500mg x 2) of pre-operative oral flucloxacillin in preventing SSI in adults undergoing excision of ulcerated skin cancers. The choice, dose, and timing of oral antibiotic were informed by our feasibility study (24), Clinician Stakeholder meeting (July 2023), surveys (10,15), evaluation of UK practice, PPI feedback, literature review and expert microbiological advice. Flucloxacillin is the first oral antibiotic option for skin infections in the UK and has low reported rates of side effects and drug interactions. Furthermore, resistance rates to flucloxacillin for SSIs are low in the UK.

5 Trial objectives/endpoints and outcome measures

5.1 Primary objectives

To investigate the efficacy of a single pre-operative 1g dose of oral flucloxacillin in preventing SSI within 30 days in adults undergoing surgical excision of an ulcerated skin cancer under local anaesthetic with planned wound closure.

• *PICO summary*

Population: Adults undergoing surgical excision of an ulcerated skin cancer under local anaesthetic with planned wound closure

Intervention: pre- operative oral flucloxacillin 1g (500mg x 2) in addition to standard clinical care

Comparator: no antibiotic (placebo) and standard clinical care

Outcome: SSI within 30 days using CDC criteria (16)

5.2 Secondary objectives

- To assess the adverse events of a single dose (1g) of oral flucloxacillin.
- To investigate antibiotic resistance in infected wounds.
- To evaluate the cost effectiveness of oral flucloxacillin and no antibiotic treatment.
- To evaluate participants' and clinicians' views on oral antibiotics in preventing wound infection.
- To investigate the feasibility of 'Selfi-wound' photos.
- To validate the WHQ for SSI assessment in skin surgery.

5.3 Tertiary objectives

- To explore patient wound burden.

5.4 Primary outcomes measure

To compare the proportion of participants in the oral flucloxacillin group with the no antibiotic (placebo) group diagnosed with Surgical Site Infection within 30 days of surgery.

5.5 Secondary outcomes measures

• The number of participants with adverse events within 30 days of surgery using the Medical Dictionary for Regulatory Activities.

• Antibiotic resistance to clinically relevant antibiotics will be evaluated in isolates from participants' wounds at diagnosis of SSI and after 7 days if no response to treatment. This will be assessed by a central microbiology laboratory (Public Health Wales).

• Health-related QoL measured by EQ-5D-5L questionnaires at baseline, 30 days and 3 months.

• Time to return to normal activity/work at 30 days and 3 months.

• Resource use (related to wound complications including SSI) and cost of hospital visits/stays - at 30 days and 3 months.

• Qualitative process evaluation assessing implementation and acceptability of oral antibiotics including facilitators and barriers.

• Feasibility of 'Selfi-wound' photos as measured by the number of participants who were able to successfully take and transmit an image of their wound images via the online system.

• Validation of WHQ remote use for SSI assessment via SWAT.

5.6 Tertiary outcome

• Qualitative process evaluation process exploring participant wound burden.

6 Trial design and setting

EXCISE is a randomised, participant, clinician and assessor-blinded, placebo-controlled trial (with internal pilot) comparing oral flucloxacillin versus no antibiotic (placebo) in adult patients undergoing ulcerated skin cancer excision in NHS UK hospitals under local anaesthetic with planned wound closure.

The trial will be undertaken in 10-15 locations across the UK. Co-applicants encompass 5 of these locations who will be Principal Investigators, members of the Trial Management Group (TMG), and lead recruiting locations (Cardiff, Oxford, Fife, Hull and Walsall). Further additional locations will be opened as required.

6.1 Risk assessment

A Trial Risk Assessment has been completed to identify the potential hazards associated with the trial and to assess the likelihood of those hazards occurring and resulting in harm. This risk assessment has been completed in accordance with the Medical Research Council/Department of Health/Medicine and Healthcare products Regulatory Agency (MRC/DH/MHRA) Joint project guidance document 'Risk-adapted approaches to the management of Clinical Trials of Investigational Medicinal Products' and includes:

- The known and potential risks and benefits to human subjects
- How high the risk is compared to normal standard practice
- How the risk will be minimised/managed

This trial has been categorised as a TYPE A, where the level of risk is no higher than the risk of standard medical care. A copy of the trial risk assessment may be requested from the Trial Manager. The trial risk assessment is used to determine the intensity and focus of monitoring activity (see section 24.1).

This clinical trial is to be conducted in compliance with the protocol, the EU Clinical Trial Regulation 536/2014 and Good Clinical Practice (GCP).

7 Location and Investigator selection

This trial will be carried out at 10-15 participating locations within the UK. All locations who are interested in participating in the trial will be required to complete a registration form to confirm that they have adequate resources and experience to conduct the trial. Where electronic health records are being used, location teams must be willing and able to take steps to avoid unintentional unblinding through EHR system.

Before any location can begin recruitment a Principal Investigator at each location must be identified. The following documents must be in place and copies sent to excise-ctr@cardiff.ac.uk:

- Confirmation of Capacity and Capability (C&C) from R&D department following sharing of local information pack.
- Favourable opinion of host care organisation/PI from Main Ethics committee.
- MHRA approval.
- A signed Trial Agreement.
- Current Curriculum Vitae and GCP training certificate of the Principal Investigator (PI).
- Completed Site Delegation Log and Roles and Responsibilities document.
- Full contact details for all host care organisation personnel involved, indicating preferred contact.
- A copy of the most recent approved version of the Participant Information Sheet(s)(PIS) and Consent Form(s) (ICF) on host care organisation headed paper.
- A copy of the most recent approved GP letter on host care organisation headed paper.
- Returned copy of the Source Data Agreement signed by the PI.
- Pharmacy confirmation that they have received the first shipment of IMP prior to opening the location. N.B. This is not a regulatory requirement more good practice.

Upon receipt of all the above documents, the Trial Manager will send written confirmation to the Principal Investigator/lead Research Nurse detailing that the centre is now ready to recruit participants into the trial. This letter/email must be filed in each location's Site File. Along with the written confirmation, the location should receive their trial drug supplies and a trial pack holding all the documents required to recruit into the Trial.

Occasionally during the trial, amendments may be made to the trial documentation listed above. CTR will issue the location with the latest version of the documents as soon as they become available. It is the responsibility of the CTR to ensure that they obtain local R&D approval for the new documents. location initiation will be by an online meeting.

The Trial Management Group (TMG) will apply for the trial to be registered with the Associate PI (API) scheme run by NIHR and will encourage the PI at each location to recruit a healthcare professional early in their research career to consider registering with the scheme.

8 Participant selection

Participants are eligible for the trial if they meet all of the following inclusion criteria and none of the exclusion criteria apply. All queries about participant eligibility should be directed to the Trial Manager before randomisation/registration. Locations are encouraged to recruit a broad range of participants, including with respect to ethnic diversity, socio-economic status, digital/health literacy and age. Where a participant undergoes excision of multiple lesions, ALL lesions must be excised using an eligible method and must not meet any trial exclusion criteria.

8.1 Inclusion criteria

1) Adult patients (≥ 16) with a clinically ulcerated suspected skin cancer (at any body site) listed for excision under local anaesthetic with planned wound closure by any secondary care speciality.*
2) First time in the EXCISE trial.
3) Ability to provide informed consent (by participant or through a participant's personal legal representative).

*Where multiple lesions are to be excised, at least one lesion must meet the above inclusion criteria

8.2 Exclusion criteria

1) Clinical evidence of skin cancer infection at baseline using CDC criteria.*
2) Skin tumour removal planned with curettage, Mohs micrographic surgery/ margin-controlled excision or shave excision.*
3) Wound left for delayed reconstruction or secondary intention healing or closed with dermal substitute.*

4) Concurrent oral antibiotic treatment (<24 hours after last dose).
5) Documented poor renal function (creatinine clearance < 10ml/min).
6) Previous allergic reaction to penicillin.

*Where multiple lesions are to be excised, all lesions must NOT meet the above exclusion criteria

9 Recruitment, Screening and registration

9.1 Internal Pilot

We have included a planned internal pilot phase, using quantitative and qualitative data, during the first 6 months of recruitment (trial months 10-15). We will review recruitment locations and participant enrolment, completeness of primary outcome data, including surgical technique adherence and a clinical review of a subset of patients who do not report a suspected SSI (see Table 1 below for Pilot Progression Criteria). We will also conduct a rapid qualitative evaluation from interviews with a sub-sample of participants and HCPs to examine the acceptability of recruitment and trial processes, attitudes about antibiotics, as well as an early assessment of clinical equipoise and contextual factors that may affect implementation (36,37).

Our recruitment estimates for the pilot phase have considered published reviews and recommendations (38-40), and that recruitment rates are slower when locations initially open. We plan for all locations to be open within the first 6 months with a staggered opening rate and slower recruitment rates in the first few months.

Pooled data of NIHR funded studies show that internal pilots typically recruit 15% of their participants within 33% of the total recruiting time period (38). These figures have been used to calculate the number of participants expected to be recruited, (n=57; 15% of 380) in 6 months (33% of the total 15-month recruitment window). This 6-month window will start when the first location is open to recruitment. We will use a traffic light system to determine feasibility and have developed a recruitment prediction based on our feasibility data, recent expressions of interest and experience on speed of location opening.

We will also monitor the proportion of participants providing primary outcome data. We would anticipate a completion rate of 85%, rates below this (<84%) will prompt a review of the process of capturing primary outcome data. We will actively monitor the SSI rate during the pilot phase of the trial, reporting these to our Independent Data Monitoring Committee (IDMC). Participants will be asked to complete a daily diary, which will record any concerns about wound infection and side effects. We also plan to record surgeon compliance with WHO surgery technique recommendations.

Table 1. Internal Pilot Progression Criteria

Progression criteria at 6 months	**Red**	**Amber**	**Green**
Recruitment rate/location/month	≤60% (n ≤1.2)	61-99% (1.3 ≥ n ≤1.9)	100% (n ≥2.0)
Number of locations opened	≤25% (n ≤2)	26%-99% (3 ≥ n ≤7)	100% (n≥ 8)
Total number of participants recruited	≤60% (n ≤34)	61-99% (35 ≥ n ≤56)	100% (n≥57)

We will use the Guidance for Reporting Involvement of Patients and the Public (GRIPP2) tool (41) for assessing the impact of patient and public involvement (PPI) and the feedback from qualitative interviews to understand the quantitative data and provide areas for improvement in processes to enhance the efficiency of the trial. The progression criteria have been designed to allow for mitigating strategies to be discussed to allow for some adaptation to recruitment processes.

We will constantly be assessing the criteria during the internal pilot phase. We will discuss the results with our Trial Steering Committee, before reporting to the NIHR HTA Programme.

9.1.1 Recruitment rates

In our observational feasibility study, the average recruitment was 4.11 patients per month, from 3 open locations (Cardiff, Oxford and Birmingham) over a 12-month period (24). During the internal pilot phase, we predict the average recruitment rate would be 2.07 participants/location/month, which accounts for slower recruitment as locations open. The remaining recruitment time after the internal pilot is completed (9 months)

would need to average 4.15 participants/location/month. PI co-applicants and expression of interest from other locations come from similar sized hospitals as those that took part in our feasibility study, therefore the recruitment rates proposed here should be achievable. We will review eligibility rates and reasons for exclusions to ensure we are being as inclusive as possible.

9.2 Participant identification

Potential participants will be identified through the NHS care pathway during their initial consultation for their skin cancer excision. Once a patient has been identified as potentially eligible to participate, the opportunity will be discussed with the patients, and they will be given a copy of the trial PIS and ICF. The patient will be given adequate time to consider the trial and given the opportunity to ask further questions.

Our feasibility study, OASIS (24) showed that the average age of patients in this study population was 77 years old. We have designed the trial in line with best practice recommendations for research involving older people (42) and developed our patient facing materials using the NIHR INCLUDE Impaired Capacity to Consent Framework to ensure accessibility of the trial for those with cognitive and other impairments (43).

Information will be provided in a range of materials and formats such as large print versions, summary information sheets, and an infographic recruitment video, developed in consultation with our PPI representatives to ensure the information is accessible, including those with cognitive and/or communication impairments such as poor vision.

Participants should be encouraged to discuss the trial with their friends and family if they wish who can support them to decide about participating and/or support them to take part.

The right of the participant to refuse to participate in the trial without giving reasons must be respected. However eligible participants who refuse to participate will be approached to ask for their reason following the SEAR framework for monitoring recruitment and inclusivity (44).

The PI or nominated delegate listed on the trial delegation log must confirm eligibility of a patient in the patient's medical notes and by completing the Eligibility checklist prior to enrolment. Randomisation will only be possible once the patient's eligibility is confirmed.

9.3 Screening logs

Investigators should keep a record of how many patients were considered for the trial by maintaining a participant screening log. A screening log of all patients will be entered into a restricted access section of the main trial database. When at the location, logs may contain identifiable information, but this must be redacted before being sent to the CTR trial inbox (excise-ctr@cardiff.ac.uk) when requested. Screening logs will be analysed according to the SEAR (Screened, Eligible, Approached, Randomised) framework (44).

9.4 Informed consent

The participant's written informed consent must be obtained using the trial Consent Form, which follows the Participant Information Sheet. The participant should be supported to understand the information about the trial and given ample opportunity to discuss it and ask questions. They should be given sufficient time after the initial invitation to participate before being asked to sign the Consent Form. Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial.

Consent may be taken by the PI or member of the trial team who is GCP trained, suitably qualified and experienced, and who has been delegated by the PI to undertake this activity. As consent is an ongoing process, at all follow-up points, research staff will confirm that the patient is willing to continue participating in the trial.

Participants' consent will be requested to collect NHS number (or equivalent – e.g. CHI number in Scotland) and postcode to utilise NHS data for future research, and they will be asked to consent to data-linked longer-term follow-up. Participants in Northern Ireland will not be eligible for data linkage due to no equivalent service.

Once the consent form is completed, one copy should be given to the participant, the original copy should be kept in the investigator site file and a further copy should be kept with participant's hospital notes. Please note, only when informed consent has been obtained from the participant, and they have been randomised/enrolled into the trial can they be considered a trial participant.

Patients participating in the trial may also opt to consent to participate in qualitative interviews (see Section 16.3). This is optional. If trial participants provide written consent on the EXCISE consent form to indicate their interest in participating in an interview, the participant will be provided with the separate information sheet with them describing the full details of the qualitative study.

Once potential interview participants have had time to consider the study information, potential interview participants will be asked by a delegated member of the research team tick the qualitative statement on the informed consent form or complete a consent to contact form as appropriate for trial participants or HCPs. For those that opt to consent to participate in an interview, the Qualitative researcher (QR) will be notified and participant details reviewed for sampling (location, age, gender, trial arm, surgical site). Those then sampled for interview will be contacted by the QR and sent the PIS for interviews, along with a consent form, elicitation guidance document, diary booklet, timeline example and stamped addressed envelope. Once potential participants have had time to consider the study information the QR will contact them to discuss consent and arrange a suitable time for an interview.

Patients who are eligible for trial participation but decline to participate may opt to consent to participate in qualitative interviews. Health professionals involved in the trial may consent to participate in qualitative interviews.

After the participant has entered the trial, the investigator must remain free to give alternative treatment to that specified in the protocol, at any stage, if they feel it to be in the best interest of the participant. However, the reason for doing so should be recorded and the participant will remain within the trial for the purpose of follow up and data analysis according to the treatment option to which they were allocated. Similarly, the participant must remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing their further treatment (see Section 13.1 or further details on Withdrawal).

9.4.1 Impaired capacity to consent

Skin cancer is associated with ageing as solar damage accumulates over the course of a lifetime (1,2). Similarly, older people are at an increased risk of developing other long-term conditions including those associated with cognitive impairment such as dementia (45). According to Alzheimer's Research UK, 1 in 6 people over the age of 80 will develop some form of dementia (46) leading to a rise in the number of older people living with comorbid cancer and dementia (47). The co-existence of these two illnesses has serious health and economic impact on patients and their families, as well as health-care systems, and there is an urgent need for treatment guidelines for this growing patient population (48).

Due to the increased prevalence of multiple long-term conditions (MLTCs) such as dementia in this patient population, the trial has been designed to include participants who lack capacity to consent. Recruiting only participants who can consent for themselves will not generate the evidence needed for this patient population (49). Where there are concerns that a potential participant may lack capacity to consent to the trial even when supported to understand the information and make a decision about participating, the location PI (or suitably qualified healthcare practitioner who has been delegated the role), will determine capacity.

In accordance with mental capacity legislation (50, 51, 52) there is a presumption that a potential participant has capacity to consent. Where a potential participant lacks capacity to consent, participation in the trial should be discussed with friends and family who may be willing to act as their personal legal representative – in accordance with the Medicines for Human Use (Clinical Trials) Regulations, 2004 (53) this is a person who, by virtue of their relationship, is suitable to act as their legal representative and is available and willing to act. An Information Sheet and Consent Form for Legal Representative will be provided, and they will be asked to provide informed consent that represents the person's presumed will. If there is any indication that the participant in any way objects, they will not be recruited. In accordance with the Medicines for Human Use (Clinical Trials) Regulations, 2004 (53), the interests of the patient will always prevail over those of the trial.

Given the short duration of the trial, it is unlikely that a participant who gives informed consent at the outset will subsequently lose capacity. However, should this occur, the participant's initial consent to participate in the trial, given while capable, remains legally valid according to the Medicines for Human Use (Clinical Trials) Regulations, 2004 (53). The participant will remain in the trial unless it becomes apparent that continued participation is not in the best interests of the participant (for medical or other reasons) or if there is any indication that the participant would object to continued participation (based on previous known wishes or any expression of distress or objection), as outlined in the Mental Capacity Act, 2005 (50), the Adults with Incapacity (Scotland) Act 2000 (51) and The Mental Capacity Act (NI) 2016 (52). This approach is outlined in the participant information sheet and consent form.

Where it is suspected that the participant lacks capacity to continue to consent and the protocol is changed or additional consent is required from participants, then a family member or friend will be approached to act as their personal legal representative (e.g. the support person outlined in 9.4.1). If the participant does not consent to consulting their legal representative upon losing capacity, or it is not possible to contact their personal legal representative, the participant should be fully withdrawn if the protocol is changed, or additional consent is required from participants. Any request made by a personal legal representative to withdraw a participant from the trial, even if outside of the above conditions, should be considered. If the participant themselves raises any objections, their withdrawal will be processed.

If their personal legal representative declines, the participant should be fully withdrawn from the trial. In the event of a suspected SSI, participants will still be asked to report to their location for treatment.

Given the short duration of the trial, we do not anticipate that a participant who lacks capacity at the outset due to pre-existing cognitive impairment would regain capacity during the trial.

9.5 Registration and Randomisation

9.5.1 Registration

After consent and prior to randomisation, the participant will be registered on the EXCISE web-based system and assigned a unique trial primary identifier (ID). Following registration, locations will complete the screening and baseline assessments including medical history, surgical and drug history using the electronic screening CRF on the trial database.

9.5.2 Randomisation

We will randomise 380 participants between the two groups (190 participants per group) with a 1:1 allocation ratio. Randomisation will occur electronically prior to surgery. Allocations will be minimised (with random

element) by SSI risk associated with reconstruction method (primary closure, skin graft or local skin flap) and anatomical site (below knee or other anatomical site) and stratified by the recruitment location.

A computerised web-based remote randomisation system will be used. The Trial Manager will also be notified that a participant has been randomised via an automated email alert mechanism to the EXCISE email inbox. This system will be maintained by the Cardiff Centre for Trials Research (CTR) and accessed by the local investigator, or location staff delegated to do so, following consent and completion of baseline assessments. In the event the online randomisation system is unavailable at location, or the location has problems accessing the online website, participants will not be disadvantaged by having their surgery delayed and will be excluded from the trial.

10 Trial Intervention

Participants will be randomised in a 1:1 ratio to receive placebo or the following treatment, which is considered as an IMP within this trial:

- Oral flucloxacillin capsules
- Placebo comprising of all excipients of the active IMP except for the absence of the active ingredients

10.1 Treatment

1g dose (500mg x 2 capsules) of pre-operative oral flucloxacillin/placebo (as per randomisation).

The Summary Product Characteristics (SmPC) for Flucloxacillin (dated 17-Sep-2024 as updated by electronic medicines compendium (eMC)) made by Flamingo Pharma (UK) Ltd will be used as the RSI.

10.2 Treatment supply and storage

Oral flucloxacillin capsules and placebo will be procured and subsequently over encapsulated, packed, labelled and numbered as per the randomisation list (provided by CTR) by SIMBEC-ORION. SIMBEC-ORION is a licensed facility meeting Good Manufacturing Practice (GMP) standards. Labelling will contain the information from Annex 13 of the Labelling Regulations. The flucloxacillin will be sourced from any manufacturer which holds a valid Marketing Authorisation (MA) for the product. The SmPC detailed below for flucloxacillin is manufactured by Flamingo pharma and is representative of the product that is going to be administered.

These medicinal products do not require any special storage conditions, below 25°C, they are stable with a long shelf life under standard conditions (room temperature/below 25°C) therefore, IMP storage temperature will not be monitored in this trial consistent with Type A clinical trials.

Trial medication packs will be released by a Qualified Person to be distributed to recruiting centres and stored in pharmacy or in designated medicine cabinets within clinical areas, whichever is standard practice at the recruiting NHS Trust/Health Board. The trial medication is for trial participants' use only and will be stored separately from NHS medications.

10.3 Treatment prescribing and dispensing

The trial medication will be dispensed by the location trial team before surgery, which reflects current standard UK practice. The IMP will be prescribed by a doctor/ nurse delegated to do so on a trial-specific prescription which will be kept on file by the research nurse for IMP accountability specifying the pack ID to be dispensed. Further guidance on IMP management and supply will be detailed in the trial specific IMP Handling Manual and provided to trial locations.

10.4 Dose modification for toxicity

The IMP is a one-off pre-operative treatment and will be administered prior to surgery. Dose modification is not permitted.

10.5 Management of toxicity and hypersensitivity reactions

Patients should be evaluated for history or risk of hypersensitivity to the active substance, to any of the ingredients listed in section 6.1 of the SMPC, or to β -lactam antibiotics (e.g. penicillins, cephalosporins). Flucloxacillin is contra-indicated in patients with a previous history of Flucloxacillin-associated jaundice/ hepatic dysfunction. Participants with previous allergic reaction to penicillin will for this reason be excluded from the trial. Participants who experience signs of post-administration reactions should be managed as per local NHS guidance and any suspected reactions should be reported to the CTR.

10.6 Management of overdose

N/A

10.7 Pre-medication

No pre-medications are required before treatment with flucloxacillin.

10.8 Permitted, Restricted, and Prohibited Medications

Flucloxacillin has interactions with other medicinal products. For medications known to be contraindicated with the IMP, concomitant treatment should adhere to precautions outlined in the SmPC. Investigators should refer to section 4.5 of the SmPC for details of interactions with other drugs.

Participants taking concurrent oral antibiotic treatment (<24 hours after last dose) will be excluded from the trial for purposes of treatment fidelity. All other concomitant medications clinically indicated are permitted.

Any antibiotics, antithrombotics and immunosuppressant medications received during the trial will be recorded. For antibiotics prescribed during follow-up, the name of the antibiotic and route of administration (oral or intravenous) will be recorded. For antithrombotic and immunosuppressant medications, use at baseline and during follow-up will be recorded. Dosage and frequency will not be collected.

10.9 Accountability procedures

Local pharmacy personnel and/or recruiting local research team with delegated responsibility will be responsible for ensuring that the trial medications are managed and dispensed to participants as per local standard practice and guidance and in accordance with the current approved protocol. Each participating location is responsible for keeping accurate records of the IMP supplied by completion of the trial IMP accountability and allocation logs. Accountability procedures will be as per the trial IMP Management plan and IMP Handling Manual, which will be signed-off prior to commencement of the trial.

10.10 Compliance

Participants will receive a one-off dose of either flucloxacillin or placebo after informed consent is received, after randomisation and prior to surgery. The research nurse or delegated location staff will confirm participant has received the intervention by recording on the accountability logs and completing the CRF.

11 Trial procedures

Table 2 below summarises the trial procedures, which will be performed at each visit by the PI or those delegated to do so. Individual trial procedures are described in detail below.

Surgical Procedures

Following randomisation, oral flucloxacillin capsules or placebo will be dispensed by the trial team before surgery, and complete accountability logs according to the IMP Handling manual.

We will recommend adherence to the WHO guidelines for reducing SSI for surgical excision and wound closure (54,55):

- Standard preparation of the surgeon including surgical scrub/ alcohol gel and sterile gloves ± gown.
- Alcoholic chlorhexidine skin preparation, except where this is contraindicated (such as the face or ears, or around mucous membranes) where an aqueous solution should be used), or aqueous povidone-iodine if both an alcohol-based solution and chlorhexidine are unsuitable.
- Absorbable or non-absorbable sutures may be used.
- Skin glue should not be applied to the wound.

- Simple (non-active) dressings should be applied post-operatively, with or without steri-strips, except where this is impractical (such as around the eyes, ear or mouth).

We will monitor adherence with WHO guidelines using a post-surgery specific Case Report Form.

Post Surgical Care Procedures

We will standardise wound care advice and all participants will be advised to contact their local recruiting centre if they have any concern about SSI to arrange a face-to-face clinical review. Outcomes will be assessed by HCPs blinded to allocation.

All participants will receive the standard wound care advice that they would normally receive as part of routine NHS standard of care with possible signs and symptoms of SSI explained to them. Participants will also be given clear written and pictorial material (designed in collaboration with our Patient Partners), including what to look for to identify a wound infection. Participants will be reassured that prompt treatment will be available for any participants with SSI. All participants will be given contact details (including out-of-hours where applicable) of their local recruiting centre and will be advised to contact their local recruiting centre if they have any concerns about wound infection or side effects from the antibiotic tablets to arrange a face-to-face review. Financial assistance will be provided towards participant transport costs for the face-to-face review (if required) to support people on low incomes to participate in the trial, in line with recommendations from the NIHR INCLUDE Socioeconomic Disadvantage Framework (56).

We recognise that some participants with symptoms of wound infection may seek medical advice locally from another health care professional e.g., GP, out-of-hours GP, Emergency Department however participants will be given emergency contact details of their local recruiting location and will be asked to contact them if an SSI is suspected. Suspected SSIs will be assessed at local recruiting location and if an SSI is confirmed, participants will be requested to provide a wound swab, and again 7 days later if infection has not responded to treatment, as per CDC criteria (16).

Follow-up procedures

Participants will be provided with a patient diary to capture their subjective journey through the trial and record any symptoms of SSI and notes on their general health, to aid in completion of follow-up assessments by the research team.

All participants will be telephoned by the local research team around days 5-10, days 15-20 and at day 30 (+/- 7 days) following surgery to ask about any concerns about wound infection or side effects.

Participants will be encouraged to identify a nominated support person (e.g. a family member) to assist them with trial-related activities, such as wound photos and completing questionnaires, which will support the inclusion of digitally excluded populations and participants with cognitive impairment/ impaired capacity.

SSI diagnosis

A structured Case Report Form will be used to standardise SSI diagnosis using the CDC criteria (16).

We will advise adherence to recommended SSI surveillance protocols as specified in "Protocol for the Surveillance of Surgical Site Infection" produced by the UK HSA (17). Should participants develop any symptoms suggestive of infection then they will be asked to contact their local recruiting centre immediately to arrange an in-person assessment using the CDC criteria. The assessment will be undertaken by a member of the research team or clinical investigator who has been trained in the diagnosis of wound infections.

11.1 Assessments

Outcomes will be assessed at baseline, 5-10 days, 15-20 days 30 days and at 3 months post-surgery. It is expected that randomisation will occur on the same day as surgery and that baseline assessments will be completed prior to randomisation. However, if necessary, randomisation may occur prior to the day of surgery. In these cases, participant eligibility and baseline data must be re-checked and confirmed on the day of surgery prior to administration of the trial intervention.

Data will be collected by the research nurses either in person or via telephone, email or post, or review of patient records, and entered in electronic format on the EXCISE database.

The baseline assessments will take place before skin surgery.

Baseline Assessments:

All screening and baseline assessments should be performed prior to randomisation to determine the participant's eligibility. Written informed consent will be obtained before any trial-specific procedures are undertaken.

The following assessments at the screening and baseline visits are:

- Completion of eligibility checklist form
- Participant informed consent
- Inclusion/ Exclusion criteria
- Demographics

- Contact details
- Full Medical History
- Concurrent medications
- Skin/ lesion examination
- ECOG Performance Status
- Rockwood Clinical Frailty Score
- Adverse events
- Participant QoL EQ-5D-5L Questionnaire
- Trial Treatment

Assessments at 5-10 days:

- Adverse events
- New antibiotics
- SSI telephone assessment with face-to-face wound review if participant/ clinician concern
- Wound swabs if SSI diagnosed
- 'Selfi-wound' photos will be requested

Assessments at 15-20 days:

- Adverse events
- New antibiotics
- SSI telephone assessment with face-to-face wound review if participant/ clinician concern
- Wound swabs if SSI diagnosed

11.2 Follow-up

Day 30 (+/- 7 days) and 3 month (+/- 7 days) follow ups will be completed by telephone/email/post by the research nurses.

30-day follow-up:

- Adverse events
- New antibiotics
- SSI telephone assessment with face-to-face wound review if patient/clinician concern
- Wound swabs if SSI diagnosed
- Participant QoL EQ-5D-5L Questionnaire and Bluebelle WHQ questionnaire.
- Time to return to normal work/ activity
- Resource use (related to wound complications including SSI including report of hospital visits/stays)

- Qualitative interviews (optional n=40)

3-month follow-up:

- Participant QoL EQ-5D-5L Questionnaire
- Time to return to normal work/ activity
- Resource use (related to wound complications including SSI including report of hospital visits/stays)

Around three attempts will be made to contact the participant at each follow-up by telephone. If it is not possible to contact participants, the participant's support person (if nominated) may be contacted as an alternative. If all contact attempts are unsuccessful, a questionnaire booklet may be posted to the participants for them to complete and return.

The follow-up period will end 3 months (+/- 7 days) after the last recruited participant has undergone surgery (at completion of their 3-month follow-up assessment).

Assessment		Source Data	Data type/Measure	Screening & Baseline	Day 5-10	Day 15-20	Day 30 (+ 7/7)	3 months (+ 7/7)	Responsible for Data Collection	Justification
1	Eligibility Assessment	Screening log, CRF, documented in medical notes	Inclusion /Exclusion criteria	X					Qualified medical professional with delegated responsibilities	Eligibility
2	Informed consent	Consent form, documented in medical notes	Informed consent	X					Qualified medical professional with delegated responsibilities and location research team who are appropriately qualified, experienced and delegated by the PI	Consent
3	Demographics	CRF	- Age - Sex - Gender - Ethnicity	X					Location research team	Baseline
4	Contact details	CRF	- Contact details (inc. Postcode) - Alternative Contact details - GP Contact details - NHS number (or equivalent for Scotland and Northern Ireland)	X					Location research team	Trial Management
5	Medical history	CRF, documented in medical notes	Co-occurring conditions	X					Participant Reported/ location research team	Baseline
6	Skin /lesion examination	CRF, documented in medical notes	Skin surgical site	X	(X)	(X)	(X)		Qualified medical professional with delegated	Baseline

Assessment		Source Data	Data type/Measure	Screening & Baseline	Day 5-10	Day 15-20	Day 30 (+ 7/7)	3 months (+ 7/7)	Responsible for Data Collection	Justification
									responsibilities	
7	Concurrent/ new medication	CRF, documented in medical notes	- Current medication - Antibiotic use	X	X	X	X	X	Participant Reported/ location research team	Baseline and Fidelity of intervention
8	Performance status/ Frailty score	CRF	- ECOG Performance Status - Rockwood Clinical Frailty Score	X					Participant Reported/ location research team	Baseline
9	Randomisation	CRF	Randomised medication	X					location research team	Randomisation
10	Dispensing of trial drugs	CRF, documented in medical notes	Trial medication	X					location research team	Baseline and Fidelity of intervention
11	Adverse event assessment	CRF, documented in medical notes	- SAEs - SARs	X	X	X	X		location research team	Pharmacovigilance
12	SSI assessment (telephone)	CRF	Primary outcome		X	X	X		Qualified medical professional with delegated responsibilities and location research team who are appropriately qualified, experienced and delegated by the PI	Primary outcome
13	SSI assessment (face-to-face)	CRF, documented in medical notes	Primary outcome		(X)	(X)	(X)		Qualified medical professional with delegated responsibilities	Primary outcome
14	Wound swab	CRF, documented in medical notes	Antimicrobial resistance analysis - MALDI- Tof - MIC - EUCAST disc diffusion		(X)	(X)	(X)		Qualified medical professional with delegated responsibilities	Secondary outcome
15	Health- related	CRF	- EQ-5D-5L	X			X	X	Participant reported	Secondary

	Assessment	Source Data	Data type/Measure	Screening & Baseline	Day 5-10	Day 15-20	Day 30 (+ 7/7)	3 months (+ 7/7)	Responsible for Data Collection	Justification
	Quality of Life		- Time to return to normal activity				X	X		Outcomes
16	Resource use	CRF	- Health economic data - Resource use				X	X	Participant reported / location research team	Secondary outcome
17	'Selfi- wound' (requested)	CRF	- Feasibility		X				Participant reported / location research team	Secondary outcome
18	Bluebelle WHQ	Questionnaire	- Response rates - Validity				X		Participant reported	SWAT
19	Qualitative interviews	- Audio recording - Patient diary - Visual timeline elicitation activity	Secondary outcomes				(X)		CTR Qualitative team	Qualitative
20	Withdrawal	Withdrawal	CRF, withdrawal form		(X)	(X)	(X)	(X)	Participant reported / location research team	Withdrawal

Table 2. Schedule of enrolment, interventions and assessments (Taken from the HRA CTIMP protocol template (2016).

12 Sample Management

In addition to wound swabs taken for standard clinical care, trial wound swabs will be collected from all participants who develop SSI and attend their local centre for review and will be repeated seven days later if the SSI does not respond to treatment, as per CDC criteria (16). All trial swabs will be sent to a central microbiology laboratory at Public Health Wales for antimicrobial resistance analysis. This will establish the most common bacterial pathogens associated with SSI and determine their susceptibility/ resistance to clinically relevant antibiotics. All trial swabs will be processed according to Standard Microbiological Investigation B11: Investigation of swabs from skin and superficial soft tissue infections (57) as described in section 18.1.

13 Withdrawal & lost to follow-up

13.1 Withdrawal

Participants have the right to withdraw consent for participation in any aspect of the trial at any time. The participants care will not be affected at any time by declining to participate or withdrawing from the trial. In addition, a participant may be withdrawn by the investigator or the Sponsor if enrolment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.
Under these circumstances, a participant may withdraw or be withdrawn from the trial for the following reasons:

- Withdrawal of consent by the participant
- Any alteration in the participants condition which justifies the discontinuation of participation in the Investigator's opinion
- Non-compliance

If a participant initially consents but subsequently withdraws from the trial, clear distinction must be made as to what aspect of the trial the participant is withdrawing from. For the purposes of this trial, these are:

1. Withdrawal from questionnaires
2. Withdrawal of use of participant contact data (personal identifying data collected for the purposes of contacting participants)
3. Withdrawal from future data linkage
4. Withdrawal from having research wound swabs taken
5. Withdrawal from all aspects of the trial (participant fully withdrawn)

The withdrawal of participant consent shall not affect the trial activities already carried out and the use of data collected prior to participant withdrawal. The use of the data collected prior to withdrawal of consent is based on informed consent before its withdrawal. Participants will be informed of this before they join the trial as outlined in the PIS. All data collected prior to participant withdrawal will be kept with the other trial data and archived after the trial analysis.

Furthermore, it is important to collect safety data ongoing at the time of withdrawal, especially if the participant withdraws because of a safety event.

In the event of a withdrawal from all aspects of the trial, any unprocessed samples at the central laboratory must be disposed.

The withdrawal CRF should be completed on the participant's behalf by the researcher/ clinician based on information provided by the participant. This withdrawal CRF should be recorded in the Excise trial database.

Any queries relating to potential withdrawal of a participant should be forwarded to the trial email inbox (excise-ctr@cardiff.ac.uk).

13.2 Lost to follow up

Participants will be identified as lost to follow-up if the research team is unable to complete the follow up at day 30 following surgery. Measures that we will take to try and get the missing information include three attempts to telephone or text the participants or the participant's support person if the participant has elected to nominate one. If we are unable to contact the participant by telephone, we will also send them a letter asking them to contact the trial centre, if the participant has agreed to provide their address. Where participants are lost to follow up or withdraw before day 30, SSI outcome data will be censored at the date of last known follow-up assessment/clinic visit/participant contact before day 30.

For avoidance of doubt, in respect to sample collection, If the participant is lost to follow up, then they are not subject to the withdrawal processes, and the original consent stands.

14 Pharmacovigilance

The PI at each location is responsible for ensuring that all location staff involved in this trial are familiar with the content of this section.

All Serious Adverse Events (SAEs) must be reported immediately (and within 24 hours of knowledge of the event) by the PI at the participating location to the CTR PV and Safety Specialist.

14.1 Definitions

Table 3: Definitions of Adverse and Serious Adverse Events and Reactions.

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response in a clinical trial participant to an investigational medicinal product which is related to any dose administered to that participant.
Serious Adverse Event (SAE)	Any adverse event that - • Results in death • Is life-threatening* • Required hospitalisation or prolongation of existing hospitalisation** • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly or birth defect • Other medically important condition***
Serious Adverse Reactions (SARs)	Any SAE occurring in a clinical trial participant for which there is a reasonable possibility that it is **related** to the IMP at any dose administered.
Suspected Unexpected Serious Adverse Reactions (SUSARs)	A SAR, the nature and severity of which is not consistent with the Reference Safety Information (RSI) for the IMP.

***Note:** The term 'life-threatening' in the definition of serious refers to an event in which the trial participant was at risk of death at the time of the event or it is suspected that used or continued used of the product would result in the subjects death; it does not refer to an event which hypothetically might have caused death if it were more severe.

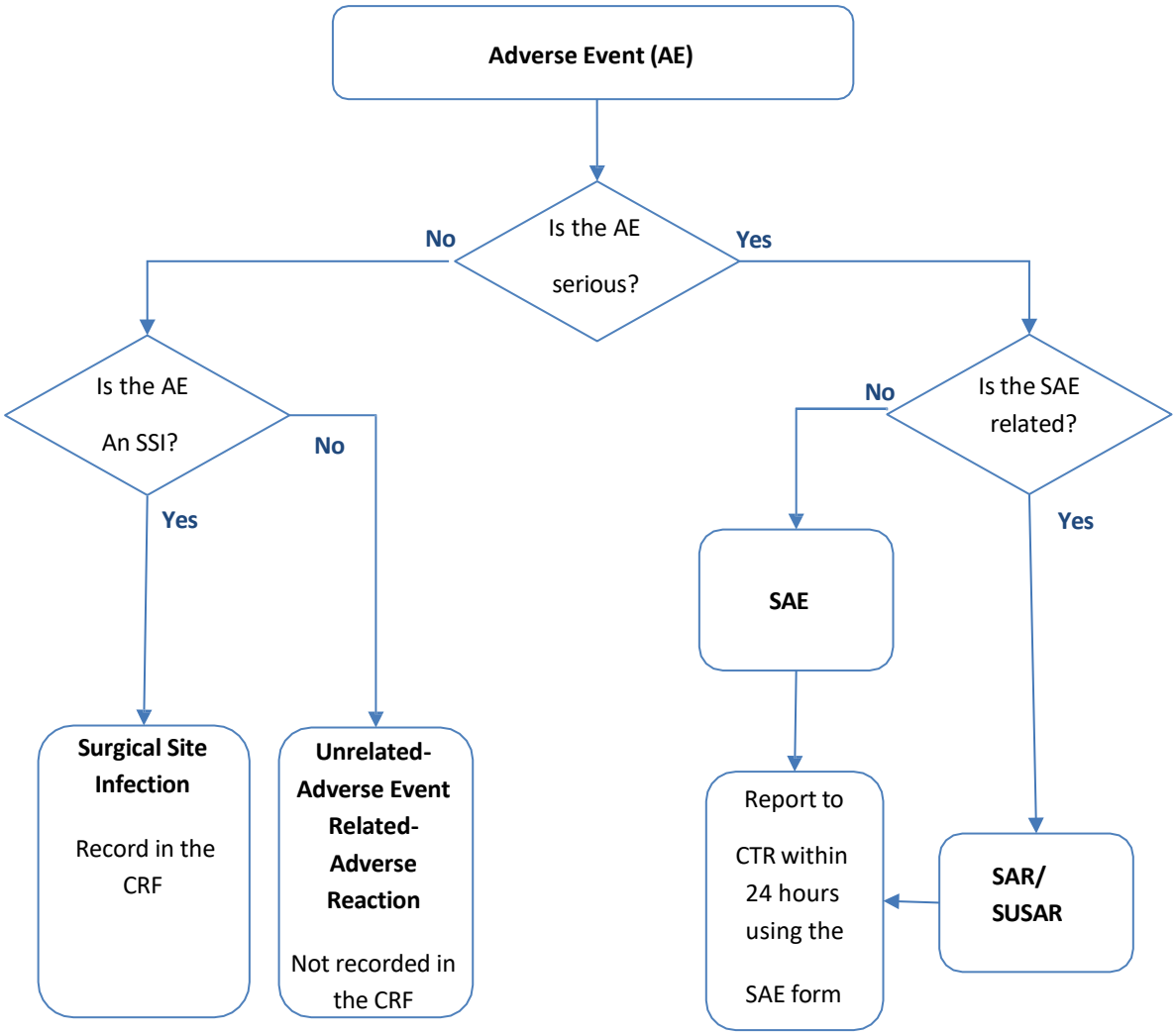
**** Note:** Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure for continued observation. Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened, or elective procedures, does not constitute an SAE.

*** **Note:** other events that may not result in death, are not life-threatening, or do not require hospitalisation, may be considered as an SAE when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

14.2 Trial Specific SAE Reporting requirements

There are no additional SAE reporting requirements in the trial.

Pre-existing conditions should only be reported if they met the definitions for an SAE and if the condition worsens by at least one CTCAE grade.



14.3 Causality

Causal relationship of SAEs and SARs in this trial will be assessed for the following:

Table 4. Causal relationship assessment of adverse events

IMP: Oral flucloxacillin **nIMPs:** N/A **Procedures:** N/A

The PI (or another delegated medically qualified doctor from the trial team) and Clinical co-Chief Investigator (or another medically qualified doctor from the Trial Management Group) will assess each SAE to determine the causal relationship according to the following categories:

Table 5: Definition of causal relationship with IMP.

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

The causality assessment given by the Principal Investigator (or delegate) cannot be downgraded by the clinical co-Chief Investigator (or delegate), and in the case of disagreement both opinions will be provided.

14.4 Expectedness

The clinical co-Chief Investigator (or another delegated appropriately qualified individual) will assess each SAR to perform the assessment of expectedness.

The expectedness assessment should be made with reference to the current Reference Safety Information (RSI) for each IMP. Expectedness decisions must be based purely on whether the event is listed in the RSI; other factors such as the participant population and participant history should not be taken into account. Expectedness is not related to what is an anticipated event within a particular disease. SARs which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected events. Fatal and life-threatening (LT) SARs should not be considered expected (unless explicitly stated in the RSI and approved by the NCA). For example, an event more specific or more severe than that described in the RSI is considered unexpected.

Table 6 below lists the RSI that should be referenced:

Table 6. Reference Safety Information

IMP	RSI to be used for expectedness assessment	Relevant section to be used for expectedness assessment
Oral flucloxacillin	SmPC for Flucloxacillin Capsules 500 mg to be used as RSI	Section 4.8 of SmPC

Reference Safety Information (RSI) on any CTR trial will be reviewed regularly according to CTR procedures.

14.5 Reporting procedures

14.5.1 Participating Location Responsibilities

The PI (or delegated medically qualified doctor from the trial team) should sign and date the SAE CRF to acknowledge that he/she has performed the seriousness and causality assessments. Investigators should also report SAEs to their own health boards or trust in accordance with local practice.

A completed SAE form for all events requiring immediate reporting should be submitted via fax or email to the CTR within 24 hours of knowledge of the event. A separate form must be used to report each event, irrespective of whether or not the events had the same date of onset.

The participant will be identified only by trial number, month, and year of birth and initials. The participant's name (or any other personal identifiers) should not be used on any correspondence.

It is also required that locations respond to and clarify any queries raised on any reported SAEs and report any additional information as and when it becomes available through to the resolution of the event. Additionally, CTR/ pharmaceutical companies may request additional information relating to any SAEs/ SARs and the location should provide as much information as is available to them in order to resolve these queries.

Serious Adverse Event (SAE) email address:

CTR-Safety@Cardiff.ac.uk

SAE Fax number: 0203 0432 376

SAEs should be reported from the time of surgery, and up to, and including 30 days after the participant receives their dose of the IMP. SARs (such as long-term side effects of trial treatment under investigation) should continue to be reported until the end of follow up as defined in the protocol.

SAEs should be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

An SAE form should contain at least the minimum information:

- Full participant trial number.
- An Adverse Event / Adverse Reaction.
- Trial intervention.
- A completed assessment of the seriousness, and causality as performed by the PI (or another appropriately medically qualified doctor registered on the delegation log).

If any of these details are missing, the location will be contacted, and the information must be provided by the location to the CTR within 24 hours.

Except SSIs, no other AEs should be reported on the CRF as Flucloxacillin is a marketed product with a significant amount of safety data available.

14.5.2 The CTR responsibilities

Following the initial report, all SAEs should be followed up to resolution wherever possible, and further information may be requested by the CTR. Follow up information must be provided on a new SAE form.

The CTR should continue reporting SAEs until 30 days after the participant receives their last dose of the investigational medicinal product. Serious adverse reactions should continue to be reported until the end of follow up.

Once an SAE is received at the CTR, it will be evaluated by staff at the CTR and sent to the Chief Investigator (or their delegate) for an assessment of expectedness.

Investigator reports of suspected SARs will be reviewed immediately and those that are identified as SUSARs are reported to the sponsor, IMP supply company, MHRA and REC.

14.6 SUSAR reporting

CAVUHB is undertaking the duties of trial Sponsor and has delegated to the CTR the responsibility for reporting SUSARs and other SARs to the regulatory authorities (NCAs and relevant ethics committees).

- SUSARs which are fatal or life-threatening must be reported to the MHRA and REC within 7 calendar days of receipt at the CTR.
- SUSARs that are not fatal or life-threatening must be reported to the MHRA and REC within 15 days of receipt at the CTR.

If report is incomplete then additional follow-up information should be reported within a further 8 calendar days of submitting the initial report, for all fatal and non-fatal, life-threatening and non-life-threatening.

Any additional, relevant information must be reported within a further 15 days.

14.7 Unblinding for the purposes of SUSAR reporting

To enable processing of a SAR in this blinded trial, expectedness should be assessed initially using the assumption that the IMP has been given to the trial participant.

If it is assessed as unexpected as per the RSI of the IMP, the SUSAR will be unblinded by the CTR safety group prior to reporting to any onward reporting.

If after unblinding it is evident that the trial participant received the placebo, this event will not require expedited reporting to the NCAs and REC, unless in the opinion of the Principal Investigator or Chief Investigator the event was related to the placebo (for example an allergic reaction to an excipient).

14.8 Safety Reports

A list of all SARs (expected and unexpected) will be reported annually to the MHRA REC and trial sponsor in the form of a Development Safety Update Report (DSUR). This report must be submitted within 60 days of the anniversary of the MHRA CTA approval date.

The CTR will report a list of all SARs (expected and unexpected) and any other safety recommendations to all PIs throughout the course of the trial. This frequency may be reviewed and amended as necessary. This reporting will be done via the Investigator safety report (ISR).

14.9 Pregnancy

14.9.1 Pregnancy reporting whilst participating in the trial

Flucloxacillin is not known to cause congenital anomalies or birth defects and is considered generally safe in pregnancy. Information on a pregnancy in a trial participant will be captured on the Trial CRF pre surgery. No further pregnancy data will be recorded.

14.10 Urgent Safety Measures (USMs)

An urgent safety measure is an action that the Sponsor, Chief Investigator or Principal Investigator may carry out in order to protect the subjects of a trial against any immediate hazard to their health or safety. Any urgent safety measure relating to this trial must be notified to the MHRA and Research Ethics Committee immediately by telephone, and in any event within 3 days in writing, that such a measure has been taken. USMs reported to the CTR will be handled according to CTR processes.

15 Statistical considerations

15.1 Randomisation

The randomisation procedure will be implemented via a web-based remote system (available 24 hours a day) as described in Section 9.5.2. Randomisation will occur prior to surgery. Allocations minimised (with random element) by SSI risk associated with reconstruction method (primary closure, skin graft or local skin flap) and anatomical site (below knee or other anatomical site) and stratified by the recruitment location. Full details will be provided in a separate randomisation protocol.

15.2 Blinding

Participants, clinicians and outcome assessors will be blinded to the randomised allocation. Further details will be included in the trial Unblinding plan.

15.3 Sample size

We will randomise 380 participants between the two groups (190 participants per group) with a 1:1 allocation ratio. This is based on a two-sided alpha of 0.05, 90% power, an assumed SSI rate of 30% for those allocated to placebo, a target effect size of 15% (absolute risk difference) and is inflated for 15% loss to follow-up.

We will conduct a futility analysis after 165 participants provide analysable outcome data (based on our assumed 15% drop-out rate, we anticipate this being after randomising 196 participants and following them

up to the primary endpoint timepoint). Using an O'Brien-Fleming boundary, our critical threshold to indicate futility will be z ≤ 0.27 (equivalent to an absolute risk difference of 2% or a one-sided p-value of 0.39). To maintain an overall alpha of 0.05 (two-sided), the maximum sample size will be 390 participants (a 3% increase on the target sample size with a fixed design).

For varying event rates, the Table 7 below demonstrates the futility threshold and corresponding effect size and one-sided p-value, based on an interim analysis after 165 participants have analysable data. For example, if the event rate in the placebo arm is 20%, our critical threshold to indicate futility will be z = 1.39 and our maximum sample size will be 256 participants. Where the event rate is greater than 30% and the maximum sample size is larger than what we have planned, we would approach the HTA Programme for a view on further funding to recruit from a larger number of locations and calculate participant costs accordingly. We will do this without impacting on overall timelines as this will be efficient given that it will not require an increase in staff time.

Our futility boundary will be non-binding, and our DMEC will be asked to consider their decision within the context of other data (e.g. secondary outcomes, safety data, etc.) (as described in the table 7 below).

Table 7. - Futility boundary

Event rate	Futility threshold*	Effect size**	One-sided p-value	Maximum sample size***
20%	1.39	7	0.08	256
25%	0.71	4	0.24	328
30%	0.27	2	0.39	390
35%	-0.06	0	0.52	444
40%	-0.28	-2	0.61	486

*Based on O'Brien-Fleming boundary. **Absolute risk difference. ***Including 15% drop-out inflation.

15.4 Missing, unused & spurious data

Further detail provided in the Statistical Analysis Plan (SAP).

15.5 Procedures for reporting deviation(s) from the original SAP

These will be submitted as substantial amendments where applicable and recorded in subsequent versions of the protocol and SAP.

15.6 Termination of the trial

Progression criteria for the internal pilot phase will be described. There is the potential for the trial to terminate early if our funder assesses the trial as not being feasible following the assessment of progress against our targets at the end of the internal pilot with input from our TSC and IDMC.

15.7 Inclusion in analysis

This analysis will include all randomised participants regardless of intervention receipt (as we will be using a treatment policy strategy for handling this intercurrent events).

16 Analysis

16.1 Main analysis

Descriptive statistics will be summarised using frequencies and percentages, means and standard deviations, or medians and interquartile ranges, as appropriate. A comprehensive Statistical Analysis Plan will be approved by the Trial Steering Committee and Trial Data Monitoring Committee prior to database lock and commencement of analysis. The findings will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement. We will incorporate the estimand framework within our protocol and statistical analysis plan (58), with the aim of specifying primary and sensitivity estimands and aligning analysis strategies accordingly.

For the primary outcome statistical analysis, we will compare the proportion of participants in each arm who experience an SSI within 30 days of surgery using logistic regression. The model will adjust for reconstruction method, anatomical site of surgery and recruitment location. This analysis will include all randomised participants regardless of intervention receipt (as we will be using a treatment policy strategy for handling this intercurrent events). For participants with multiple wounds that are excised, an SSI occurring in at least one of these wounds will count toward the primary outcome event rate. We anticipate deaths occurring within the 30-day post- surgery period being extremely rare but will handle any instances by incorporating them as a poor outcome (composite strategy). Findings will be reported as odds ratios, 95% confidence intervals, and p-values.

Secondary outcomes will be analysed similarly, with linear, Poisson (or negative binomial), and flexible parametric survival models fitted as appropriate.

Missing data and non-adherence patterns will be described. We will explore their extent and mechanisms and apply appropriate statistical methods for handling these (e.g., multiple imputation, complete case analysis, inverse probability of treatment weighting). Adherence patterns will be characterised using the ABC taxonomy (59). Furthermore, when developing the trial protocol, we will use the estimand framework to outline

strategies for handling intercurrent events. Details of all analyses will be available in the EXCISE Statistical Analysis Plan.

16.1.1 Sub-group & interim analysis

Exploratory subgroup analyses will be hypothesis-generating in nature and be used to study the extent to which the proportions may differ for our primary outcome across the following subgroups:

- Reconstruction method (primary closure, skin graft, local skin flap);
- Anatomical site (below knee, other anatomical site);
- Specialty recruiting the participant (dermatology, other specialities (including plastic surgery, ear, nose and throat surgery and maxillofacial);
- Surgical setting (procedure room, theatre);
- Suture type used (antimicrobial coated sutures, non-antimicrobial sutures

We will also consider SSI events at the wound level (i.e., accounting for multiple excised wounds within participants).

We will conduct an interim futility analysis after 165 participants provide analysable outcome data (based on our assumed 15% drop-out rate, we anticipate this being after randomising 196 participants and following them up to the primary endpoint timepoint). This analysis will be the same model as the primary analysis: a logistic regression model to compare the proportion of participants in each arm who experience an SSI within 30 days of surgery adjusted for reconstruction method and anatomical site of surgery and recruitment location. Details of all interim analyses is available in the EXCISE Interim Statistical Analysis Plan.

16.2 Cost effectiveness analysis

With the potential for SSI's increasing use of health care resources (60) alongside the impact on quality of life (12) whilst considering the economic impact of antibiotic stewardship programmes (61), a health economic evaluation as part of the EXCISE trial will be conducted to assess the cost- effectiveness of a single pre operative dose of oral flucloxacillin and standard care compared to no antibiotic and standard care for ulcerated skin cancers. The evaluation will be designed, conducted and reported following best-practice guidelines (62), with a Health Economic Analysis Plan (HEAP) produced as part of a comprehensive SAP as detailed earlier. A UK NHS/ Personal Social Services Perspective will be taken for the base-case (primary)

analysis. Discussions with the EXCISE research team and patient representatives during the development of the EXCISE grant submission highlighted the impact of managing SSIs to the patient and society, thus an additional (restricted) societal perspective to collect additional costs (e.g., out of pocket expenses) alongside time away from usual activities (e.g., loss of workdays) will be included as supplementary analysis. Economic outcomes will be collected as part of the EXCISE data collection schedule, described earlier.

Resource use data associated with the primary surgical procedure (e.g., length of visit/stay) and antibiotic use will be gathered via the trial case report forms. Subsequent health and care resource use data related to wound complications, including SSI, will be collected, alongside key personal costs and lost workdays. The resource use data collection measure/schedule will be developed in collaboration with the EXCISE research team and patient representatives, drawing upon good practice to balance the requirement for comprehensive information against the burden (both participant and researcher) of completion (63,64). The internal pilot phase will assess the collection of economic outcome measures and inform the first iteration of the HEAP. Published UK unit costs will be used to value resource use in £ sterling to the most relevant price year available at time of final analysis. Total and per participant costs will be presented based on the available case dataset to provide a comprehensive summary of the resource use and costs associated with the intervention and comparator groups over the trial period.

The EQ-5D 5L will be used to derive health utilities to inform the calculation of Quality Adjusted Life Years as the preferred measure by NICE to capture HRQOL in adults for use in a cost-utility analysis (CUA). With the lack of any validated PROM to capture utilities lost/ gained related to a skin-cancer specific SSI, the EQ-5D has been used in other SSI trials in the UK and is described in a recent handbook that has documented utility based QoL measures in melanoma populations (65). The most appropriate method at the time of analysis to derive utilities for a UK population (e.g. pending completion of the on-going UK EQ-5D 5L valuation exercise (Euroqol) in 2024 or using the recognised cross-walk function to the 3L version (66-68). The primary clinical outcome measure will be used in a cost-effectiveness analysis. For the primary analyses, no discounting will be undertaken as the horizon will be <12 months.

Adjusted analyses using suitable regression models will be conducted. Missing data will be examined and accounted for by suitable measures e.g., multiple imputation for missing observations of costs and utilities, following Rubin's rules. Imputed data will be used within our base-case analysis with complete case analysis used as a sensitivity analysis. Analysis based on the ITT trial population to calculate the incremental cost per QALY at 3 months with calculation of incremental net monetary benefit (iNMB), presented across different cost-effectiveness thresholds. A cost-effectiveness analysis (CEA) will present the incremental cost per SSI prevented at 30 days, as part of a complementary set of analyses and to reflect other comparable CEAs in the field (69). Deterministic sensitivity analyses will examine the impact of uncertainty in our findings e.g., changing parameters, alongside the supplementary analysis to include patient costs, and appropriate

subgroup analyses (e.g., anatomical site). For the CUA, bootstrapping will be undertaken to assess joint uncertainty. A cost-effectiveness acceptability curve will present the probability that either one of the techniques is cost-effective, based on the commonly used NICE willingness to pay threshold of £20-30,000 per QALY gain.

With the restricted trial horizon, in addition, the aim will be to explore longer-term cost-effectiveness, from a UK NHS/ PSS perspective, through building a decision analytic model. The rationale for this consideration is that clinical and patient representatives have expressed potential for longer term impact on HRQOL, particularly given the differences could be small within the EXCISE horizon. Appropriate caution will be taken in planning this exploratory analysis to ensure any extrapolation would be useful, feasible and plausible as part of presenting a comprehensive picture of cost-effectiveness. Initial discussions with the EXCISE team and patient representative suggest a 1-year time horizon would be plausible to capture any potential longer-term costs and consequences of an SSI related to the initial surgery. Evidence from EXCISE will be key to inform parameters. If the time horizon goes beyond 1 year, discounting will be applied for costs and effects (3.5%). A rapid literature review will be undertaken to identify data inputs (e.g., longer-term utility estimates associated with an SSI (70), alongside clinical opinion to supplement EXCISE data. The model will be built in MS Excel, with the model structure, inputs and assumptions agreed with the EXCISE team and clinicians, prior to analysis. A CUA based on the agreed time horizon(s) will be presented, similar to the primary analysis, presented above. Uncertainty in the parameters used to populate the model will be examined through deterministic sensitivity analysis, with joint uncertainty explored using probabilistic sensitivity analysis.

16.3 Qualitative Study and Process Evaluation

It is important to encompass assessment of the fidelity of possible influences on treatment outcomes in the design and implementation of surgical randomised controlled trials (71).

Our aim is to understand the factors affecting trial compliance, wound management and reporting SSI. We will ensure representation across locations, patient demographic characteristics. We will also explore the participants' wound burden through the participants perspective.

We will conduct semi-structured interviews with trial participants (n=40) sampled purposively, to ensure appropriate diversity, and include those reporting good and poor outcomes from each trial arm, with interviews conducted following the 30-day wound assessment. Potential patient interview participants will be given a PIS about the qualitative interview study.

For patients willing to take part in the qualitative aspects of the EXCISE trial, they will be asked by the local location PI or Research Nurse to complete a consent to contact form. For those that opt to consent to participate in an interview, the QR will be notified and participant details reviewed for sampling (location, age,

gender, trial arm, surgical site). Those then sampled for interview will be contacted by the QR and sent the PIS for interviews, along with a consent form, elicitation guidance document, diary booklet, timeline example and stamped addressed envelope. Once potential participants have had time to consider the study information the QR will contact them to discuss consent and arrange a suitable time for an interview.

Trial participants approached for interview will be invited to complete a diary and visual timeline elicitation activity to capture their subjective journey through the trial. The diary and timeline will be used in the conduct of in-depth semi structured interviews with trial participants. The inclusion of a diary and visual timeline will aid and enhance the communication between the researcher and participant and provides data in an alternate mode of expression type that can help researchers understand complexity and open up discussions that may have remained unspoken and unexplained. The representation of participant's experience through diaries and timelines will promote narrative accounting and allow the participant and researcher to focus on eliciting a shared understanding of the acceptability of treatment received including views on antibiotics, barriers and facilitators and the wound burden.

We will include a sample of participants (n=8) deemed ineligible or declined to take part, to explore views on antibiotic prescribing and use, and barriers to participation. These participant interviews will be undertaken post-screening.

In-depth semi-structured interviews will be undertaken with healthcare professionals (n=20) purposively sampled to include pharmacists (across 10-15 locations). Interviews will explore issues of implementation, equipoise, and the experience and acceptability of prescribing in practice.

All interviews will be undertaken remotely via telephone or videoconference, audio recorded, transcribed and anonymised. Patients will be invited to include a relative or friend in the interview if they wish.

We will develop an a-priori framework and framework analysis of qualitative data will be undertaken. This systematic five stage method accommodates multiple data sources such as diaries, timelines and interviews and allows for the comparison of themes across treatment centre, trial arm, participant outcome and participant/interviewee category.

We will undertake a rapid evaluation with a sub-sample of interviews with trial participants (n=8) and HCPs (n=4) during the pilot phase to explore acceptability of the study design and outcome measures. Data will be analysed thematically and we will pay attention to eligibility and recruitment experiences and challenges, facilitators and barriers affecting recruitment, including patient preferences and any issues with clinical equipoise and implementation. Findings from a rapid evaluation of early interviews will be fed back to the TMG during the pilot phase with recommended actions.

17 Data Management

The detailed data management processes used in the EXCISE trial are documented in the EXCISE Data Management Plan.

Source Data is defined as *"All information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents."*. There is only one set of source data at any time for any data element, as defined in the site source data agreement. The source data for the EXCISE trial will be from a variety of sources as described in Table 2.

17.1 Data collection

Data will be collected using an electronic CRF system with paper CRF back-up if required. Training for the completion of trial CRFs will be provided to the appropriate trial staff before trial commencement at location initiation.

17.2 Completion of CRFs

All assessments and data collection will be completed using web-based CRFs. This is a secure encrypted system accessed by username and password and complies with General Data Protection Regulation 2018. If the web-based system is not accessible, paper CRFs will be used to record data. The data will then be inputted into the web-based system once it is accessible. A full Data Management Plan will accompany this protocol and will be stored in the TMF.

Electronic CRFs

Locations will be provided with access details to the EXCISE data entry and randomisation system at their location initiation training.

A user password will be supplied to investigators upon completion of all processes required prior to opening. location staff will only have access to their participants and not see other locations' participants. Web based data collection forms should be completed as described in the EXCISE Site Manual.

Paper CRFs

Paper CRFs will be used If the electronic database is not available or if participants prefer follow-up via post. Data will be entered on to the database by location staff at a later point. In accordance with the principles of GCP, the PI is responsible for ensuring accuracy, completeness, legibility and timeliness of the data reported to the CTR in the CRFs.

CRF pages and data received by the CTR from participating trial locations will be checked for missing, illegible or unusual values (range checks) and consistency over time.

If missing or questionable data are identified, a data query will be raised directly on the EXCISE database and the location shall be requested to respond. The CRF pages should not be altered. All answered data queries and corrections should be signed off and dated by a delegated member of staff at the relevant location.

The WHQ will be distributed by post/ email for participants to complete and return (by stamped addressed envelope, included) 30 days after surgery. The WHQ may also be completed over the phone/ in person with a location research nurse.

The CTR will send reminders for any overdue data. It is the location's responsibility to submit complete and accurate data in timely manner. Further details of data management procedures will be specified in the Data Management Plan.

17.3 Qualitative Data Management

Recordings of qualitative interviews will be captured on a password-protected and encrypted recording device. Demographic data about participants will be captured on a password-protected Cardiff University laptop and/ or on completed paper consent to contact forms. All files containing personal data will be password-protected and stored in a folder on the Research drive of the secure Cardiff University server with restricted access. A trial identification number will be used for filenames, which will not include any personal details such as participants' names.

Completed consent forms and consent to contact forms will be securely electronically transferred by the research nurse at the location to the research team at Cardiff University via FastFile or a Trust-approved file transfer system and uploaded to the Research drive of the secure Cardiff University server. Interview recordings will be transferred from portable devices to the Research drive of the secure Cardiff University server as soon as practicably possible and permanently deleted from the portable device. Paper field notes will be typed up and saved on the Research drive of the secure Cardiff University server as soon as practicably possible, and hard copy notes shredded.

Interview recordings will be securely sent to be transcribed and anonymised by an approved transcription company. A data processing agreement will be in place between Cardiff University and the transcription company. Returned transcripts will be saved on the Research drive of the secure Cardiff University server and checked for any errors in transcription or anonymisation. Interview transcripts will be uploaded to NVivo 12 for analysis.

Participants will not be personally identified in any report or publication of findings. Written quotes of what the participant has said in the interview may be used word for word, but quotes will be anonymised.

Participant names will not appear in any publications. Full details of qualitative data management are specified in the EXCISE Data Management Plan.

18.0 Translational research or sub trial

18.1 Microbiology work

In addition to wound swabs taken for standard clinical care, trial wound swabs will be collected from all participants who develop SSI and attend their local centre for review and will be repeated seven days later if the SSI does not respond to treatment, as per CDC criteria (16). Locations will be encouraged to conduct wound swabs according to the International Wound Infection Institute's Principle of best practice (72) where locations do not have trust specific guidance. Training material detailing the Levine technique will be provided to delegated research staff carrying out wound swabs. All trial swabs will be sent to a central microbiology laboratory at Public Health Wales for antimicrobial resistance analysis. This will establish the most common bacterial pathogens associated with SSI and determine their susceptibility/ resistance to clinically relevant antibiotics. Samples will not be stored after antimicrobial resistance analysis is completed and will be disposed of in accordance with the Human Tissue Authority's Code of Practice.

In our feasibility observational study, participants in one recruiting centre had surface swabs of ulcerated tumours analysed prior to surgery to identify the most common microorganisms (n=101) (24). Staphylococcus aureus and coagulase-negative staphylococci were the most prevalent, the latter being common skin contaminants. Of the staphylococci (*S. aureus* and coagulase-negative staphylococci) isolated, 6.4% were flucloxacillin resistant (multi-drug resistant *S. aureus*).

All trial swabs will be processed according to Standard Microbiological Investigation B11: Investigation of swabs from skin and superficial soft tissue infections (57). Briefly, trial swabs will be cultured using a spiral plater onto both selective and non-selective media, incubated overnight and all relevant bacteria identified by Matrix Assisted Laser Desorption Ionisation – Time of Flight (MALDI-ToF) mass spectrometry. For staphylococci we will include Minimum Inhibitory Concentration (MIC) determination for vancomycin/teicoplanin. We are aware of the limitations of MALDI-ToF and do not envisage finding any significant streptococcus isolates. If we do isolate any streptococci, we would identify using the conventional tests.

Quantitative counts of all clinically relevant bacteria at abundance levels deemed significant will be performed. If the same coagulase-negative staphylococci strain is repeatedly isolated from a series of wound swabs in high abundance and pure, with clinical signs of infection, then it will be considered clinically significant. Community/ commensal- associated organisms will be considered non-diagnostic of SSI.

Susceptibility testing using European Committee on Antimicrobial Susceptibility Testing (EUCAST) disc diffusion methods and interpretative guidelines (https://www.eucast.org/clinical_breakpoints). Any antibiotic

resistance found will be confirmed by molecular methods were applicable. This additional microbiological work will provide information for recommendations for appropriate targeted antibiotic treatment and effect a national policy change.

We will perform phenotypic testing using the standardised EUCAST disc diffusion test. Cefoxitin discs will be used to determine flucloxacillin susceptibility/resistance (disc diffusion screen is understood to be better than MIC determination). We can perform Real-Time PCR to confirm mecA/C gene if in any doubt.

- Packaging and transport information:

Packaging and transport information provided to locations with local information pack prior to location opening.

- Lab addresses/Responsible person:

PHW Microbiology Cardiff (SACU), Heath Park, Cardiff, CF64 4JW

18.2 Study Within A Trial (SWAT): assessment of the Wound Healing Questionnaire (WHQ) as a diagnostic tool for SSI in skin surgery

The CDC criteria are widely used to diagnose SSI, however face-to-face assessment is required which is inconvenient for patients and costly for healthcare systems. We have chosen to validate the WHQ as a SWAT because it was developed for use as a remote diagnostic tool. The WHQ was developed and validated, as part of a NIHR funded programme, to assess SSI in closed primary wounds after discharge from hospital following abdominal general surgery or caesarean section and can be completed by patients and clinicians (25,26). Other tools for assessing SSI, for example, ASPESIS, NINNS, POWI, also require face-to-face assessment. We asked participants to complete the WHQ via post/ electronic mail in our feasibility study and we found it to be an acceptable and low-cost self-reporting measure (24). However, the WHQ questionnaire has not been fully validated in people undergoing skin surgery and so we have incorporated this as a SWAT.

The acceptability, scale structure and validity of WHQ as a diagnostic tool for SSI with closed wounds in our skin surgery cohort will be assessed. The WHQ will be distributed either by post/ email for participants to complete and return (by stamped addressed envelope, included) or in person/ over the telephone with a research nurse 30 days after surgery. Reference diagnoses of whether SSI had occurred since the time of surgery will be determined as the primary outcome of the EXCISE trial. We will register this SWAT protocol with the MRC Trials Methodology Hub Research SWAT repository (73).

Acceptability will be assessed by calculating response rates, structural validity using confirmatory factor analysis, internal consistency by calculating Cronbach's alpha, and criterion validity by comparing estimated

SSIs using the WHQ with SSIs defined by the CDC criteria and calculating the area under the receiver operating characteristic curve value. Data obtained through the semi-structured interviews conducted with patient participants as part of the process evaluation will be used to examine the experience of completing the WHQ, understanding and its acceptability for use within this context. In addition, we will conduct an online focus group with a sample of patients (n=12) to explore themes arising from the interviews relevant to completion and acceptability of the WHQ. Skin surgery is usually carried out as an outpatient procedure and so people undergoing skin surgery are discharged home. Remote assessment of SSI in closed wounds following skin surgery is needed for surveillance and research.

Dissemination of the results will be in line with NIHR guidance, and published open-access once results are available, without delaying the results from the main trial.

18.3 Feasibility of wound photograph 'Selfi- wound'

The 'Selfi-wound' method has been developed and tested as a simple, standardised and acceptable method for patients to take and transmit wound images suitable for remote assessment of SSI following abdominal and vascular surgery (74). However, the feasibility of the 'Selfi- wound' method has not been in assessed following skin cancer surgery. Our feasibility study, OASIS (24) showed that the average age of patients in this study population was 77 years old and thus it would be important to test if the 'Selfi- wound' method will be feasible in this traditionally digitally excluded population.

All participants will be given detailed and pictorial instructions (developed in collaboration with our Patient Partners) for taking and sending 'Selfi-wound' photos (74). Participants will be contacted via email at 5-10 days following surgery and requested to return the 'Selfi- wound' photo by directly uploading the images onto the trial database.

The proportion of participants who were able to successfully take and transmit an image of their wound images via the online system of those from which we would expect an image (all participants in the trial at that timepoint) will be calculated along with a 95% confidence interval using Wilson's method. Picture quality and clinical assessment will not be conducted.

19 Protocol/GCP non-compliance

The PI should report any non-compliance to the trial protocol or the conditions and principles of Good Clinical Practice to the CTR in writing as soon as they become aware of it. The CTR will assess the nature and severity of any issues of non-compliance in accordance with their Standard Operating Procedure (SOP).

A trial-related deviation is a departure from the ethically approved trial protocol or other trial document or process (e.g., consent process or administration of trial intervention) or GCP or any applicable regulatory requirements. Any deviations from the protocol will be documented in a non-compliance form and filed in the EXCISE trial master file (TMF).

A CTR SOP is in place describing the procedure for identifying non-compliances, escalation to the central safety team and assessment of whether a non-compliance/deviation may be a potential Serious Breach.

20 End of Trial definition

The follow-up period will continue for 3 months from the time of surgery. The end of the trial is defined as the date of final data capture (i.e. the act of entering the final data into the trial database) of the last participant to meet the trial endpoints.

Database lock, defined as the final lock of the database when no further locks are required, will be requested when all cleaning and validation of the data in the database is complete (within 6 months of the end of the trial).

The sponsor, or its delegate, must notify the MHRA and main REC of the end of a clinical trial within 90 days of its completion or 15 days if the trial is terminated early.

21 Archiving

The TMF and TSF containing essential documents will be archived at an approved external storage facility for a maximum of 25 years in line with the Sponsor and Cardiff University archiving process for clinical research. The CTR will archive the TMF and TSFs on behalf of the Sponsor.

All essential documents generated by the trial will be kept in the TMF. This data will be stored confidentially on password-protected servers maintained on the Cardiff University Network. Electronic files will only be accessible to researchers responsible for the running of the trial and the CI.

In line with the International Conference on Harmonization (ICH) GCP requirement, electronic clinical trial data will be shared with the location investigators at the end of the trial. The processes for supplying a copy of the clinical trial data are documented in the Returning Data to Trial Sites SOP (as detailed in the data management plan). The PI is responsible for the archival of the ISF at the location on approval from the Sponsor. Essential documents pertaining to the trial shall not be destroyed without permission from the Sponsor. All procedures for data storage, processing and management will comply with the General Data Protection Regulations (GDPR) 2018.

22 Regulatory Considerations

22.1 CTA

The trial is being performed under a CTA from the MHRA. The CTA approval has been obtained before the start of the trial in accordance with Part 3, Regulation 12 of The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031).

22.2 Ethical and governance approval

This protocol has approval from a Research Ethics Committee (REC) that is legally "recognised" by the United Kingdom Ethics Committee Authority for review and approval.

This trial protocol will be submitted through the relevant permission system for global governance review depending on the location of the lead location i.e., Health and Care Research Wales for Wales-led trial. The trial will be conducted in accordance with the recommendations for physicians involved in research on human participants adopted by the 18th World Medical Assembly, Helsinki 1996, and later revisions.

Approval will be obtained from the host care organisation who will consider local governance requirements and location feasibility. The Research Governance approval (confirmation of Capacity and Capability (C&C)) of the host care organisation must be obtained before recruitment of participants within that host care organisation. Classification of whether any changes to the protocol is defined as a substantial amendment or not will be based on HRA guidance and sponsor assessment. All amendments will be reviewed by the TMG, and if necessary, sponsor representative, for approval prior to being submitted, via IRAS and email, to REC, HRA, and if necessary, the MHRA. The central trial team will alert all location trial teams and R&D departments once approval has been received for the amendment. The amendment history will be listed in the protocol and in the amendment log which is filed in the EXCISE TMF.

Minor amendments will not require prior approval by the REC.

If the trial is stopped due to serious adverse events or an urgent safety measure, it will not be recommenced without reference to the REC responsible for the trial. A summary of the results will be submitted to the REC responsible for the trial within one year of completion of trial closure.

22.3 Data Protection

The CTR will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained. Data will be stored in a secure manner and will be registered in accordance with the with the General Data Protection Regulation 2018

standards. The data custodian and the translational sample custodian for this trial is the CI at Cardiff and Vale University Health Board.

This includes the collection of NHS number (or equivalent), name, date of birth, gender and postcode to register and trace participants, and the collection of NHS number (or equivalent) to utilise NHS data for future research through NHS England (formerly NHS Digital), Secure Anonymised Information Linkage (SAIL) in Wales and Information Services Division (ISD) in Scotland. Northern Ireland has no data access request service (DARS) similar to that offered by NHS Digital or other UK nation equivalents. Participants recruited in Northern Ireland will not be included in this aspect of the trial.

22.4 Indemnity

This is an NHS-sponsored research trial, and the NHS indemnity scheme therefore applies. If there is negligent harm during the 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. The NHS indemnity scheme does not cover non-negligent harm.

- Non-negligent harm: This trial is an academic, investigator-led and designed trial sponsored by Cardiff and Vale University Health Board and coordinated by the CTR. The Chief Investigator, local Investigators and CTR do not hold insurance against claims for compensation for injury caused by participation in a clinical trial and therefore cannot offer any non-negligent harm indemnity. The Association of the British Pharmaceutical Industry (ABPI) guidelines will not apply.
- Negligent harm: In accordance with Technical Note 12 Indemnity for Clinical Research for research Sponsored by a Welsh body, Welsh Risk Pool Services provides indemnity cover against successful negligence claims arising from the management and conduct of the trial. Where NHS employees are responsible for the design of a trial, indemnity cover will also be provided for negligent harm arising from the trial design. Cardiff and Vale University Health Board does not accept liability for any breach in the other NHS Organisations duty of care, or any negligence on the part of employees of these NHS Organisations.

All participants will be recruited at NHS locations and therefore the NHS indemnity scheme/ NHS professional indemnity will apply with respect to claims arising from harm to participants at location management organisations.

22.5 Trial sponsorship

The trial is being sponsored by Cardiff and Vale University Health Board. The Health Board shall be responsible for ensuring that the trial is performed in accordance with the following:

- The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031) and subsequent amendments.
- Conditions and principles of Good Clinical Practice.
- Declaration of Helsinki (1996) and subsequent amendments
- UK Policy Framework for Health and Social Care Research.
- The General Data Protection Regulation 2016.
- The Human Tissue Act 2004.
- Other regulatory requirements as appropriate.

The trial will be conducted in compliance with the protocol and Good Clinical Practice as required by the regulations.

Delegated responsibilities will be assigned to the locations taking part in this trial. The Sponsor has delegating certain responsibilities to Cardiff University (CTR), the Co-Chief Investigators, Principal Investigators, host locations and other stakeholder organisations as appropriate in accordance with the relevant agreement that is informed by regulation and trial type.

22.6 Funding

This project was funded by the National Institute for Health Research Health Technology Assessment (NIHR HTA) Programme (NIHR160872).

23 Trial management

Expertise in trial management is provided for by the CTR, a UK Clinical Research Collaboration registered Clinical Trials Unit, who ran the feasibility and supports this application. The trial will be conducted in accordance with CTR standard operating procedures, Good Clinical Practice, General Data Protection Regulation, and the UK Policy Framework for Health and Social Care Research. The CTR will fully coordinate this trial, governance, approvals, data collection, analysis and publication. The UK DCTN has supported this trial since inception, including funding our feasibility study and will provide key ongoing support for trial delivery and dissemination.

23.1 TMG (Trial Management Group)

TMG members will be required to sign up to the remit and conditions as set out in the TMG Charter. Trial Management Meetings will be held with the CIs, co-applicants and trial delivery team on a monthly basis. Recruitment will be carefully monitored and communicated amongst the team. Regular newsletters, including reports of recruitment, will be sent to all participating locations and team members, to promote ongoing engagement with the trial.

23.2 Trial Steering Committee (TSC)

A TSC comprising an independent chair, two other independent members, and two lay representatives. The TSC will meet prior to trial launch to review the protocol, roles and responsibilities, timelines for meetings (particularly for the internal pilot) and agree on their respective roles, responsibilities, and remit. The TSC and IDMC will meet at least twice a year.

TSC members will be required to sign up to the remit and conditions as set out in the TSC Charter.

23.3 Independent Data Monitoring Committee (IDMC)

An IDMC comprising an independent chair and two other independent members. The IDMC will meet prior to trial launch to review the protocol, roles and responsibilities, timelines for meetings (particularly for the internal pilot) and agree on their respective roles, responsibilities, and remit. The IDMC will meet at least twice a year.

IDMC members will be required to sign up to the remit and conditions as set out in the IDMC Charter.

24 Quality Control and Assurance

24.1 Monitoring

The clinical trial risk assessment has been used to determine the intensity and focus of central and on-location monitoring activity in the EXCISE trial. Low monitoring levels will be employed and are fully documented in the trial monitoring plan.

Investigators should agree to allow trial related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. Participant consent for this will be obtained. Where electronic health records (EHR) are being used, trial teams and monitors should check EHR process early in trial and periodically thereafter.

Findings generated from on-location and central monitoring will be shared with the Sponsor, CI, PI & local R&D.

24.2 Audits & inspections

The trial is participant to inspection by the MHRA as the regulatory body. The trial may also be participant to inspection and audit by Cardiff and Vale University Health Board under their remit as Sponsor. The CI or PI organisations/institution(s) will permit trial-related monitoring, audits, REC/ IRB review, and regulatory inspection(s), providing direct access to source data / documents. The location must inform the CTR of any MHRA inspections.

25 Public Involvement and Engagement

Full details of the public involvement and engagement for the trial are summarised below and detailed in the EXCISE PI&E plan. PPI members will attend TMG, TSC and PAG meetings.

We will convene a PAG of 5-8 members who will meet (virtually) 7 times throughout the trial; 3 times during year one, and then every 6 months. The PAG will include patients and carers and those from diverse and socioeconomic backgrounds. They will co-produce the content of the participant-facing materials. We will develop visual summaries and infographics to optimise accessibility of patient facing information, using the NIHR INCLUDE frameworks (49) to design our materials. The PAG will also review all data collection materials (patient diaries and report forms) to ensure we capture the key information, balanced with the need for a proportionate measure to minimise patient and researcher burden. They will review progress, address areas where trial documentation could be improved and plan dissemination of key findings.

26 Publication policy

All publications and presentations relating to the trial will be authorised by the TMG, as per the publication policy. In addition to the requirements of the NIHR HTA Programme publication model, we will publish the main trial results in international, high-impact, peer-reviewed journals and present at dermatology, surgical or cancer-focussed research conferences. With the assistance of our collaborators and lay representatives, we will disseminate the trial findings to a wide NHS and general audience and vigorously promote the uptake of the trial results into clinical care. This will include presentations at meetings and written executive summaries for key stakeholder groups.

At a local level, we will interact with and promote research findings through wider NHS Trusts and the NIHR Clinical Research Networks. Nationally we will engage with NICE and professional surgical organisations/societies, as well as national charities (such as CRUK, Melanoma Focus, Melanoma UK, SKCIN, UK DCTN). We anticipate the results will directly impact clinical guidelines, which to date do not include recommendations regarding antibiotic use to prevent SSI in skin surgery.

27 Milestones

The EXCISE trial is a 36-month trial with the following project timeline:

- Month 1-9: Trial set-up, contracts, regulatory approvals, Investigational Medicinal Product manufacture.
- Month 10-15: Internal pilot, location set-up and recruitment.
- Month 16: Review of internal pilot.
- Month 16-24: Complete recruitment.
- Month 30: Last participant last follow-up.
- Month 31-36: Data cleaning, analysis, prepare papers and report; stakeholder event.

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