.

Health Research Authority

FULL/LONG TITLE OF THE TRIAL

The CABI trial: An unblinded parallel group randomised controlled feasibility trial of long course antibiotic therapy (28 days) compared to short course (≤10 days) in the prevention of Complicated intra-ABdominal Infection relapses in adults treated for Complicated intra-ABdominal Infection.

SHORT STUDY TITLE / ACRONYM

CABI: Antibiotic duration for Complicated intra-ABdominal Infection.

This protocol has regard for the HRA guidance and order of content.

RESEARCH REFERENCE NUMBERS

Leeds Teaching Hospitals Trust R&I number:

The University of Leeds reference number:

IRAS

TRIAL REGISTRY NUMBER AND DATE

Clinical trials.gov: NCT

PROTOCOL VERSION NUMBER AND DATE

Version 0.92 18.11.2016

SPONSOR

The University of Leeds

FUNDER

SIGNATURE PAGE

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

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

I also confirm that I will make the findings of the 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.

For and on behalf of the Study Sponsor:

Signature: Date:
...../...../.....
.....

Name (please print):

.....

Position:
.....

Chief Investigator:

Signature: Date:
..../...../.....

Name: (please print):

.....

Statistician:

Signature:
.....

Name: (please print):

.....

Position:
.....

KEY TRIAL CONTACTS

Chief Investigator	Andrew Kirby 0113 3923929 a.kirby@leeds.ac.uk
Trial Co-ordinator	Andrew Kirby 0113 3923929 a.kirby@leeds.ac.uk
Sponsor	University of Leeds 0113 3434897 Clare Skinner
Funder(s) and support in kind	The University of Leeds 0113 34 37587 governance-ethics@leeds.ac.uk Leeds Teaching Hospitals NHS Trust 0113 39 20152 leedsth-tr.lthtresearch@nhs.net Department of Surgery, Leeds Teaching Hospitals NHS Trust 0113 2066877 dermotburke@nhs.net
Clinical Trials Unit	None
Key Protocol Contributors	Dermot Burke 0113 2066877 dermotburke@nhs.net Andrew Kirby 0113 3923929 a.kirby@leeds.ac.uk Dr Shafaque Shaikh S.Shaikh@leeds.ac.uk

	Dr Anne Melhuish annemelhuish@nhs.net Dr Shadia Ahmed shadiaahmed@nhs.net
Statistician	None
Trials pharmacist	Caroline Bedford
Research Nurse Lead	Catherine Moriarty
Health economics	Armando Vargas-Palacios
Committees	Trial Steering Committee (TSC) Committee contact Dr Andrew Kirby 0113 3923929 a.kirby@leeds.ac.uk

TRIAL SUMMARY

Trial Title	The CABI trial: An unblinded parallel group randomised controlled feasibility trial of long course antibiotic therapy (28 days) compared to short course (≤10 days) in the prevention of Complicated intra-ABdominal Infection relapses in adults treated for Complicated intra-ABdominal Infection.	
Short title	CABI: Antibiotic duration for Complicated intra-ABdominal Infection.	
Clinical Phase	Phase II/Feasibility	
Trial Design	A randomised controlled unblinded parallel group trial	
Trial Participants	Adults hospitalised with complicated intra-abdominal infection	
Planned Sample Size	60	
Treatment duration	Up to 10 days or 28 days.	
Follow up duration	90 days from start of antibiotic treatment for CABI	
Planned Trial Period	February 2017-February 2019	
	Objectives	Outcome Measures
Primary	To determine • The willingness of participants to be randomised • The willingness of clinicians to allow patients to be recruited • The number of eligible patients • Follow up rates	Screening logs, recruitment rates and follow up rates will be recorded
A full study which may follow this feasibility study would have clinical objectives as primary and secondary objectives. In order to determine the feasibility of collecting data relevant to these clinical objectives, e.g. rate of relapse, we have included these objectives within the secondary objectives. We do not include them as true objectives in the sense that we anticipate obtaining evidence relevant to the objective e.g. we do not expect to demonstrate that different treatment strategies are associated with different rates of relapse.		
Secondary	To reduce the rate of relapse after treatment of complicated intra-abdominal infection. To reduce the rate of all infections after treatment of	Relapse of complicated intra-abdominal infection. All infections within 90 days of CABI diagnosis.

	complicated intra-abdominal infection.	
	To reduce the rate of antibiotic consumption	Days of antibiotic therapy within 90 days of antibiotic therapy.
	To reduce length of hospital stay after diagnosis of complicated intra-abdominal infection	Length of hospital stay after diagnosis of a CABI & total days of hospitalisation within 90 days of diagnosis.
	To reduce mortality after treatment of complicated intra-abdominal infection.	Mortality 90 days after diagnosis of CABI.
	To reduce rates of complications from antibiotic therapy including Clostridium difficile infection (CDI) diarrhoea and catheter related blood stream infection (CRBSI)	CDI and CRBSI rates within 90 days of diagnosis.
	To reduce the number of source control procedures required for the management of CABI	Number of source control procedures within 90 days after diagnosis of CABI.
	To improve quality of life after treatment of complicated intra-abdominal infection.	Quality of life scores (EQ-5D) at time of diagnosis of CABI, 30 and 90 days post diagnosis of a CABI, as well at the times of relapses.
	To improve the health-economics of managing complicated intra-abdominal infection.	Costs of healthcare treatment within 90 days after diagnosis of CABI.
Medicinal Product(s)	Antibiotics for the treatment of CABI. The choice of antibiotic will be that of the treating physicians.	

	A list of recommended antibiotics will be provided as not all antibiotics are likely to be effective for complicated intra-abdominal infection. This list will be comprehensive but not exhaustive. Treating physicians will not be restricted to the list of recommended antibiotics. Antibiotics must be used within their licenced indications. All will be antibiotics routinely used in the NHS (within the British National formulary (BNF)). Recommended regimens will provide antibacterial activity against Gram positive, Gram negative and anaerobic bacteria. Where antibiotic susceptibilities of bacteria believed to be causing CABI are available, these should be considered in the choice of antibiotic. The recommended antibiotic list is: 1- Amoxicillin (or glycopeptide/linezolid), ciprofloxacin and metronidazole 2- Amoxicillin (or glycopeptide/linezolid), aztreonam and metronidazole 3- Amoxicillin (or glycopeptide/linezolid), gentamicin and metronidazole 4- Amoxicillin-clavulanic acid (+/-glycopeptide/linezolid) 5- Piperacillin—tazobactam 6- Cefuroxime and metronidazole 7- Ertapenem (+/- glycopeptide/linezolid) 8- Meropenem (+/- glycopeptide/linezolid) 9- Tigecycline (+/-ciprofloxacin)
Formulation, Dose, Route of Administration	British National Formulary recommended doses are required in this study. The standard doses of the recommended antibiotics are: Amoxicillin 1g IV or PO 8 hourly Ciprofloxacin 400mg IV 12 hourly or 500mg PO 12 hourly Amoxicillin-clavulanic acid 1.2g IV 8 hourly (not recommended orally) Cefuroxime 1.5 grams IV 8 hourly Metronidazole 400mg PO 8 hourly or 500mg IV 8 hourly Aztreonam 1g IV 8 hourly Tigecycline 100mg loading dose followed by 50mg 12 hourly IV. Ertapenem 1g IV 24 hourly Meropenem 1g IV 8 hourly Piperacillin-tazobactam 4.5g IV 8 hourly Linezolid 600mg IV or PO 12 hourly

	Glycopeptides/Aminoglycosides: Dosed according to renal function and therapeutic drug monitoring results.

FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL/NON FINANCIALSUPPORT GIVEN
The University of Leeds	Employment of Mr Dermot Burke Employment of Dr Andrew Kirby Employment of Dr Shafaque Shaikh
Leeds Teaching Hospitals NHS Trust	Employment of Anne Melhuish Employment of Caroline Bedford Employment of Catherine Moriarty
Department of Surgery, Leeds Teaching Hospitals NHS Trust	Facilities for recruitment and intervention
Resources available	Dr Andrew Kirby has 5 programmed activities per week available to support research. Research support is also provided by Catherine Moriarty and the colorectal research staff.

ROLE OF STUDY SPONSOR

The University of Leeds is the Sponsor of the trial and employer of the Chief Investigator. This is an investigator-led single-site trial. The study is managed and conducted by the Chief Investigator, with the UoL / LTHT Sponsor overseeing the activity to ensure appropriate regulatory and governance procedures are in place.

ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

The trial steering committee (TSC)

The TSC will provide overall supervision of the trial concentrating on the trial's progress, including adherence to the approved protocol, subject safety, and consideration for new information. This group will monitor the on-going relevance and need for the trial in view of published literature and be responsible for the on-going compliance to ethical and regulatory standards. The CI is responsible for maintaining the TSC documentation during the course of the trial to ensure compliance with the Trial Master File.

Committee members include:

Chair: Dr Andrew Kirby
Research doctor: Mr Dermot Burke
Research doctor: Dr Shafaque Shaikh
Research doctor: Dr Shadia Ahmed
Research Nurse: Catherine Moriarty
Trials pharmacist: Caroline Bedford
Sponsors representative (invited to meetings)
Frequency of meetings: Pre-initiation meeting, End of study meeting.
Meeting documentation: A formal meeting report will be written and disseminated to TSC members, the sponsor and the lead research nurse

Data Management Committee (DMC)

A DMC will not be required for the following reasons: The low risk nature of the trial, the open design, the small size of the trial (single site feasibility study) and the established safety profiles of the IMPs.

Protocol contributors

Mr Dermot Burke

Dr Andrew Kirby

Dr Shafaque Shaikh

Dr Anne Melhuish

Dr Shadia Ahmed

Caroline Bedford

Catherine Moriarty

The sponsor was not directly involved in the design of the trial outside of the grant application review process. A funder will have no input into conduct, data analysis and interpretation, manuscript writing, or dissemination of results. A funder will not control the final decision regarding any of these aspects of the trial.

The protocol has been reviewed by service users through a Leeds Patient and Public Involvement in Research Group.

KEY WORDS: Antibiotic; Complicated intra-abdominal infection;

Duration, Pharmacodynamics, Relapse, Resistance.

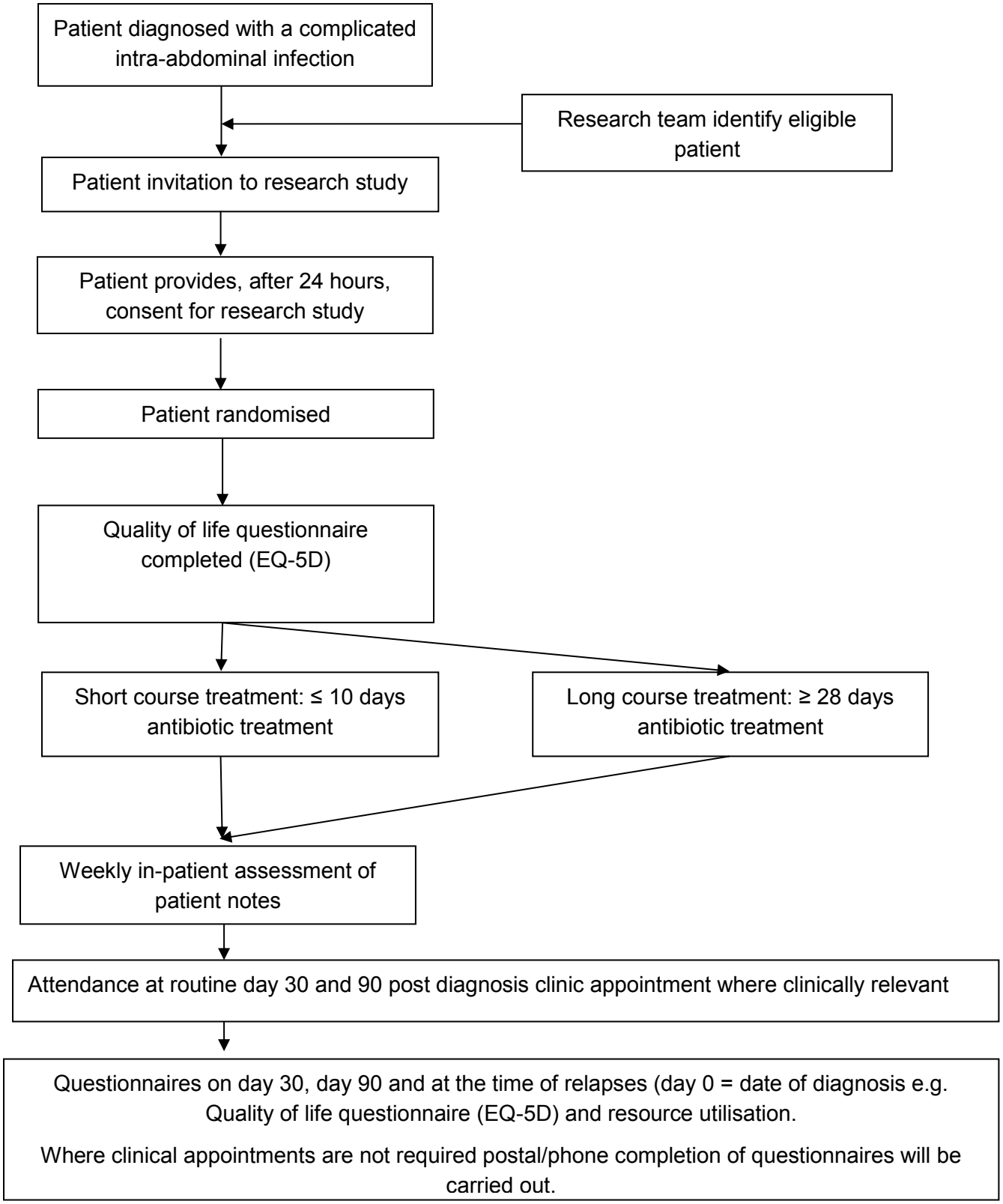
LIST of CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
BNF	British National Formulary
CA	Competent Authority
CDI	Clostridium difficile infection
CI	Chief Investigator
CABI	Complicated intra-abdominal infection
CRBSI	Catheter related blood stream infection
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	European Commission
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
IV	Intravenous

MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
NHS R&D	National Health Service Research & Development
NIMP	Non-Investigational Medicinal Product
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PO	Per Os (By mouth (oral))
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File

TRIAL FLOW CHART



STUDY PROTOCOL

The CABI trial: An unblinded parallel group randomised controlled feasibility trial of long course antibiotic therapy (28 days) compared to short course (≤10 days) in the prevention of Complicated intra-ABdominal Infection relapses in adults treated for Complicated intra-ABdominal Infection.

1 BACKGROUND

Complicated intra-abdominal infection (CABI) extends beyond the hollow viscus of origin into the peritoneal space and is associated with either abscess formation or peritonitis [Solomkin 2010]. CABIs are heterogeneous in aetiology and include spontaneous infections arising from a perforated viscus, including the stomach, biliary tree, colon, appendix and reproductive organs. In addition there are post-operative complications such as peritonitis, abscess, and failure of surgical anastomoses. CABIs are also heterogeneous in their characteristics. A recent review of organ space Surgical Site Infections (SSI-Os) after colorectal surgery demonstrated that infections were varied with regard their location, as well as size and number and nature of collections, and presence of an ongoing source e.g. anastomotic breakdown (Rothwell 2016). Despite the varied origin of these infections, there are similar management strategies which centre on the source control, e.g. drainage of intra-abdominal fluid collections, and administration of antibiotic therapy. CABIs are a common in-hospital clinical challenge, in part due to the varied pathology they are caused by, and are associated with significant morbidity and mortality (DeFrances 2005, Brun-Buisson 1995). Despite this burden of disease, there is little clinical evidence with which to base treatment on, even before taking account of their heterogeneous nature. One study of CABI following source control procedures evaluated a short course of antibiotics (4 days) compared to a course of up to 2 weeks after clinical and biochemical improvement (up to 10 days). Whilst there was little difference in outcomes, both groups had a high relapse rate of approximately 15%. In addition, it is common for source control procedures not to be completed in routine clinical practice, being completed in only 17% of Leeds patients with post-operative CABI (Rothwell 2016). In this Leeds data of post-operative CABIs, where source control rates are low relapse rates were 40% (Rothwell 2016). For CABI infections, standard UK management is variable and involves between 4 and 42 days' antibiotics. This indicates an unacceptably high relapse rate in patients treated for CABI where source control is and is not undertaken. We therefore propose to investigate if long course antibiotic therapy (28 days) is clinically more effective than short

course antibiotics (4 days) in preventing relapses of CABI. This study will include patients who have and have not undergone source control procedures which will be completed as per standard practice.

2 RATIONALE

Complicated intra-abdominal infections require source control when possible, e.g. a surgical procedure to remove an infection, and antibiotic therapy to obtain cure. Source control is not always possible. CABIs are associated with mortality and prolongation of hospitalisation. After apparently effective treatment, potentially including source control procedures and antibiotics, infections can relapse. There are a number of reasons for relapse; one is that antibiotic treatment may not have been given for long enough to eradicate the bacteria from, what should be, a sterile intra-abdominal cavity. Antibiotics are given until a patient is better, but not until all bacteria are eradicated, allowing them to regrow and re-start an infection. Standard antibiotic duration is variable: some doctors provide long courses and others short. We therefore want to compare durations, to see if longer courses of antibiotics are able to help prevent these relapses, or if shorter courses are as effective but have fewer side effects. We have not identified closely related strategies which may optimise the management of CABIs.

The research hypothesis is therefore: In patients with CABI, regardless of source control intervention, there will be a lower relapse rate when treated with 28 days of antibiotics compared to ≤10 days of antibiotics.

2.1 Assessment and management of risk

Risks: Standard practice with regarding the duration of antibiotic therapy is variable. Therefore there are not specific risks above normal clinical practice for this research study. The choice of antibiotic used in this study is within antibiotics those routinely used in NHS practice. The decision as to the use of a source control procedure is not altered by being involved in this study.

This trial has been categorised by the MHRA as: Not a CTIMP

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1 Primary objectives

To determine

- The willingness of participants to be randomised
- The willingness of clinicians to allow patients to be recruited
- The number of eligible patients
- Follow up rates

3.2 Secondary objectives

A full study which may follow this feasibility study would have clinical objectives as primary and secondary objectives. In order to determine the feasibility of collecting data relevant to these clinical objectives, e.g. rate of relapse, we have included these objectives within the secondary objectives. We do not include them as true objectives in the sense that we anticipate obtaining evidence relevant to the objective e.g. we do not expect to demonstrate that different treatment strategies are associated with different rates of relapse.

To reduce the rate of relapse after treatment of complicated intra-abdominal infection.

To reduce the rate of all infections after treatment of complicated intra-abdominal infection;

To reduce the rate of antibiotic consumption;

To reduce length of hospital stay after diagnosis of complicated intra-abdominal infection;

To reduce mortality after treatment of complicated intra-abdominal infection

To reduce rates of complications from antibiotic therapy including Clostridium difficile infection (CDI) diarrhoea and catheter-related blood stream infection (CRBSI);

To reduce the number of source control procedures required for the management of CABI;

To improve quality of life after treatment of complicated intra-abdominal infection;

To reduce the cost of healthcare treatment associated with treatment of complicated intra-abdominal infection.

3.3 Outcome measures

3.31 Primary outcomes

Screening logs, recruitment rates and follow up rates will be recorded to determine the feasibility of performing a larger study.

3.32 Secondary endpoints/outcomes

Relapse (definite or probable CABI relapse) of complicated intra-abdominal infection within 90 days of diagnosis of primary CABI.

Primary CABI: The diagnosis of a definite CABI will be assigned with:

- A combination of radiological AND clinical features consistent with CABI including a fluid collection or perforated viscus, a temperature of ≥38 degrees and a neutrophilia (neutrophil count > 7.5 x 10*9/L), or
- Intra-operative confirmation of an abscess
- Day 0: The first day of infection will be defined as the first day effective antibiotic therapy was initiated for the treatment of CABI. This date may precede the day the CABI was confirmed radiologically. Effective therapy will be considered not to be on going if microbiological results suggest antibiotic resistance and there is at the same time clinical failure to antibiotic therapy.

Relapse CABI:

- A relapse can only occur after surgical and antibiotic therapy to manage the primary CABI has been considered successful. This will normally be demonstrated by antibiotics being stopped and no further source control procedures planned.
- The diagnosis of a definite CABI relapse will be assigned with:
    - A combination of radiological AND clinical features consistent with CABI including a fluid collection, a temperature of ≥38 degrees and a neutrophilia (neutrophil count > 7.5 x 10*9/L)
    - Intra-operative confirmation of an abscess, or
- The diagnosis of a probable CABI relapse will be assigned when:
    - In the absence of radiological imaging, but where no other source of infection was identified, and the patient was managed for a relapsed CABI.

All infections within 90 days of CABI diagnosis.

Days of antibiotic therapy within 90 days of antibiotic therapy.

Length of hospital stay within 90 days of diagnosis of a CABI.

Total days of hospitalisation within 90 days of diagnosis.

90 day mortality after diagnosis of CABI.

Adverse events of CDI and CRBSI within 90 days of CABI diagnosis.

Number of source control procedures required for the management of CABI within 90 days of CABI diagnosis.

Quality of life scores (EQ-5D) at time of diagnosis of CABI, 30 and 90 days post diagnosis of a CABI, as well at the times of relapses.

Costs of healthcare treatment within 90 days after diagnosis of CABI.

4 TRIAL DESIGN

An unblinded parallel group randomised controlled feasibility trial of long course antibiotic therapy (28 days) compared to short course (≤10 days) in the prevention of Complicated intra-ABdominal Infection relapses in adults treated for Complicated intra-ABdominal Infection. The choice of antibiotic will be decided by the clinical team caring for the patient; hence the trial compares strategies of antibiotic prescribing (i.e. short course vs long course) rather than individual drugs or specified combinations of drugs. The antibiotic prescribed will be chosen according to the available clinical and microbiological data, in conjunction with local antibiotic guidelines, and will be altered according to good clinical care as new results and clinical information become available. During the study period, a clinician with specialist training in infection will provide consultation as needed to select antibiotics and advise on management.

5 STUDY SETTING

Leeds Teaching Hospitals NHS Trust

Interventions will be carried out by the following staff

- Recruitment and allocation: Research nurse and research doctor.
- Informed consent and eligibility will be requested and carried out by a medically qualified doctor. Research nurses will not be permitted to request consent.
- Intervention: Antibiotic duration will be dictated by randomisation.
- Outcome data collection: Research nurse or research doctor.

6 ELIGIBILITY CRITERIA

This study is pragmatic as it is intended that the intervention would be applied to all patients with CABI without there being restrictive eligibility criteria.

6.1 Inclusion criteria

- Age: Adults >18 years
- Capable of giving informed consent
- No practical or clinical barriers to consuming 28 days of antibiotic therapy, which may include consumption of antibiotics at home.

6.2 Exclusion criteria

Patients will be excluded if they have:

- a CABI diagnosed within the previous year
- their CABI was diagnosed >6 days prior to screening
- primary appendicitis
- intra-abdominal infection associated with pancreatitis, pelvic inflammatory disease, primary (spontaneous) bacterial peritonitis (SBP), continuous ambulatory peritoneal dialysis peritonitis (CAPD peritonitis) and *Clostridium difficile* infection.
- Concurrent infection requiring more than ten days of therapy.
  These criteria intend to ensure:
- we are studying primary episodes of CABI
- that the cases included are not biased towards more complicated cases
- we exclude primary appendicitis for which good data already exists
- In the case of necrotising pancreatitis, SPB and CAPD peritonitis these pathologies are excluded as they consist of a discrete disease process.
- Infection with a highly resistant bacterium such that antibiotic treatment is considered to be a significantly sub-optimal by the treating microbiologist e.g. multi-resistant carbapenemase producing Entrobacteriacea.

Clarifications of which infections are to be included and excluded from CABI are provided below.

Included conditions	Excluded conditions
Post-operative surgery CABI including colorectal (including appendiceal), biliary, small bowel and gastric surgery (including iatrogenic perforations) e.g. peri-anastomotic abscess.	Uncomplicated cholecystitis/cholangitis/gall bladder empyema (no perforation or extra-biliary abscess)
Gastrointestinal fistula communicating with the peritoneal space	Skin and soft tissue infection/abscess not communicating with the peritoneal space
Oesophageal rupture into the peritoneal space & perforated duodenal/gastric ulcer	Spontaneous bacterial peritonitis & continuous ambulatory peritoneal dialysis
Ischaemic bowel and volvulus with perforation	Primary complicated or uncomplicated appendicitis managed surgically.
Perforations associated with malignancies	Intraabdominal infection associated with pancreatitis
Complicated diverticulitis & perforated Meckel's diverticulum	Pelvic inflammatory disease
CABI secondary to inflammatory bowel disease pathology	Adnexal abscess without communication to the peritoneal cavity
Primary complicated appendicitis managed conservatively	Clostridium difficile colitis with perforation (long course antibiotics unlikely to be acceptable for this group
Renal/Adrenal/Liver/Spleen abscess communicating with the peritoneal cavity.	
Adnexal abscess communicating with the peritoneal cavity	

6.3 Removal from the study

Clinicians will be free to prescribe antibiotics after the planned treatment duration has elapsed if their clinical assessment supports such a prescription. For example, the patient may develop a new infection. They will also be able to stop antibiotics if there is a clinical indication, for example, a patient may have an allergy or other adverse event to an antibiotic. These patients may therefore have their assigned intervention modified. This will not result in these patients being removed from the study, they will instead be assessed on an intention-to-treat basis.

Haematological or biochemical abnormalities at the end of assigned treatment duration will not be sufficient basis to withdraw a patient from an assigned duration of therapy.

7 TRIAL PROCEDURES

Schedule of procedures: Appendix 2.

7.1 Recruitment

Participants who are screened for trial entry and are not randomised will have data collected for Consolidated Standards of Reporting Trials (CONSORT) reasons to allow reporting of the generalisability of the results. Anonymised information on participants who are not randomised for will include: Age, Gender, Charlson's co-morbidity index, site of origin of CABI, underlying pathology, admitted to HDU/ITU, perforated viscus at onset of CABI, whether the patient is registered or not registered, the reason not eligible for trial participation, or if they are eligible but declined and the reason for declining.

7.1.1 Patient identification

Participant eligibility screening process.

Patients will be identified for trial entry by a number of methods including:

- Notification by a member of the patient's clinical team, to the research team, a patient has been diagnosed with a CABI. This is only expected to happen after the patient has been seen whilst an in-patient.
- Identification by a member of the patient's clinical team that a patient has a CABI by reviewing clinical notes or radiological reports.

Initial approach: The member of staff making the initial approach will be involved in the care of the patient. Eligibility will be confirmed by a medical practitioner.

7.1.2 Screening

No non-routine (non-clinically indicated) tests will be required for study entry.

CT scans completed as part of routine care will contribute to the diagnosis of CABI.

7.1.3 Stratification

Patients with each intervention arm will be stratified into two groups on a 1:1 basis

- Post-operative CABIs (CABI within 90 days of surgery)
- Non post-operative CABIs

Each intervention arm will therefore contain 15 post-operative CABIs and 15 non-post operative CABIs.

No ordering of patient recruitment to these groups is required

7.2 Consent

The Principal Investigator (PI) retains overall responsibility for the informed consent of participants at their site and will ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki.

Delegation of consent:

Informed consent will be obtained prior to the participant undergoing procedures specifically for the purposes of the trial.

The right of a participant to refuse participation without giving reasons will be respected.

The participant will remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment. They will be provided with a contact point where he/she may obtain further information about the trial.

The PI takes responsibility for ensuring that all vulnerable subjects are protected and participate voluntarily in an environment free from coercion or undue influence.

The consenting protocol:

- There will be discussion between the potential participant and an individual knowledgeable about the research - its nature and objectives and the possible risks associated with their participation.
- The presentation of written material (invitation letter, patient information leaflet and consent form [approved by the REC and in compliance with GCP], local regulatory requirements and legal requirements) will be given to potential participants.
- There will be an opportunity for potential participants to ask questions.
- There will be an assessment of capacity. Participants must be capable of giving consent for themselves. A capable person will:
    - understand the purpose and nature of the research
    - understand what the research involves, its benefits (or lack of benefits), risks and burdens
    - understand the alternatives to taking part
    - be able to retain the information long enough to make an effective decision
    - be able to make a free choice

- be capable of making this particular decision at the time it needs to be made (though their capacity may fluctuate, and they may be capable of making some decisions but not others depending on their complexity)
- where participants are capable of consenting for themselves but are particularly susceptible to coercion, it is important to explain how their interests will be protected

Where a participant is able to consent but later becomes incapacitated the participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected, or any other research procedures carried out on or in relation to the participant.

The full consent process will be documented in the patient's medical record along with a copy of the signed consent form and Patient Information Sheet. A further copy of the consent form will also be provided to the patient. The original consent form will be maintained in the TMF.

7.3 The randomisation scheme

Simple randomisation with a 1:1 allocation ratio will be used to allocate patients.

7.3.1 Method of implementing the allocation sequence

The allocation sequence will involve:

- Generation of an unpredictable allocation sequence
- Concealment of that sequence until assignment irreversibly occurs

A web-based randomisation/treatment allocation system will be used.

- The allocation system will provide sealed envelopes to be accessed upon a decision to allocate a participant to a treatment arm.
- Sixty patients will be randomised equally to the control or intervention arm by generating four lists of random numbers using an online sequence generator (https://www.random.org/sequences/) (list 1/2: post-operative patients-control and intervention, list 3/4, non post-operative patients, control and intervention). A person not associated with the study will generate these lists. Sealed envelopes containing labels with 'control' or 'intervention' will be designated with numbers generated by the above sequence generator.
- Patients will be randomised after providing their consent to participate in the study.

- A copy of allocation information will be documented in the patients' notes.

7.4 Baseline data

Data required prior to being eligible for study entry include:

- Full blood count demonstrating the patient has elevated neutrophils.
- CT scan with radiology reports being consistent with a CABI.
- Both the CT scan and full blood count will be undertaken as part of routine clinical practice and are not therefore trial specific procedures.

7.5 Trial assessments

Baseline assessment-Visit 1-In patient within 2 days of recruitment

- Medical/surgical history
- Antibiotic history
- QofL assessment

Weekly assessments-Visit 2a, 2b, etc. In-patient only (7days +/-3 days)

- Medical/surgical history
- Antibiotic history

Questionnaires-"Visit" 3

- QofL assessment: day 30, day 90 and at time of relapse where possible
- By post or in-person.**

Final assessment-Visit 4-In-patients or surgical clinic/home (day 90 +/- 10 days)

- Medical/surgical history
- Antibiotic history
- Resource utilisation questionnaire

**= Day 30/90 assessments will occur at the time of routine clinic appointments where possible, or via post/phone as required.

Schedule of procedures

Procedures	Screening	Baseline Within 2 days of recruitment	Treatment Phase Weekly (+/- 3 days) assessments whilst an in-patient	Questionnaires Day 30, 90 and at relapse where possible	Final visit Day 90 (+/- 10 days)
Informed consent	x	Visit 1	Visit 2a,2b etc.	Visit 3	Visit 4
Demographics		x			
Medical history	x	x	x		x
Physical examination					
Vital signs					
CT scan	x				
Concomitant medications		x	x		x
Eligibility assessment	x				
Randomisation	x				
Dispensing of trial drugs			x		
Adverse event assessments			x		x
Compliance with intervention			x		x
Questionnaires		x		x	

7.6 Long term follow-up assessments

None

7.7 Withdrawal criteria

It is always within the remit of the physician responsible for a patient to amend a patient's treatment based on clinical need.

Subjects will be not be withdrawn from the study if their treatment is amended but followed up and analysed on an intention to treat basis.

7.8 Safety assessment and stopping treatment

Standard NHS processes will be undertaken to monitor the safety of patients.

Treatment will be stopped according to the research protocol for participants, but clinicians will not be restricted from initiating antibiotics, according to their assessment of clinical need, at any time for a participant not receiving antibiotics.

7.9 End of trial

The date of the last visit of the last patient undergoing the trial is the trial end definition.

The PI will notify the REC at the end of the trial within 90 days of its completion or within 15 days in the event of early termination.

8 TRIAL MEDICATION

8.1 Name and description of medicinal product(s)

Antibiotics for the treatment of CABI.

The choice of antibiotic will be that of the treating physicians.

A list of recommended antibiotics will be provided as not all antibiotics are likely to be effective for complicated intra-abdominal infection. This list will be comprehensive but not exhaustive. Treating physicians will not be restricted to the list of recommended antibiotics.

Antibiotics must be used within their licenced indications. All will be antibiotics routinely used in the NHS (within the British National formulary (BNF)). Recommended regimens will provide antibacterial activity against Gram positive, Gram negative and anaerobic bacteria. Where antibiotic susceptibilities of bacteria believed to be causing CABI are available, these should be considered in the choice of antibiotic.

The recommended antibiotic list is:

1- Amoxicillin (or glycopeptide/linezolid), ciprofloxacin and metronidazole
2- Amoxicillin (or glycopeptide/linezolid), aztreonam and metronidazole
3- Amoxicillin (or glycopeptide/linezolid), gentamicin and metronidazole
4- Amoxicillin-clavulanic acid (+/-glycopeptide/linezolid)
5- Piperacillin—tazobactam
6- Cefuroxime and metronidazole
7- Ertapenem (+/- glycopeptide/linezolid)
8- Meropenem (+/- glycopeptide/linezolid)
9- Tigecycline (+/-ciprofloxacin)

British National Formulary recommended doses are required in this study. The standard doses of the recommended antibiotics are:

Amoxicillin 1g IV or PO 8 hourly

Ciprofloxacin 400mg IV 12 hourly or 500mg PO 12 hourly

Amoxicillin-clavulanic acid 1.2g IV 8 hourly (not recommended orally)

Cefuroxime 1.5 grams IV 8 hourly
Metronidazole 400mg PO 8 hourly or 500mg IV 8 hourly
Aztreonam 1g IV 8 hourly
Tigecycline 100mg loading dose followed by 50mg 12 hourly IV.
Ertapenem 1g IV 24 hourly
Meropenem 1g IV 8 hourly
Piperacillin-tazobactam 4.5g IV 8 hourly
Linezolid 600mg IV or PO 12 hourly
Glycopeptides/Aminoglycosides: Dosed according to renal function and therapeutic drug monitoring results.

8.2 Legal status of the drugs

Licensed in the UK

8.3 Summary of Product Characteristics (SmPC)

As a non CTIMP study using standard treatments SmPCs are not provided.

8.4 Drug storage and supply

As per standard NHS storage and supply procedures.

8.5 Preparation and labelling of Medicinal Product

As per standard NHS preparation and labelling.
Trial-specific labelling is not required where the MP:
• has a marketing authorisation in the UK, and
• is being used within the terms of its marketing authorisation, and
• is dispensed to a trial participant in accordance with a prescription given by an authorised healthcare professional and is labelled in accordance with the requirements of Schedule 5 to the Medicines for Human Use (SI 1994/3194) (Marketing Authorisations Etc) Regulations 1994 that apply in relation to dispensed relevant medicinal products.

8.6 Dosage schedules

Dosing regimens will be devised by treating clinicians with the exception of the duration of therapy.

8.7 Dosage modifications

Modifications as per standard NHS practice.

8.8 Known drug reactions and interaction with other therapies

Treating clinicians will be responsible for assessing treatment reactions and interactions.

8.9 Concomitant medication

Not applicable.

8.10 Trial restrictions

No trial restrictions have been set.

8.11 Assessment of compliance

A compliance check will be carried out and documented at each in-patient visit by assessing patient's drug charts. No routine outpatient assessments are planned before the end of study visit. An end of study out-patient visit will include a compliance check on antibiotic consumption through discussion with the participant to quantitatively estimate antibiotic consumption. Compliance (or non-compliance) checks will be documented on case report forms.

9 PHARMACOVIGILANCE

Pharmacovigilance procedures for this trial are based on this study being classified as a CTIMP. These procedures will be modified if the study is not classified as a CTIMP.

9.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically-qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if

	they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product • in the case of any other medicinal product, in the investigator's brochure (IB) relating to the trial in question

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

9.2 Operational definitions

(S)AEs, (S)ARs and SUSARs will be defined according to standard definitions, section 9.1.

9.3 Recording and reporting of (S)AEs, (S)ARs AND SUSARs

SAEs, S(AR)s and SUSARS will be recorded on case report forms.

AEs will not be reported to the sponsor. AEs will not be recorded on case report forms.

SAEs will be reported to the sponsor, except for specific exemption, via e-mail (governance-ethics@leeds.ac.uk) using a form provided by the sponsor with 24 hours of the research team becoming aware of the event. SAEs which are exempt form reporting to the sponsor are those which occur commonly in this patient population. The reason for this is that it is not possible to determine if an event which is common is related to a study intervention. SAE exemptions are:

- Infections including surgical wound infections, respiratory, urinary and skin infections (including fungal infections).
- Failure of a surgical procedure-specifically anastomotic breakdown or development of a fistula.
- Deterioration of the existing condition specifically progression of a cancer.
- Treatment which was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition, e.g. pre-planned hip replacement operation which does not lead to further complications.
- Any admission to hospital or other institution for general care where there was no deterioration in

condition.

ARs will not be reported to the sponsor. ARs will not be recorded on case report forms.

SARs will be reported to the sponsor, except for specific exemptions, via e-mail (governance-ethics@leeds.ac.uk) using a form provided by the sponsor with 24 hours of the research team becoming aware of the event. The exemptions to SAR reporting are because this is a trial using antibiotics within their licensed indications at standard doses with well documented adverse reaction profiles. SARs will not be reported to the sponsor if reporting will not improve the knowledge regarding the safety profile of the drug, i.e. if the event or reaction is listed as known event within the drug's Summary of Product Characteristics.

SUSARs will be reported to the sponsor, except for specific exemptions, via e-mail (governance-ethics@leeds.ac.uk) using a form provided by the sponsor with 24 hours. All SAEs assigned by the PI or delegate (or following central review) as both suspected to be related to MP-treatment and unexpected will be classified as SUSARs and will be reported to the Medicines and Healthcare Products Regulatory Agency (MHRA) via the yellow card scheme.

The period of time over which ARs, SAEs, SARs and SUSARs may be recorded starts at the date of consent and finishes at 90 days post initiation of CABI treatment.

The period of time over which SAEs, SARs and SUSARs may be reported starts at the date of consent and finishes at 90 days post initiation of CABI treatment.

All **SAEs* / SUSARs** occurring from the time of **randomisation** until 90 days post diagnosis of CABI must be recorded on the appropriate sponsors SAE reporting form. Where they are to be reported to the sponsor, they will be e-mailed to the sponsor within 24 hours of the research staff becoming aware of the event. Once all resulting queries have been resolved, the sponsor will request the original form should also be posted to the Sponsor and a copy to be retained on site.

For each **SAE / SAR/ SUSAR** the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to trial drug / investigation), in the opinion of the investigator
- whether the event would be considered expected or unexpected.

Any change of condition or other follow-up information should be faxed to the Sponsor as soon as it is available, or at least within one working day of the information becoming available. Events will be followed up until resolved or a final outcome reached.

9.4 Responsibilities

Principal Investigator (PI):

Checking for AEs and ARs when participants attend for treatment / follow-up.

1. Using medical judgement in assigning seriousness, causality and expectedness using the Reference Safety Information approved for the trial. The reference information sheet for the trial is each drugs SmPC.
2. Ensuring that all SAEs and SARs (including SUSARs) are recorded and reported to the sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs and SARs (including SUSARs) are chased with Sponsor if a record of receipt is not received within 3 working days of initial reporting.
3. Ensuring that ARs are recorded and reported to the Sponsor in line with the requirements of the protocol.

Chief Investigator (CI) / delegate or independent clinical reviewer:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.
3. Using medical judgement in assigning expectedness.
4. Immediate review of all SUSARs.

Trial Steering Committee (TSC):

In accordance with the Trial Terms of Reference for the TSC.

9.5 Notification of deaths

Death is considered as an SAE and will be reported to the sponsor in line with SAE reporting.

9.6 Pregnancy reporting

Where pregnancy is relevant to an antibiotic being recommended as an IMP e.g. caution for use, the clinical care team responsible for the patient will be informed and asked to determine a participant's pregnancy status (to determine a participant is not pregnant) before being administered the IMP.

Participants will be asked to report to the research team if they become pregnant during treatment.

9.7 Overdose

Overdosing will be notified to the sponsor within 24 hours of the research staff becoming aware of the event. Overdosing will be documented on the sponsors protocol deviation form.

Overdosing is an unexpected event in this study. Overdosing would not result in a participant being removed from the study for analysis purposes. A patient's treating clinician would be responsible for managing the antibiotic regimen in such a patient.

9.8 Reporting urgent safety measures

If any urgent safety measures are taken, the CI/Sponsor shall immediately, and in any event no later than 3 working days from the date the measures are taken, inform the relevant REC of the measures taken and the circumstances giving rise to those measures. Urgent Safety Measures will be sent to the MHRA via the yellow card scheme in addition to the REC

9.9 The type and duration of the follow-up of subjects after adverse events.

Follow-up care for subjects after an adverse drug reaction will be one week.

Adverse events will be identified by review of patient's medical notes.

9.10 Development safety update reports

The CI will not provide DSURs.

10 STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation

This study is a feasibility study to determine:

- the willingness of participants to be randomised
- the willingness of clinicians to recruit participants
- the number of eligible patients available to be recruited
- follow-up rates
- practicalities related to the trial.

Participants who leave the trial will not be replaced. We are not intending to estimate size of effects with any pre-defined accuracy therefore no formal sample size calculation has been performed.

10.2

Planned recruitment rate

We aim to recruit one to two patients per week over a one to two year period.

10.3 Statistical analysis plan

10.3.1 Summary of baseline data and flow of patients

Baseline data will be summarised in table format.

Flow of patients will be presented in a flow diagram.

10.3.2 Primary outcome analysis

Outcomes will be assessed as proportions.

10.3.3 Secondary outcome analysis

Outcomes will be assessed as proportions or means as appropriate.

Intention to treat and per protocol analyses will be completed.

Analysis of outcomes at 60 days post treatment will be compared to outcomes at 90 days post initiation of treatment where possible.

10.4 Subgroup analyses

Outcomes will be stratified by source control intervention used therapeutically for the management of the primary CABI. The definition of source control used for this study will be: any procedure that stops the ongoing contamination of the peritoneal cavity and removes the majority of the contaminated intraperitoneal contents to the extent that no further acute interventions are felt to be necessary. Depending on the site and origin of the infection, multiple techniques could be satisfactory to obtain source control. Acceptable procedures might include simple drainage via open, laparoscopic, or percutaneous means, repair of a perforated viscus, resection and primary re-anastomosis of a perforated viscus, resection of a perforated viscus and proximal diversion, or proximal diversion without resection as long as adequate drainage is obtained. The adequacy of source control for any given patient will be determined by the local surgeon as adequate or inadequate.

Outcomes will be stratified by the CABI being assigned as a post-operative CABI and non post operative CABI

10.5 Adjusted analysis

Not applicable

10.6 Interim analysis and criteria for the premature termination of the trial

An interim analysis will not be performed.

10.7 Subject population

Subject populations whose data will be subjected to the study analysis are: Protocol-compliant population: Any subject who was randomized and received the protocol required study drug exposure and required protocol processing.

10.8 Health economics evaluation

A healthcare utility tool, the EQ-5D, will be used to estimate quality adjusted life years (QALYs-area under the curve analysis) for individual participants. This will allow the healthcare utility of the two interventions, short course and long course antibiotics, to be compared. Baseline patient characterises will be obtained to allow for baseline differences in QALYs to be controlled. The QALY will be the primary outcome measure within the economic evaluation. The EQ-5D will be determined at the start of the study, at day 30, day 90 and where possible at the time of relapses. Secondary outcome measures within the economic evaluation will be healthcare costs including: Length of hospital stay, surgical procedures, antibiotic costs, intravenous access costs, nights in critical care and nights on a ventilator. The costs of these healthcare activities will be determined using the following resources: www. www. www. The health economics evaluation will be carries out according to the NICE guidance on economic evaluation: https://www.nice.org.uk/process/pmg4/chapter/incorporating-health-economics

Days in hospital, high dependency units, and surgical interventions will be measured to estimate economic impact. Formal health economics advice is being requested.

11 DATA HANDLING

11.1 Data collection tools and source document identification

Data collection will be by paper case report forms (CRFs).

Records of all participating patients (sufficient information to link records e.g., CRFs, hospital records and samples), all original signed informed consent forms and copies of the CRF pages will be kept. Records will be stored in a locked room at the Old Medical School, Leeds General Infirmary, Leeds.

All research forms will be labelled with a patients study number.

11.2 Data handling and record keeping

- Data entry: Data will be added to an excel database stored on Leeds Teaching Hospitals NHS Trust. Access to trust computers is password protected.
- Data will be stored on a central server that is backed up.
- A data quality audit will be completed during and at the end of the study.

- Data will be stored on paper.
- Data will be pseudonymised.
- Data entry will be by a clinical researcher (clinical research nurse or research doctor).
- The PI will be responsible for data entry, quality and analysis.
- Arrangements to pseudonymise the data: Data (case report forms) will be given a study number at the time of collection. A database linking study numbers to patients will be created and be separate to the data. Both paper and electronic records will be kept as part of a data disaster recovery plan.
- Pseudonymised data will be analysed on the University of Leeds computer system, which is password protected. Data will be stored centrally.

11.3 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

11.4 Archiving

- Archiving will be authorised by the Sponsor following submission of the end of study report.
- The research group will be responsible for archiving all research data collected.
- Paper archiving will be for 5 years from the end of the study and be based in a locked room in the Old Medical School, Leeds General Infirmary.

12 MONITORING, AUDIT & INSPECTION

- Any authorised body will be supported by the trial site in monitoring the study. These may include providing information for remote monitoring, or putting procedures in place to monitor the study internally.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Research Ethics Committee (REC) review& reports

- Before the start of the trial, approval will be sought from a REC for the trial protocol, informed consent forms and other relevant documents.
- Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the study (and/or NHS R&D departments before they can be implemented in practice at sites).
- All correspondence with the REC will be retained in the Trial Master File/Investigator Site File.
- An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended.
- It is the Chief Investigator's responsibility to produce the annual reports as required.

- The Chief Investigator will notify the REC of the end of the study.
- If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.
- Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

13.2 Peer review

Peer review has been completed by Dr Jon Sandoe, Consultant Microbiologist, Leeds Teaching Hospitals NHS Trust and Matthew Scarborough, Oxford University Hospitals.

13.3 Public and Patient Involvement

PPI assessment has been undertaken in collaboration with Leeds Patient and Public Involvement Group. This has resulted in clarifications/amendments to the protocol e.g. criteria for leaving the trial.

13.4 Regulatory Compliance

- The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments
- Before any site can enrol patients into the trial, the Chief Investigator/Principal Investigator or designee will apply for NHS permission from the site's Research & Development (R&D) department
- For any amendment that will potentially affect a site's NHS permission, the Chief Investigator/ Principal Investigator or designee will confirm with that site's R&D department that NHS permission is ongoing (note that both substantial amendments, and amendments considered to be non-substantial for the purposes of REC may still need to be notified to NHS R&D)

13.5 Protocol compliance

- Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used, e.g. it is not acceptable to enrol a subject if they do not meet the eligibility criteria or restrictions specified in the trial protocol.
- Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

13.6 Notification of Serious Breaches to GCP and/or the protocol

A "serious breach" is a breach which is likely to affect to a significant degree

(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial.

- The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase

13.7 Data protection and patient confidentiality

All investigators and trial site staff will comply with the requirements of the Data Protection Act 1998 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

This includes:

The creation of coded, depersonalised data where the participant's identifying information is replaced by an unrelated sequence of characters.

Secure maintenance of the data and the linking code in separate locations using encrypted digital files within password protected folders and storage media.

Limiting access to the minimum number of individuals necessary for quality control, audit, and analysis.

The PI is the data custodian.

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

None to declare

13.9 Indemnity

The University of Leeds is providing**:**

1. Insurance and/or indemnity to meet the potential legal liability of the sponsor for harm to participants arising from the management of the research.
2. Insurance and/or indemnity to meet the potential legal liability of the sponsor or employer for harm to participants arising from the design of the research.

The NHS is providing:

3. Insurance and/or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research.

The sponsor has not made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises.

13.10 Amendments

All amendments must be sent to the sponsor's office that will be responsible for classifying the amendment as substantial or non-substantial and directing the research team as to which authorities the amendment should be submitted.

An amendment history will be maintained in the trial master file.

13.11 Post trial care

No post trial care is planned, or relevant to this trial.

13.12 Access to the final trial dataset

The trial management and data (safety) monitoring group will have access to the final data set.

14 DISSEMINIATION POLICY

14.1 Dissemination policy

Consort Guidelines will be reviewed prior to generating any publications for the trial to ensure they meet the standards required for submission to high quality peer-reviewed journals.

The data will be owned by The University of Leeds.

On completion of the trial, the data will be analysed and tabulated and a Final Study Report prepared where the full study report can be accessed

We plan to notify the participants of the outcome of the trial by provision of the publication and via a specifically designed newsletter.

14.2 Authorship eligibility guidelines and any intended use of professional writers

Authorship will include:

On the final trial report: The Trial Steering Committee

For individually named authors: According to The International Committee of Medical Journal Editors' definitions for authorship criteria for manuscripts submitted for publication.

15 REFERENCES

Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis. 2010;50(2):133-64.

Rothwell A, Burke D, Burnside G, Kirby A. Characteristics of Organ Space Surgical Site Infection after colorectal surgery. In preparation.

DeFrances CJ, Cullen KA, Kozak LJ. National Hospital Discharge Survey:2005 annual summary with detailed diagnosis and procedure data. VitalHealth Stat 13 2007; 165:1–209.

Brun-Buisson C, Doyon F, Carlet J, et al. Incidence, risk factors, and outcome of severe sepsis and septic shock in adults: a multicenter prospective study in intensive care units. French ICU Group for Severe Sepsis. JAMA 1995; 274:968–74.

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007; 370: 1453–1457.

Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 2009; 338: b2393.

16. APPENDICIES

16.1 Appendix 1-Risk

Risks associated with trial interventions: LOW ≡ Comparable to the risk of standard medical care				
Justification: Briefly justify the risk category selected and your conclusions below (where the table is completed in detail the detail need not be repeated, however a summary should be given): Both intervention arms are within standard practice.				
What are the key risks related to therapeutic interventions you plan to monitor in this trial?		How will these risks be minimised?		
IMP/Intervention	Body system Hazard Likelihood	Activity (mitigation)	Frequency	Comments
Antibiotic (all)	Gastrointestinal tract Clostridium difficile associated diarrhoea Low	Standard NHS monitoring/ precautions	Continuous	
Intravenous antibiotic	Vascular Venous catheter infection Low	Standard NHS monitoring/ precautions	Continuous	
Allergy	All Rash-Anaphylaxis Low	Standard NHS monitoring/ precautions	Continuous	
Antibiotic (all)	All Various drug side effects, cautions, contra-indications and interactions as detailed in each drugs summary of product characteristics/ British National Formulary	Standard NHS monitoring/ precautions	Continuous	

	Low			
Outline any other processes that have been put in place to mitigate risks to participant safety: MHRA assessment of the trial protocol Trial oversight committees Independent protocol review National Research Ethics Committee Review				

16.3 Appendix 2 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made