Observ**A**tional study to investigate
Surgical site **I**nfection in ulcerated **S**kin
cancers (OASIS):

Observational study to estimate the proportion of post-operative infection following excision of ulcerated skin tumours.

PROTOCOL VERSION NUMBER 1.3

10/12/19

Sponsor:	Cardiff and Vale University Health Board (CAVUHB)
Sponsor ref:	RD 17/DEC/7165
Funders:	UK Dermatology Clinical Trials Network (UK DCTN) Dermatology Forum for Wales CAVUHB Dermatology Department Research Funds
Funder ref:	UK DCTN Pump Priming Award 2017
REC ref:	**19/SC/0047**
IRAS number:	243011
NCT number:	NCT03782727

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the relevant study regulations and GCP guidelines.
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 study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:		
Name	**Signature**	**Date**

General Information This protocol describes the OASIS clinical study, and provides information about the procedures for entering participants into the study. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other participants. 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 study.

Contact details – Chief Investigator & Co-Investigators

CHIEF INVESTIGATOR

Dr Rachel Abbott

Consultant Dermatologist

The Welsh Institute of Dermatology

University Hospital of Wales

CF14 4XW

Tel : 02920 743181

E-mail : rachel.abbott@wales.nhs.uk

CO-INVESTIGATORS

Dr Rubeta Matin

Consultant Dermatologist

Oxford University Hospitals NHS Foundation Trust

rnhmatin@doctors.org.uk

Dr Agustin Martin-Clavijo

Consultant Dermatologist,

University Hospitals Birmingham NHS Foundation Trust

E-mail: agustin.martin-clavijo@uhb.nhs.uk

Dr Aaron Wernham

Dermatology Registrar, University Hospitals Birmingham NHS Foundation Trust

E-mail : aaron.wernham@nhs.net

Dr Stela Ziaj

Dermatology Registrar, Cardiff and Vale University Health Board

Email: stela.ziaj@wales.nhs.uk

Dr Robin Howe

Consultant Microbiologist, Cardiff and Vale University Health Board

E-mail : robin.howe@wales.nhs.uk

Dr Emma Thomas-Jones

Research Fellow/ Senior Trial Manager

Cardiff University

E-mail: Thomas-JonesE@cardiff.ac.uk

Tim Pickles

Research Associate in Statistics

Cardiff University

E-mail: PicklesTE@cardiff.ac.uk

SPONSOR contact details:

Cardiff and Vale University Health Board

University Hospital of Wales

Heath Park

Cardiff CF14 4XW

Study Co-ordination:

The OASIS study is being coordinated by Dr Emma Thomas-Jones,

Research Fellow/ Senior Trial Manager

Centre for Trials Research

College of Biomedical & Life Sciences

Cardiff University

7th Floor, Neuadd Meirionnydd

Heath Park

Cardiff CF14 4YS

E-mail: Thomas-JonesE@cardiff.ac.uk

Tel: +44(0)29 20687520

Table of Contents

Glossary of abbreviations

CAVUHB	Cardiff and Vale University Health Board
CI	Chief Investigator
CRF	Case Report Form
CTR	Centre for Trials Research
GCP	Good Clinical Practice
GP	General Practitioner
HB	Health Board
HCRW	Health and Care Research Wales
HRA	Health Research Authority
OASIS	Observational study to investigate surgical site infection in ulcerated skin cancers
PI	Principal Investigator
R&D	Research and Development
REC	Research Ethics Committee
SSI	Surgical site infection
UK DCTN	UK Dermatology Clinical Trials Network

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**
Non-substantial	1.2	19/03/19	p.18: 'type of procedure' added to paragraph 3 ie. data recorded after skin surgery p.22: 'type of procedure' added to list of data recorded on Case Report Form.
Non-substantial	1.3	04/12/19	p.19: • 'Whether the participant has been recruited to the study previously • Number of skin lesions being excised • Number of skin lesions being excised that are ulcerated (if more than one ulcerated lesion, then the patient and researcher should agree on an index lesion for the OASIS study)' Above text added to paragraph 1 ie. data recorded before surgery with additional changes highlighted in red below: • Suspected type of index skin cancer (clinical diagnosis) – to be confirmed on histology

			• Site of procedure(s) • Size of index skin cancer (mm) • Size of index tumoral ulceration p.22-3: • 'Whether the participant has been recruited to the study previously • Number of skin lesions being excised • Number of skin lesions being excised that are ulcerated (if more than one ulcerated lesion, then the patient and researcher should agree on an index lesion for the OASIS study)' Above text added to list of data recorded on Case Report Form with additional changes highlighted in red below: • Suspected type of index skin cancer (clinical diagnosis) – to be confirmed on histology • Site of procedure(s) • Size of index skin cancer (mm) • Size of index tumoral ulceration (mm)

List summary of protocol amendments here whenever a new version of the protocol is produced. Ensure details are also updated in a full protocol change log.

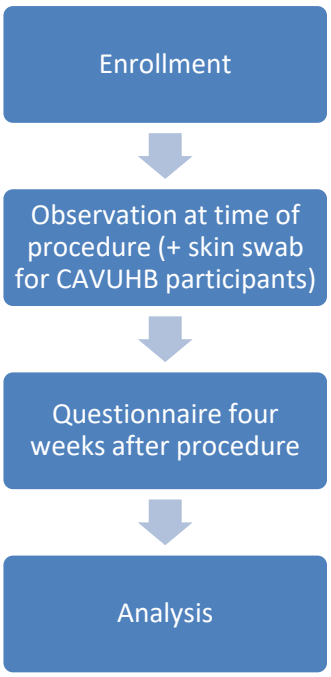
2 Synopsis

Short title	**O**bserv**A**tional study to investigate **S**urgical site **I**nfection in ulcerated **S**kin cancers
Acronym	OASIS
Internal ref. no.	
Clinical phase	N/A
Funder and ref.	UK Dermatology Clinical Trials Network (UK DCTN) Dermatology Forum for Wales CAVUHB Dermatology Department Research Funds
Study design	Observational prospective study
Study participants	People undergoing surgical excision of ulcerated skin cancer of any type at any body site in the dermatology departments at the University Hospital of Wales Cardiff; Churchill Hospital, Oxford and Queen Elizabeth Hospital, Birmingham.
Planned sample size	311
Inclusion criteria	> 18 years old
Exclusion criteria	1) Evidence of wound infection at the time of the procedure 2) Skin tumour removal undertaken curettage or Mohs micrographic surgery 3) People without the capacity to consent for the study 4) People who are on systemic immunosuppressive treatment 5) People who are already taking oral antibiotics
Treatment duration	N/A

Follow-up duration	4 weeks
Planned study period	8 months (recruitment phase) + 1 month (follow-up phase) + 5 months (analysis and write up phase)
Primary objective	To ascertain the proportion of surgical site infections following excision of ulcerated skin tumours in Dermatology Departments.
Secondary objectives	Feasibility work to inform the design of a future randomised controlled trial to investigate whether the use of peri-operative antibiotics in ulcerated skin tumours reduces the proportion of patients with surgical site infection.
Primary outcomes	Proportion of participants with surgical site infection (SSI) identified by postal questionnaire four weeks after surgery.
Secondary outcomes	a) The proportion of participants, over eight months from screened, eligible and willing to be randomised in a future trial to: a. no treatment b. topical treatment c. a few days of oral antibiotics d. a week of oral antibiotics b) The proportion of participants recruited over eight months from eligible. c) The proportion of participants completing the study (responding to the postal questionnaire) over eight months from eligible. d) Assess feasibility of 'wound selfies' or wound photographs taken in the department as an objective outcome measure. e) The proportion of participants with SSI who were prescribed oral antibiotics at the time of surgery. f) Ulcerated tumour swab analysis results.
Intervention	*N/A*

3 Study summary & schema

3.1 Participant flow diagram



3.2 Study lay summary

Study title: ObservAtional study to investigate Surgical site Infection in ulcerated Skin cancers (OASIS)

We aim to recruit 311 participants to this study from three UK Dermatology departments. We will invite people with suspected skin cancers whose lesions have a broken surface (also known as ulcerated) who will undergo surgery.

This study is being carried out because it is possible that patients with skin cancers with ulceration might be at greater risk of developing a wound infection after surgery. The aim of this study is to determine how many people with ulcerated skin cancers develop an infection of the wound after it has been surgically removed.

People with ulcerated skin cancers who will have surgery will be invited to participate in the study. If they agree, a member of the research team will explain the study and consent them to participate in the study. At the time of surgery, information will be collected about the participant, skin tumour and procedure. The participant will be given standardised advice

regarding wound care and further care will be as per each centre's 'normal clinical care'. If participants are diagnosed with a wound infection then they will asked to take a 'wound selfie' and share the photo with the research team. The research team will contact the participant via questionnaire which will be sent four weeks by post or e-mail after the procedure to determine whether they had any concerns about post-operative infection and whether any action was taken.

Additionally, all participants at the University Hospital of Wales will have a surface swab taken from their ulcerated skin cancer and these will be analysed in the Public Health Wales laboratory at the University Hospital of Wales, Cardiff. The aim of this aspect of the study is to identify the most common bacteria in ulcerated tumours.

4 Background

Non-melanoma skin cancer is the most common cancer in the UK with a rising worldwide incidence.[1] For the majority of patients, surgical excision remains the gold standard treatment, however the role of peri-operative antibiotics in preventing post-operative infection remains controversial. Ulcerated tumours occur commonly in dermatological surgical lists ranging from 19-33%.[2-4] In a prospective evaluation of excised skin cancers by our group, including patients undergoing excision at the University Hospital of Wales, Cardiff and the Queen Elizabeth Hospital, Birmingham, one third of skin cancers were clinically ulcerated.

The true proportion of patients developing post-operative infection following surgery in ulcerated skin cancers is needed to determine the sample size for a randomised controlled trial to evaluate the potential benefit of peri-operative antibiotics. Few studies have assessed this accurately although rates of infection have been reported to be as high as 33% in a small single-centre cohort study.[2] A recently published randomised controlled trial reported SSI in 30% of participants with ulcerated tumours undergoing excision who were not randomised to receive perioperative intravenous cefazolin.[5] This is significantly higher than quoted figures for all skin cancer excisions (2-8%).[6-8] A larger Australian study reported a three-fold increase in the risk of post-operative infection for excision of ulcerated tumours but did not report frequency of SSI.[3]

Antibiotic resistance is currently one of the most significant threats to patient safety.[9] Overuse of antibiotics and inappropriate prescribing are well recognized factors which

contribute to antibiotic resistance. Furthermore, a survey of UK Dermatological surgeons, conducted in collaboration with the UK Dermatology Clinical Trials Network (UK DCTN), has shown that there is no agreed consensus on the timing of antibiotic prescribing, choice of antibiotic or length of antibiotic course.[10]

To further inform the design of a pilot study, our extended UK DCTN surgical trainee research group has conducted a Critically Appraised Topic to assess the efficacy of perioperative antibiotics in reducing the risk of SSI following excision of ulcerated skin cancers, which confirmed the need for a well-designed RCT to answer this question.[11]

5 Study objectives/endpoints and outcome measures

5.1 Primary objectives

- To determine the proportion of participants developing SSI following excision of ulcerated skin tumours in three Dermatology Departments: University Hospital of Wales, Cardiff; Churchill Hospital, Oxford and Queen Elizabeth Hospital, Birmingham

5.2 Secondary objectives

- Feasibility work to inform the design of a future randomised controlled trial to investigate whether the use of peri-operative antibiotics in ulcerated skin tumours reduces the proportion of participants with SSI.

5.3 Primary outcomes measure

The main objective is to determine the proportion of participants with SSI within four weeks of surgery. The research team will arrange to contact the participant four weeks after the procedure via a validated questionnaire (see details below) to determine whether they had any concerns about post-operative infection and what action was taken. SSI is broadly defined as the presence of one of the following criteria associated with the wound: abscess, cellulitis, discharge, delayed healing, discolouration, friable granulation tissue, unexpected pain/ tenderness, pocketing at base of wound, abnormal smell, wound breakdown.[12] A systematic review has acknowledged the use of several different classifications for SSI and the lack of a standardised tool for diagnosing SSI.[13] In response to this, Macefield *et al.* have developed a single patient and observer measure for post-discharge SSI assessment and have given us permission to use the tool in this study.[14]

5.4 Secondary outcomes measure(s)

- The proportion of participants, over eight months from screened, eligible and willing to be randomised in a future trial to:
    a. no treatment
    b. topical treatment
    c. a few days of oral antibiotics
    d. a week of oral antibiotics
- The proportion of participants recruited over eight months from eligible.
- The proportion of participants completing the study (responding to the postal questionnaire) over eight months from eligible.
- Assess feasibility of 'wound selfies' or wound photographs taken in the department as an objective outcome measure.
- The proportion of participants with SSI who were prescribed oral antibiotics at the time of surgery.
- Ulcerated tumour swab analysis results

6 Study design and setting

Clinicians in the dermatology department will identify eligible participants at the time of initial consultation in outpatient clinic.

Identification of potential participants will be by the clinical care team, or the clinical members of the research team involved in care of potential participants. Potential participants will be signposted to the research team by the clinical care team.

Patients will be approached by a trained member of the clinical team or research nurse following clinical checks against the inclusion and exclusion criteria. They will be provided with an information leaflet and any other information about the study they request. The patient will be given sufficient information to ensure they fully understand the nature and risks of the study and are given as much time as they require to consider their participation. If they are willing to participate, they will be consented and admitted to the study at the time of surgery. Prior to the procedure relevant clinical information will be recorded in the Case Report Form (CRF) including demographic data, tumour site, tumour size, and size of tumoural ulceration. Participants will be asked whether they would prefer to be contacted via post or e-mail with

the follow-up questionnaire. Histopathological data will be collected on tumour type when it is reported. Participants and clinicians will be asked whether they would agree for the patients to be randomised to no antibiotics, topical treatment eg. Inadine™ dressings, a short course of antibiotics or a longer course of antibiotics in a future RCT. Following the procedure, information about whether oral antibiotics were prescribed will be recorded on a standardized CRF. All participants will be provided with the same information leaflet detailing standard post-operative advice and further care will be as per each centre's 'standard clinical care' which will also be recorded. Standard practice is usually for the patient to contact the local dermatology department where the procedure was carried out, or the patient's local GP practice or for the patient to attend A&E.

If participants are diagnosed with SSI they will be asked to take a photo of their wound on a camera phone and then to share the photo with the Cardiff University Centre for Trials Research (CTR) via email. Reeves *et al.* have described this practice as a 'wound selfie' and report that the term is readily understood.[15] If participants are not able to take of photo of their wound then they will be invited to attend the department to have a photograph taken by medical photography. Including both options will allow us to compare the feasibility of obtaining wound photos via each method. All participants will be sent a questionnaire by the research team four weeks following their procedure by post or by e-mail to enquire specifically whether the participant was diagnosed and treated for wound infection. These data will be collected by Cardiff University CTR who will co-ordinate the study.

Additionally, all participants at University Hospital of Wales will have a surface swab taken from their ulcerated skin tumour and these will be analysed in the Public Health Wales laboratory at the University Hospital of Wales, Cardiff. The aim of this aspect of the study is to identify the most common organisms that colonise ulcerated tumours. Previous studies have commented on growth from ulcerated tumours, however it is not clear if this was conducted in a research laboratory setting.[16] This will help to guide antibiotic choice in a future randomized controlled trial.

6.1 Risk assessment

This study has been categorised as a Low Risk, where the level of risk is no higher than the risk of standard medical care.

7 Site and Investigator selection

This study will be carried out at three centres: Cardiff and Vale University Health Board, Churchill Hospital, Oxford and Queen Elizabeth Hospital, Birmingham.

8 Participant selection

Participants are eligible for the study if they meet all of the following inclusion criteria and none of the exclusion criteria apply.

8.1 Inclusion criteria

- Dermatology Department patients > 18 years undergoing surgical excision of ulcerated skin cancer of any type affecting any body site

8.2 Exclusion criteria

- Evidence of wound infection at the time of the procedure
- Skin tumour removal undertaken using curettage or Mohs micrographic surgery
- People without the capacity to consent for the study
- People who are on systemic immunosuppressive treatment
- People who are already taking oral antibiotics for any other reason

9 Recruitment, Screening and registration

9.1 Participant identification

Clinicians in the dermatology department will identify eligible participants at the time of initial consultation.

9.2 Screening logs

A screening log of all ineligible and eligible but not consented/not approached will be kept to inform any obstacles to enrolment in a future trial.

9.3 Recruitment rates

A total of 311 participants will be recruited at an expected rate of 39 per month. This is based on a previous audit in this centre which demonstrated that 55 people would have been eligible

for the study over a 3-week period. Assuming that just under half would agree to participate in the study, we anticipate recruiting 9 participants per week.

9.4 Informed consent

Where eligibility is indicated, patients will be provided with a brief explanation of the study by the clinical team. Assenting patients will be provided with a full verbal explanation of the study and Participant Information Leaflet (PIL) to consider by the clinical team. This will include detailed information about the rationale, design, and personal implications of the study. Following information provision, patients will be able to consider participation until the planned time of surgery and will be given the opportunity to discuss the study with their family and other healthcare professionals before they are asked whether they would be willing to take part in the study. Assenting patients will then be invited to provide informed, written consent. Assessment of eligibility and the informed consent process will be undertaken by a member of the clinical team, who are qualified by training and/or experience in taking informed consent to GCP standards or by a research support office/ nurse. The right of the patient to refuse consent without giving reasons will be respected. Further, the patient will remain free to withdraw from the study at any time without giving reasons and without prejudicing any further treatment. The participant's written informed consent must be obtained using the Participant Consent Form, which follows the Participant Information Leaflet. A record of the consent process detailing the date of consent and the version of the consent form used will be kept in the patient healthcare records. The original consent form will be retained in the Investigator Site File.

Please note, only when written informed consent has been obtained from the participant and they have been enrolled into the study can they be considered a study participant.

After the participant has entered the study, the investigator must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels 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 study for the purpose of follow up and data analysis according to the treatment option to which he/she has been allocated. Similarly, the participant must remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing his/her further treatment.

9.5 Registration

9.5.1 Registration

A record of the consent process detailing the date of consent will be kept in the patient healthcare records. To register a patient onto the OASIS study investigators or designee should complete the registration section of the Case Report Form (CRF). This will include:

- Site code
- Site name
- Participant full name
- Participant postal address or e-mail address
- Participant phone number
- Participant age
- Participant gender
- Date of consent of participant

10 Withdrawal & lost to follow-up

10.1 Withdrawal

Participants have the right to withdraw consent for participation in any aspect of the study at any time. The participants care will not be affected at any time by declining to participate or withdrawing from the study.

1. If a participant initially consents but subsequently withdraws from the study all their data will be removed. However participants cannot withdraw data after it has been anonymised for analysis.

10.2 Lost to follow up

1. Participants will be identified as lost to follow up if we are unable to contact them four weeks after their procedure.
2. Measures that we will take to try and get the missing information include three attempts to telephone or text the participants. If we are unable to contact the participant by telephone then and we will also send them a letter asking them to contact the study centre.'

11 Study procedures

The following are to be recorded *before* skin surgery on the CRF:

- Whether the participant has been recruited to the study previously
- Number of skin lesions being excised
- Number of skin lesions being excised that are ulcerated (if more than one ulcerated lesion, then the patient and researcher should agree on an index lesion for the OASIS study)
- Suspected type of index skin cancer (clinical diagnosis) – to be confirmed on histology
- Site of procedure(s)
- Size of index skin cancer (mm)
- Size of index tumoral ulceration

Participants and the clinicians performing the procedure will be asked whether they would agree for the participant to be randomised to no antibiotics, topical treatment eg. Inadine™ dressings, a short course of antibiotics or a longer course of antibiotics in a future RCT.

The following will be recorded ***after*** skin surgery on the CRF:

- Type of procedure
- Whether Inadine™ dressing applied to wound
- Whether topical antibiotics applied to wound
- Whether oral antibiotics prescribed

A questionnaire [Appendix 1] will be sent to participants by post or email at four weeks. A stamped-addressed envelope will be sent with the questionnaire for the reply if required.

11.1 Assessments

Assessment data required *if participant develops suspected wound infection*:

- Photograph of wound ('wound selfie'): the photos will be sent to the CTR to determine whether this is a feasible method of assessing wounds, however the photos will not be analysed.

Figure 1. Schedule of enrolment, interventions and assessments[1]

Procedures	**Visits (insert visit numbers as appropriate)**			
	Screening	**Baseline**	**(If concern about SSI)**	**(Follow Up)**
Eligibility assessment	X			
Informed consent		X		

[1] Taken from the HRA CTIMP protocol template (2016).

Demographics		X		
Clinician / Participant agreement for future RCT		X		
Procedure data		X		
Skin swab (only CAVUHB participants)		X		
Wound photograph			X	
Questionnaire				X

11.2 Follow-up

Final data will be collected by questionnaire *four weeks after the procedure*. Any further follow-up appointments in the clinic will be based on clinical discretion and no further appointments will occur specifically for the study.

11.3 Skin swabs (CAVUHB participants only)

Participants enrolled to the study at the University Hospital of Wales, Cardiff will have swabs of ulcerated skin tumours taken and analysed in the Public Health Wales laboratory at the University Hospital of Wales, Cardiff.

It is the responsibility of the study site to ensure that samples are appropriately labelled in accordance with the study procedures to comply with the current Data Protection legislation. Biological samples collected from participants as part of this study will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act.

Swabs of the ulcerated tumours will be taken with no prior cleaning prior to skin surgery. Completed swabs will be deposited in specimen collection baskets within the dermatology department and will be shipped to the laboratory via the standard portering system.

Swabs will be cultured onto a range of non-selective and selective media. Bacterial pathogens will be semi-quantified and identified using MALDI-ToF and other tests where applicable. Microbiological infection will be determined according to local Standard Operating procedures,

based upon UK national Standards in Microbiology Investigations (SMI) guidelines. After the skin swabs have been processed then they will be destroyed according to laboratory regulations.

The aim of this is to identify the most common organisms that grow in ulcerated tumours which will help to guide antibiotic choice in a future randomised controlled trial.

Currently, there is no consensus on which antibiotic would be most appropriate to reduce the risk of surgical site infection in ulcerated skin tumours. This may be partly explained by the paucity of data regarding pathogens of ulcerated skin tumours. One single-centre study in Australia isolated Staphylococcus aureus in 93 of 97 ulcerated lesions and gram-negative bacteria (including Klebsiella, Acinetobacter, Proteus, Serratia and Escherichia species) in 7 of 97 ulcerated lesions.[16] However, it is not clear whether this was conducted in a research laboratory setting or in a clinical setting where the laboratory would aim to identify the presence of known skin pathogens.

12 Statistical considerations

12.1 Sample size

Given the wide range in reported SSI from published case series between 2-33%, we anticipate a SSI of approximately 10% in our participants with ulcerated skin tumours. Our aim is to recruit 311 participants with an intended sample size of 283 participants (allowing for a dropout rate of 10%). This will give a 95%CI of between 6.9% to 13.5%.

12.2 Missing, unused & spurious data

Any instances of unused or spurious data will be reported. If the quantity of missing data becomes an issue in this study, suitable analyses techniques will be used to impute data as required.

12.3 Procedures for reporting deviation(s) from the original protocol

Protocol deviations, non-compliances or breaches are departures from the approved protocol. Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the CTR. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach. These will be reported by the PI to the CTR and will be followed up by the study manager.

12.4 Inclusion in analysis

All screened patients will be reported. For each analysis, only patients with relevant evaluable data will analysed. Where relevant, differences between those with and without the relevant evaluable data will be reported as a check for bias.

13 Analysis

13.1 Main analysis

All analyses will report a proportion and 95% confidence interval. Where appropriate (i.e., if the proportion is <5%), the 95% confidence interval will be reported as per Wilson's method.[17]

14 Data Management

14.1 Access to Data

Direct access will be granted to authorised representatives from the sponsor and host institution for monitoring and/or audit of the study to ensure compliance with the relevant data protection legislation.

14.2 Data Recording and Record Keeping

The registration section of the Case Report Form (CRF) will include:

- Site code
- Participant full name
- Participant address or email address

Participant phone number

- Participant age (at study enrolment)
- Participant gender
- Date of consent of participant

The clinical part of the CRF will include:

- Whether the participant has been recruited to the study previously
- Number of skin lesions being excised

- Number of skin lesions being excised that are ulcerated (if more than one ulcerated lesion, then the patient and researcher should agree on an index lesion for the OASIS study)
- Suspected type of index skin cancer (clinical diagnosis) – to be confirmed on histology
- Site of procedure(s)
- Size of index skin cancer (mm)
- Size of index tumoral ulceration (mm)

Participants and the clinicians performing the procedure will be asked whether they would agree for the participant to be randomised to no antibiotics, topical treatment eg. InadineTM dressings, a short course of antibiotics or a longer course of antibiotics in a future RCT.

- Whether InadineTM dressing applied to wound
- Whether topical antibiotics applied to wound
- Whether oral antibiotics prescribed

Type of procedure

All data and personal information will be stored in locked filing cabinets in fireproof locations in restricted areas.

Data processing and data sharing arrangements will be documented in the Statement of Activities between each participating site and the sponsor. Data from the clinical part of each CRF, together with the participant's name, address and phone number should be returned to the CTR for data entry within four weeks of the visit via an encrypted secure file transfer service in accordance with the General Data Protection Regulation and Data Protection Act 2018. The CRF is to be retained at the local site. 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. Data received by the CTR from participating study sites 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 on a data clarification form. The data clarification form will be sent to the relevant participating site. The site shall be requested to respond to the data query on the data clarification form. The case report form 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 participating site. The completed data clarification

form should be returned to the CTR and a copy retained at the site in a site file along with the participants' CRFs. The CTR will send reminders for any overdue data. It is the site's responsibility to submit complete and accurate data in timely manner.

Each participant's name, address or e-mail address and phone number will be shared with the CTR so that the follow-up questionnaires can be sent from the CTR where the data will be collected. The participant's phone number may be used to obtain missing information. All paper data and personal information will be stored in locked filing cabinets in fireproof locations in restricted areas. Electronic data will be stored on university servers, accessed via password protected, encrypted, firewall protected and backed up computers. All personal data will be confidentially destroyed at the end of the study. Once the participant's data has been collected they will be allocated a unique participant identification number (PID, assigned sequentially as each patient is registered). The PID will be used for the purpose of data analysis. The data generated by the study will be analysed by the CTR team led by Tim Pickles, Research Associate in Statistics and Dr Emma Thomas-Jones, Research Fellow/ Senior Trial Manager.

14.3 Participant Confidentiality and Data Protection

All investigators and study site staff must comply with the requirements of the General Data Protection Regulation and Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. All research staff and delegated site staff will be trained in data protection and data management.

14.4 Record Storage and Retention

Essential documents pertaining to the trial shall not be destroyed without permission from the Sponsor. The TMF and ISF containing essential documents will be kept for a minimum of 5 years after completion of study. The CTR will send the Trial Master File to the sponsor at end of study for archiving. Documents (paper and electronic) will be retained in a secure location during and after the study has finished. Each PI at any participating site will archive the essential documents generated at the site for the agreed archiving period.

Study data			
	CRF	*Wound 'selfies'*	*Questionnaire*
Demographic data	*X*		
Procedure data	*X*		
Follow up data			*X*
Skin swab result (UHW ppts only)	*X*		
Photos of infected wounds		*X*	

15 Protocol/GCP non-compliance

The Principal Investigator will report any non-compliance to the study protocol or the conditions and principles of Good Clinical Practice to the CTR in writing as soon as they become aware of it.

In the event that a serious breach of the protocol or GCP is suspected, this must be reported to the sponsor immediately. The sponsor will investigate the breach and any preventative and or corrective actions required will be undertaken by the research team. REC will be informed by the Chief Investigator if a serious breach is identified.

16 End of Study definition

The follow up period will continue for 4 weeks after the last participant's last data item.

The end of the study is defined as the date of final data capture to meet the study endpoints. In this case end of study is defined as the date on which the last participant is contacted by telephone four weeks after registration.

CI or a delegate will notify the main REC of the end of a clinical study within 90 days of its completion or within 15 days if the study is terminated early.

17 Regulatory Considerations

17.1 Ethical and governance approval

The study will be assessed for governance and legal compliance by HCRW. Once all checks are satisfied HCRW will issue HRA/HCRW approval. The study should not commence at any site until local confirmation of capacity and capability is also received via email by the CI/ PI. Before the start of the study, approval will be sought from HCRW and REC for the protocol, informed consent forms and other relevant documents Amendments that require review by HCRW and REC will not be implemented until approval is granted. The CI (or delegate) should submit any amendments to their National Coordinating Unit, HCRW. The HCRW Permissions Service will assess and approve the amendment.

17.2 Data Protection

The sponsor 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 General Data Protection Regulations 2018.

17.3 Indemnity

This is an NHS-sponsored research study, and the NHS indemnity scheme therefore applies. If there is negligent harm during the study 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.

17.4 Study sponsorship

Cardiff and Vale University HB will act as Sponsor for the OASIS study. The HB shall be responsible for ensuring that the study is performed in accordance with the following:

- Conditions and principles of Good Clinical Practice.
- Declaration of Helsinki (1996).
- UK Policy Framework for Health and Social Care Research (2017).
- The Data Protection Act 1998.
- Other regulatory requirements as appropriate.

The Sponsor has/will be delegating certain responsibilities to Cardiff University (CTR), the CI, PIs, host sites and other stakeholder organisations as appropriate in accordance with the relevant agreement that is informed by regulation and study type.

17.5 Funding

The UK DCTN has awarded £10,000 for this study. Dermatology Forum for Wales has awarded £500 towards this study. The shortfall of £1,055.25 will be met by CAVUHB Dermatology Department Research Fund.

18 Quality Control and Assurance

18.1 Monitoring

The clinical study risk assessment has been used to determine the intensity and focus of central and on-site monitoring activity in the OASIS study. Low monitoring levels will be employed.

Investigators agree to allow study related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. Participant consent for this will be obtained. Findings generated from on-site and central monitoring will be shared with the Sponsor, CI, & PI.

19 Publication policy

In addition, the study has been developed with the help and funding support of the UK Dermatology Clinical Trials Network (UK DCTN) and full acknowledgement will be given in all publications.

20 References

1. Lomas A, Leornardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of non-melanoma skin cancer. Br J Dermatol. 2012;166:1069-80.
2. Weatherhead SC, Lawrence CM. Preoperative integrity of skin surface predicts infection risk. BMJ 2009;338:b516.
3. Penington A. Ulceration and antihypertensive use are risk factors for infection after skin lesion excision. ANZ J Surge 2010;80:642-5.
4. Wernham AGH, Fremlin GA, Verykiou S, Harper N, Chan S, Matin RN, Abbott RA. Feasibility analysis to evaluate the role of peri-operative antibiotics in reducing infection rates in ulcerated skin cancers. Br J Dermatol. 2016; 175 (suppl.S1) p107-132.
5. Dreher R *et al.* Antibiotic prophylaxis with cefazolin in reducing the infection rate of non-melanomcytic skin tumours: a randomized clinical trial. Eur J Plast Surg 2017;40:133-136.
6. Futoryan T, Grande D. Postoperative wound infection rates in dermatological surgery. Dermatol Surg 1995;21:509-14.
7. Wrigh TI, Baddour L et al. Antibiotic prophylaxis in dermatologic surgery: Advisory statement2008. JAAD 2008;59:464-73.
8. Heal C, Buettner P et al. Risk factors for wound infection after minor surgery in general practice. Med J Aust 2006;185:255-8.
9. Wernham AG[1], Fremlin GA[2], Verykiou S[3], Harper N[4], Chan SA[5], Stembridge N[6], Matin RN[7], Abbott RA[8]. Survey of dermatologists demonstrates widely varying approach to perioperative antibiotic use - time for a randomized trial? Br J Dermatol. 2016 Sep 2. doi: 10.1111/bjd.15025. [Epub ahead of print]
10. The NHS antibiotic aware campaign, http://www.nhs.uk/NHSEngland/ARC/Pages/AboutARC.aspx
11. Chan SA1, Wernham AGH *et al*.Do perioperative antibiotics reduce the risk of surgical site infection? A critically appraised topic. Br J Dermatol. In press.
12. Cutting KF, Harding KG. Criteria for identifying wound infection. Journal of wound care 1994;3:198-201.
13. Gibbons C, Bruce J *et al*. Identification of risk factors by systematic review and development of risk-adjusted models for surgical site infection. Health Technol Assess. 2011;15(30):1–156. iii-iv

14. Macefield RC, Reeves BC, Milne TK, Nicholson A, Blencowe NS, Calvert M, Avery KNL, Messenger DE, Bamford R, Pinkney TD, Blazeby JM on behalf of the Bluebelle Study Group. Development of a single, practical measure of surgical site infection (SSI) for patient report or observer completion. J Inf Prev. 2017;18(4):170–79
15. Reeves BC *et al*. A mixed-methods feasibility and external pilot study to inform a large pragmatic randomised controlled trial of the effects of surgical wound dressing strategies on surgical site infections (Bluebelle Phase B): study protocol for a randomised controlled trial. Trials 2017;18:401.
16. Czarnecki D, Meehan C, Nash. Prevention of post excisional wound infections: a comparison of oral cephalexin with topical muprirocin and topical cetrimide-chlorhexidene cream. International Journal of Dermatology 192:31;359-360.
17. Wilson EB. Statistical Inference. *Science* 1926; **63**(1629): 289-96.

21 Appendices

1. Questionnaire

Appendix 1: Questionnaire

Since you left hospital after having surgery.... Response categories

1 Was there redness spreading away from the wound? (erythema/cellulitis) Not at all / A little / Quite a bit / A lot
2 Was the area around the wound warmer than the surrounding skin? Not at all / A little / Quite a bit / A lot
3 Was any part of the wound leaking fluid? Not at all / A little / Quite a bit / A lot
a) Was it clear fluid? (serous exudate) Not at all / A little / Quite a bit / A lot
b) Was it blood-stained fluid? (haemoserous exudate) Not at all / A little / Quite a bit / A lot
c) Was it thick and yellow/green fluid (pus/purulent exudate) Not at all / A little / Quite a bit / A lot
d) I do not know
4 Have the edges of any part of the wound separated/gaped open on their own accord? (spontaneous dehiscence) Not at all / A little / Quite a bit / A lot
a) Did the skin separate? Not at all / A little / Quite a bit / A lot
b) Did the deeper tissue separate? Not at all / A little / Quite a bit / A lot
c) I do not know
5 Has the area around the wound become swollen? Not at all / A little / Quite a bit / A lot
6 Has the wound been smelly? Not at all / A little / Quite a bit / A lot
7 Has the wound been painful to touch? Not at all / A little / Quite a bit / A lot
8 Have you had, or felt like you have had, a raised temperature or fever? Not at all / A little / Quite a bit / A lot (fever <38^{o}C)
9 Have you sought advice because of a problem with your wound, other than at a routine planned follow-up appointment? Yes / No
If yes, please tell us who you sought advice from:
a) A doctor or nurse at the GP surgery/medical centre/walk-in centre Yes / No
b) A doctor or nurse at the hospital Yes / No
c) A midwife or health visitor Yes / No
d) Another health advisor Yes / No
Please describe who the other health advisor was _____
10 Has anything been put on the skin to cover the wound? (dressing) Yes / No
If yes,
a) Was this done by a doctor or nurse at the GP surgery/ medical centre/walkin centre? Yes / No

b) Was this done by a nurse/midwife/health visitor at home? Yes / No
c) Was this done by you/your partner/friend/family member? Yes / No
d) Was this done by a doctor/nurse/midwife at the hospital? Yes / No
e) Please describe what was put on to cover the wound _____
11 Have you been back into hospital for treatment with a problem with your wound? Yes / No

12 Have you been given antibiotics for a problem with you wound? Yes / No / Don't know
If yes,
a) Were the antibiotics given as tablets/liquid? Yes / No / Don't know
b) Were the antibiotics given via drip? Yes / No / Don't know
If you know the name of the antibiotic(s) you have taken, please write it here
_____
13 Have the edges of your wound been deliberately separated by a doctor or nurse? Yes / No / Don't know

14 Has your wound been scraped or cut to remove any unwanted tissue? (debridement of wound) Yes / No / Don't know

15 Has you wound been drained? (drainage of pus/abscess) Yes / No / Don't know
16 Have you had an operation under general anaesthetic for treatment of a problem with your wound? Yes / No / Don't know