FULL TITLE OF THE TRIAL

The EXTEND trial: Fixed-extended-duration antibiotics (28 days) compared to standard care antibiotic durations in adult patients with complicated intra-abdominal infection and their impact on treatment failure-a phase III multicentre, open label, two-arm, parallel group, pragmatic, randomised controlled trial with internal pilot.

SHORT TRIAL TITLE

The EXTEND trial: EXTENDed antibiotic durations compared to standard antibiotic durations for patients with complicated intra-abdominal infection.

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

RESEARCH REFERENCE NUMBERS

- IRAS: 302989
- Funders Number: NIHR131784

TRIAL REGISTRY NUMBER AND DATE

- International Standard Randomised Controlled Trial Number Register (ISRCTN): ISRCTN72819021
- Clinicaltrials.gov: NCT05148702

PROTOCOL VERSION NUMBER AND DATE

- Version: 1.2
- Date: 23.5.2022

SPONSOR

- The University of Leeds

This study/project is funded by the NIHR [Funders Number: NIHR131784. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended. I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor. I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: Not required Date: N/A

Name (please print): N/A

Position: N/A

Chief Investigator:

Signature:  Date: 07/06/2022

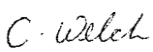
Name: ANDREW KIRBY

Chief Investigator:

Signature:  Date: 07/06/2022

Name: DERMOT BUIRKE

Statistician:

Signature:  Date:07/06/2022

Name: CHARLIE WELCH

KEY TRIAL CONTACTS

Chief Investigators	Andrew Kirby 0113 3923929 a.kirby@leeds.ac.uk	Dermot Burke 0113 392 3465 d.burke@leeds.ac.uk
Trial manager	Ms Lesley Sinclair 01904 324158 lesley.sinclair@york.ac.uk	
Trial Co-ordinator	Dr Catherine Knowlson 01904 325878 catherine.knowlson@york.ac.uk	
Sponsor	University of Leeds 0113 3434897 Clare Skinner: governance-ethics@leeds.ac.uk	
Funder	National Institute for Health and Care Research (NIHR)_ Health Technology Assessment funding scheme	
Clinical Trials Unit	York Clinical Trials Unit	
Key Protocol Contributors	Dr Shadia Ahmed, Mr Dermot Burke, Dr Rebecca Harmston, Professor Catherine Hewitt, Dr Andrew Kirby, Dr Catherine Knowlson, Professor Thomas Pinkney, Miss Olivia O'Connor, Dr Tamas Szakmany, Dr Puvan Tharmanathan, Dr Armando Vargas-Palacios, Mr Charlie Welch	
Statistician	Mr Charlie Welch	
Health economics	Armando Vargas-Palacios	
Committees	Trial Steering Committee (TSC) Committee chair: Professor Graeme MacLennan	
	Data Monitoring and Ethics Committee (DMEC) Committee chair: Andrew Cohen	
	Trial Management Committee (TMG) Committee chairs: Dr Andrew Kirby and Mr Dermot Burke	
	End point committee Committee contact: Dr Andrew Kirby	
Associate PI Scheme contacts	CTU API champion: Dr Catherine Knowlson API ambassador: Dr Shadia Ahmed	

i. LIST of CONTENTS

GENERAL INFORMATION	Page No.
TITLE PAGE	1
RESEARCH REFERENCE NUMBERS	1
SIGNATURE PAGE	2
KEY TRIAL CONTACTS	3
i. LIST of CONTENTS	4
ii. LIST OF ABBREVIATIONS	6
iii. TRIAL SUMMARY	8
iv. FUNDING	10
v. ROLE OF SPONSOR AND FUNDER	10
vi. ROLES & RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITTEES, GROUPS AND INDIVIDUALS	10
vii, PROTOCOL CONTRIBUTERS	12
viii. KEYWORDS	12
ix. TRIAL FLOW CHART	13
SECTION	
1. BACKGROUND	14
2. RATIONALE	15
3. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS	16
4. TRIAL DESIGN	22
5. TRIAL SETTING	24
6. PARTICIPANT ELIGIBILITY CRITERIA	24
7. TRIAL PROCEDURES	26
8. TRIAL STRATEGIES	30
9. PHARMACOVIGILANCE	32

10. STATISTICS AND DATA ANALYSIS	37
11. DATA MANAGEMENT	47
12. MONITORING, AUDIT & INSPECTION	48
13 ETHICAL AND REGULATORY CONSIDERATIONS	49
14. DISSEMINATION POLICY	52
15. REFERENCES	52
16. APPENDICIES	
Appendix 1 – Trial management / responsibilities	55
Appendix 2 – Principal Investigator responsibilities	56
Appendix 3 – Data collected at baseline	56
Appendix 4 – Schedule of Procedures	61
Appendix 5 – Safety Reporting Flow Chart	62
Appendix 6 – A full list of specific SAEs which do not need to be reported	63

ii. LIST OF ABBREVIATIONS

AE	Adverse Event
AMR	Anti-Microbially Resistant/Anti-Microbial Resistance
AR	Adverse Reaction
CI	Chief Investigator
cIAI	Complicated Intra-abdominal infection
C.difficile	Clostridium difficile
CPE	Carbapenemase producing Enterobacteriaceae
CRF	Case Report Form
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DMEC	Data Monitoring and Ethics Committee
ESBL	Extended spectrum beta-lactamases
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials
LTHT	Leeds Teaching Hospitals Trust
MHRA	Medicines and Healthcare products Regulatory Agency
MRSA	Meticillin resistant Staphylococcus aureus
NHS R&D	National Health Service Research & Development
NIHR	National Institutefor Health and Care Research
PI	Principal Investigator
PIS	Participant Information Sheet
RCT	Randomised Control Trial

REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UoL	University of Leeds
VRE	Vancomycin resistant Enterococcus

iii. TRIAL SUMMARY

Trial Title	The EXTEND trial: Fixed-extended-duration antibiotics (28 days) compared to standard care antibiotic durations in adult patients with complicated intra-abdominal infection and their impact on treatment failure-a phase III multicentre, open label, two-arm, parallel group, pragmatic, randomised controlled trial with internal pilot.	
Short title	The EXTEND trial: EXTENDed antibiotic durations compared to standard antibiotic durations for patients with complicated intra-abdominal infection.	
Clinical Phase	Phase III	
Trial Design	Multicentre, open label, two-arm, parallel group, pragmatic, randomised controlled trial with internal pilot.	
Trial Participants	Adult patients with complicated intra-abdominal infection.	
Planned Sample Size	1166	
Treatment duration	Standard care: Clinically decided antibiotic duration. Intervention care: A fixed-extended-duration of 28 days antibiotics	
Follow up duration	180 days	
Planned Trial Period	3 years 6 months (recruitment and follow-up)	
	Objectives	Outcome Measures
Primary	To compare the effectiveness of fixed extended duration antibiotic treatment with standard duration antibiotic treatment with respect to rate of treatment failure in patients treated for complicated intra-abdominal infection.	Treatment failure within 180 days of randomisation.
Secondary	To compare the effectiveness of fixed extended duration antibiotic treatment with standard duration antibiotic treatment with respect to:	

	1. Quality of life in patients treated for complicated intra-abdominal infection.	EQ-5D-5L
	2. Treatment in terms of impact on an ordinal ranking outcome score.	DOOR analysis
	3. A range of secondary outcome measures (measured from day 0 to day 180).	Time to treatment failure. Number and type of source control procedures. Relapse of cIAI. Number of episodes of treatment failure: Only one episode of treatment failure can occur within a 10 day period. All-cause mortality (time to event) Length of hospital stay Re-admissions C. difficile infection Anti-microbial resistant (AMR) infections Days of antibiotic therapy (in-patient and outpatient, including anti-fungal therapy) Acute kidney injury Complications Days of ventilation Days of renal replacement therapy

iv. FUNDING AND SUPPORT IN KIND

FUNDER(S) and contact details	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
National Institute of Health Research (NIHR) Health Technology Assessment	Sole funder of research

v. ROLE OF TRIAL SPONSOR AND FUNDER

The University of Leeds (UoL) is the Sponsor of the trial and employer of the Chief Investigator. This is an investigator-led multi-site trial. The study is managed and conducted by the Chief Investigator, with the UoL overseeing the activity to ensure appropriate regulatory and governance procedures are in place. The sponsor was not directly involved in the design of the trial.

The funder is the National Institute for Health and Care Research (NIHR). The funder undertook review of the trial design prior to contracting the research. The trial will be conducted as contracted without involvement of the sponsor except the funder will be consulted for approval if major amendments to design and conduct are planned after review by an independent DMEC and TSC

Neither sponsor/funder will have input into data analysis/interpretation and manuscript writing. The funder will not control the final decision regarding any of these aspects of the trial.

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

Trial Management Committees

- Trial Steering Committee (TSC) has the role/responsibilities of providing 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 rights, safety and well-being of the participants are the most important considerations and will prevail over the interests of science and society. YTU is responsible for maintaining the TSC documentation during the course of the trial to ensure compliance with the Trial Master File. The TSC must have a majority independent representation and include the Chair. The TSC must meet regularly and send reports to the sponsor and funder. The TSC will agree proposals for substantial protocol amendments and provide advice to the

sponsor and funder regarding approvals of such amendments. The TSC will provide advice to the investigators on all aspects of the trial/project. Lay members or patient representatives are included. Independent members must make up a minimum of 75% of the TSC membership.

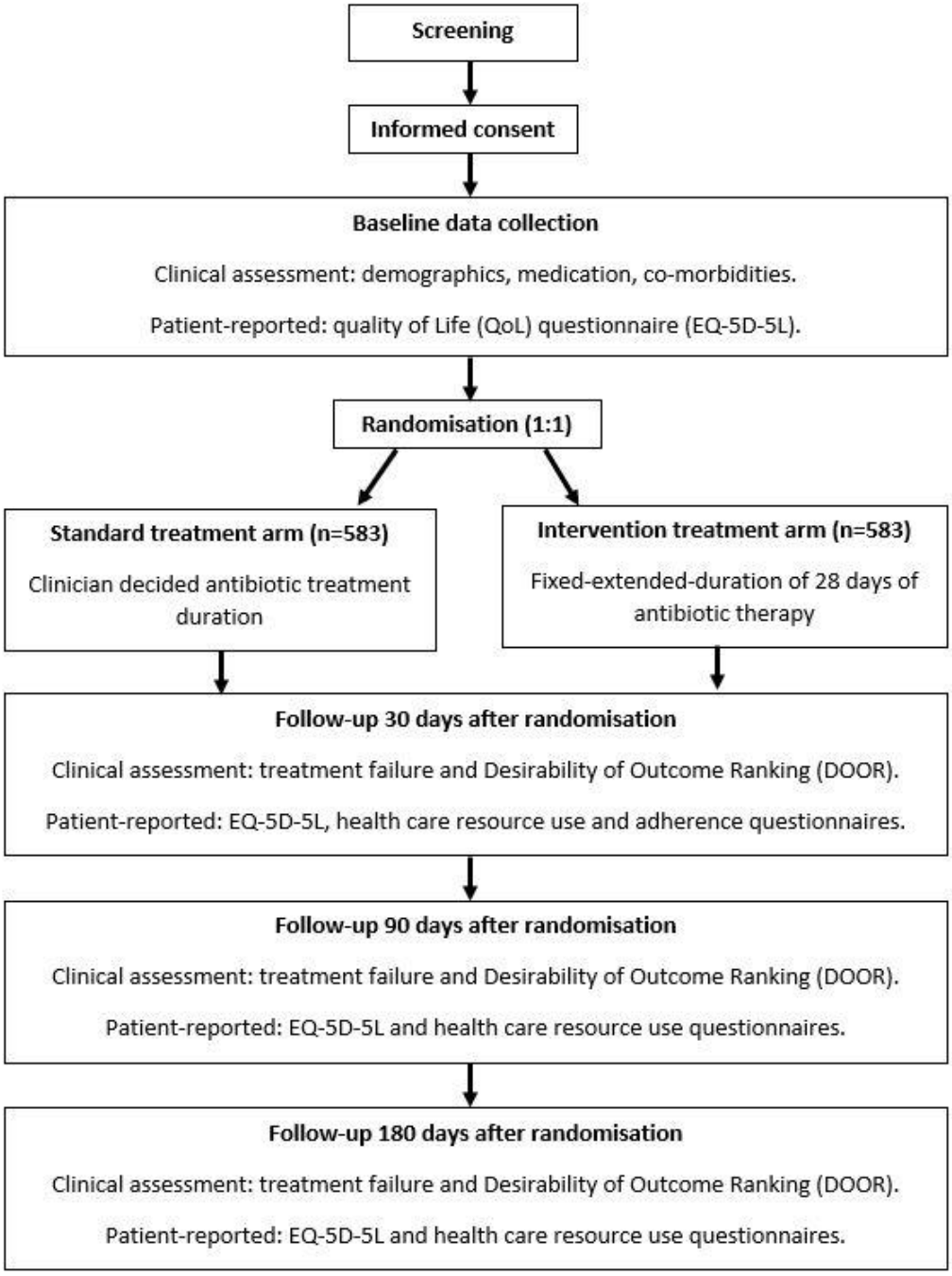
- The Data Monitoring and Ethics Committee (DMEC) will be a committee of independent experts external to the study assessing the progress, safety data and critical efficacy endpoints of the study. The DMEC will also review essential parts of study conduct e.g., protocol adherence and patient withdrawal. In order to do this the DMEC will review unblinded study information (on a patient level and treatment group level) during the conduct of the study. Based on its review the DMEC will provide the TSC, sponsor and funder with recommendations regarding study modification, continuation or termination. Independence is a key characteristic of the DMEC, and committee members will be completely uninvolved in the running of the trial and not be in a position to be unfairly influenced (either directly or indirectly) by people, or institutions, involved in the trial. The implementation of DMEC recommendations will be the responsibility of the TMG and sponsor. The DMEC will include a clinician with expertise in the field, a biostatistician and a person able to consider ethical aspects.
- The Trial Management Group (TMG) will meet regularly to ensure all practical details of the trial are progressing well and working well and everyone within the trial understands them. The TMG will be made up of chief investigators and co-applicants, with others with necessary expertise invited to join as needed.
- End Point Committee: Dr Kirby, Dr Ahmed and Mr Burke will form a blinded end-point committee doe review of outcomes outside LTHT. A separate committee will be for to review outcomes for patients within LTHT including Dr Szakmany, Dr O'Connor and Mr Pinkney. Clinicians from outside the TMG will be trained to take on these roles during the trial.

vii. Protocol contributors

Contributor	Role
Dr Shadia Ahmed	Trial design including consideration of pilot trial conduct.
Mr Dermot Burke	Trial design including surgical input.
Dr Rebecca Harmston	Trial design including consideration of patient representation aspects.
Professor Catherine Hewitt	Trial design, conduct and statistical aspects
Dr Andrew Kirby	Trial design including microbiological input.
Dr Catherine Knowlson	Trial design and conduct
Professor Thomas Pinkney	Trial design including surgical input.
Miss Olivia O'Connor	Trial design including trainee surgical input.
Dr Tamas Szakmany	Trial design including critical care input
Dr Puvan Tharmanathan	Trial design, conduct and patient representation
Dr Armando Vargas-Palacios	Trial design including health economic aspects
Mr Charlie Welch	Trial design, conduct and statistical aspects

viii. KEY WORDS: Complicated intra-abdominal infection; Trial; Antibiotic; Duration.

ix. TRIAL FLOW CHART



1 BACKGROUND

Introduction: The management of complicated intra-abdominal infection (cIAI) is one of the main infection challenges in surgical patients. Complication rates are high and uncertainty over the optimal antibiotic strategy remains [1]. cIAIs extend beyond a hollow viscus (an organ with a lumen such as the bowel) in the abdomen into the peritoneal cavity and are associated with either abscess formation or peritonitis. cIAIs are the second commonest cause of sepsis in patients on intensive care units (ICUs) and cause significant morbidity and mortality [2,3]. Current treatment approaches for cIAI fail to prevent complications, including death, cIAI relapse requiring additional source control procedures and extra-abdominal infections (wound infections, urinary tract infections and respiratory tract infections). Sepsis, which can result from cIAI relapse and extra-abdominal infections, causes longer term functional, cognitive and mental health impairments [4]. cIAIs are heterogeneous in aetiology and include spontaneous infections from a perforated intra-abdominal viscus, and post-operative infections. However, cIAIs have a common disease process which is bacterial infection of the peritoneal space. Hence, all cIAIs are managed with surgical or radiological source control (e.g., resection of damaged bowel), plus antibiotic therapy. There are uncertainties about the duration of antibiotic therapy that best prevents relapse and prevents extra-abdominal infections in patients with cIAI. A national audit of cIAI management in the UK showed there is variation in antibiotic treatment strategies, and there remains no UK guidance on the management of cIAIs [5,6]. However, for serious infections outside the abdomen with a high treatment failure rate (e.g., brain abscess, lung abscess, mastoiditis, septic arthritis, osteomyelitis, and prostatitis), microbiologists often give at least 28-days of antibiotic therapy [7]. The effectiveness of a fixed-extended-duration strategy of 28-days in UK patients with cIAI is unknown, having only been studied in a feasibility trial, leaving an evidence gap for the NHS [8]. We will investigate whether such a treatment strategy improves the longer-term outcomes for these patients; and determine whether this approach is likely to be an efficient use of NHS resources. This proposal aims to investigate the clinical and cost-effectiveness of an unproven approach to patient management in comparison to standard care within the NHS.

Review of existing evidence: Systematic reviews of the evidence have been completed by the Surgical Infection Society (SIS 2017) and Chinese Society of Surgical Infection (CSIS 2020) [9,10]. The SIS encourages a 4-day antibiotic duration as a treatment for cIAI. However, this strategy is difficult for clinicians to adhere to, as demonstrated by the STOP-IT trial where 18% of patients randomised to a four day treatment strategy received more than the allocated 4 days of treatment (receiving a median of 11 days). In addition, a UK cIAI audit found a median antibiotic duration of 12 days (IQR 7-18 days). We therefore excluded a 4-day duration of antibiotics as a standard treatment comparator. The CSIS recommend up to 10 days antibiotics for severe cIAI. Guidance from the World

Society of Emergency Surgery on cIAI recommends shorter durations of antibiotics should be prescribed where possible, but clinician judgement and inflammatory blood markers should be used in determining a treatment end date [11].

There are three published RCTs of antibiotic durations for cIAI; STOP-IT, DURAPOP and a cIAI feasibility trial [8, 12,13]. These trials all compared different antibiotic durations and together provide a signal of efficacy for longer antibiotic treatment durations. STOP-IT reported that a median of 4 days antibiotics was as effective as a median of 8 days, with surgical-site infection, recurrent intra-abdominal infection, or death occurring in 21.8% as compared with 22.3% respectively (p=0.92). However, despite the limited difference in treatment durations, the longer antibiotic durations significantly delayed time until relapse (p=<0.001), which is consistent with an incompletely treated infection. DURAPOP assessed antibiotic durations for ICU patients with cIAI and compared 8 to 15 days of antibiotics. DURAPOPs secondary outcomes reported a significantly lower rate of radiological drainage in patients treated with 15 vs. 8 days antibiotics (9%, 11/116 vs. 19%, 23/120, p=0.04). Other outcomes signalled a 15 day treatment strategy may have benefits including: median length of ICU stay (12 days vs.13 day, p=0.14), rate of bacteraemia (4% vs.11%, p=0.059) and rate of microbiological failure (16% vs. 23%, p=0.13). The cIAI feasibility trial was a 30 patient RCT conducted in Leeds, UK, and designed after consultation with a Leeds Cancer-Patient and Public Involvement (LC-PPI) group [8]. It compared 28-days antibiotics to ≤10 days for patients with cIAI. It found a relapse rate of 4/17 (24%) in the ≤10-day arm, vs. 0/13 (0%) in the 28-day arm. Infections outside the abdominal cavity were diagnosed in 6/17 (35.3%) of those in the ≤10-day arm, vs. 1/13 (7.9%) in those treated for 28-days. Current UK practice and outcomes in patients with cIAI is described by a 417-patient observational study across 30 UK hospitals [5]. In the 17.3% of patients with relapse the median time until relapse was 18 days (IQR: 13-30 days); in the 11.3% of people who died the median time to death was 23 days (IQR: 12-51 days). Antibiotic treatment had a median duration of 12 days (IQR 7-18 days). The rate of adverse events in patients treated for cIAI varies by the patients group studied. Mortality rates have been reported at up to 50% in at risk populations with severe illness, and at 10 to 20% in studies from more broad populations of patients. The need for additional source control procedures, rate of relapses and rate of treatment failure likewise varies by population and definition, being reported in 20 to 60% of patients [2,3,15-19].

2 RATIONALE

The cIAI feasibility trial and a survey of clinicians showed there is equipoise with regards to this issue and a desire to see good evidence on this. Our UK data suggests that current practice results in unacceptably high rates of cIAI relapse and extra-abdominal infection. As a guiding rule, shorter

antibiotic durations are important to combat antimicrobial resistance, but this is not true when these shorter courses need repeating and result in more days in hospital. Optimal care for patients should be our primary concern. The impact of the proposed EXTEND trial, which is studying fixed-extended-duration antibiotics in patients with complicated intra-abdominal infection, will be to improve patient outcomes by providing clinicians with reliable evidence to support them in making the best treatment choices for their patients. If the longer duration strategy is more effective than standard treatment, it is likely to offer direct benefits to the NHS in terms of costs. The literature supports this as when efficacy of antibiotic therapy for cIAI increases, cost savings have been demonstrated. Cost savings included shorter hospital stays and an increase in QALYs [20,21]. Reductions in cIAI relapse will also reduce the use of radiological and surgical NHS resources.

2.1 Assessment and management of risk

This trial is a non-CTIMP (Clinical Trial of Investigational Medicinal Product) trial being a trial of treatment duration strategy, as opposed to a trial of an IMP. Participation in the trial is not known to offer risks to participants that are overall higher or lower than the risk of standard medical care.

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Objectives

3.1 Primary objective

- To complete a multicentre, open label, two-arm, parallel group, pragmatic, randomised controlled trial with internal pilot to determine if a fixed-extended-duration of 28-days antibiotic treatment is superior to standard care based on clinical outcomes and quality of life assessed over six months of follow up.

3.2 Secondary objectives

- To conduct a detailed economic evaluation to assess the cost-effectiveness of these comparisons at the end of the treatment phase and throughout the life of the patients.
- To assess, by means of a study within a trial (SWAT), the effect on trial recruitment of a picture story book patient information resource.

3.3 Outcome measures/endpoints

We have designed the trial such that the majority of data can be collected electronically from routinely generated data e.g., routine observations, blood tests and prescription charts. This allows data collection to be streamlined and efficient for research staff.

3.4 Primary endpoint/outcome

The primary outcome measure is: Treatment failure within 180 days of randomisation.

For in-patients, treatment failure is defined when a patient meets objective criteria for both inflammation and infection within a 5 day period. Meeting of the criteria for inflammation may precede or follow the date that criteria for infection were met (the first day of an eligible antibiotic treatment course). These criteria are:

Criteria for Inflammation

- A fever (≥ 37.8 degrees Celsius) or hypothermia (≤36 degrees Celsius), plus
- A neutrophilia (>7.5 x10^9/L) or neutropaenia (<1.8 x10^9/L), plus
- A CRP over 100 mg/L

PLUS, criteria for infection

- Initiation of a new antibiotic treatment course of ≥ 5 days, or
- A change in antibiotic treatment continued for ≥ 5 days, or
- Initiation of a new antibiotic treatment, or a change in antibiotic treatment, and death within 5 days, or
- Bacteraemia with a recognised intestinal pathogen.

New or changed antibiotic treatments must not be antibiotic prophylaxis, a change to achieve oral administration from intravenous antibiotics only, a change to reduce the spectrum of activity (targeted antibiotic treatment) or made due to antibiotic allergy only. New/changed antibiotics can include additional antibiotics, added to an ongoing treatment regimen. The first day of an eligible new/changed antibiotic treatment is called the antibiotic reference date. Inflammation 5 days either side of this antibiotic reference date can be assessed against the criteria for inflammation. A blinded endpoint committee will assess and classify data including but not limited to inflammation and antibiotic treatments to assign participants with treatment failure.

Once discharged, treatment failure requires re-admission to hospital and the in-patient criteria above to be met. Alternatively, they must have been admitted to hospital and have consumed antibiotics for > 48 hours prior to admission. Treatment failure cannot be assigned based on inflammation (fever, neutrophilia and CRP>100mg/L) detected within the 5 days after an operative procedure (surgical or radiological). Treatment failure can be assigned based on pre-operative inflammation and post-operative antibiotic changes. Treatment failure cannot be assigned due to evidence of inflammation or infection, as defined above, within the first 5 days of antibiotic treatment for the initial cIAI. If treatment is extended beyond the intervention duration this should be considered a new antibiotic treatment course.

Treatment failure measurement: A patient's temperature is measured as part of routine clinical care two to four times daily and recorded in their medical records when in hospital. Patients have the neutrophil count and CRP measured, by means of a blood test, when admitted to hospital, or when an infection is suspected. It will be required that these blood tests are completed within 3 days of an antibiotic prescription and monitored every 72 hours while receiving antibiotic therapy until there has been a reduction in CRP concentration of ≥25%, as per standard clinical practice. Patients' medication charts will be assessed to identify new or changed antibiotic consumption. A blinded endpoint committee will review evidence of inflammation plus antibiotic consumption, in combination with documented antibiotic allergies and microbiology reports, from the preceding two weeks. This review will determine if antibiotic consumption is a new or change in antibiotic treatment, and not prophylaxis, a change made to achieve a narrowing of spectrum, an oral switch only or made due to allergy only. The DMEC will audit the blinded endpoint committee and the audit will be reviewed within the internal pilot.

Intestinal pathogens include: Anaerobes (e.g., Bacteroides), Enterobacterales (e.g., Citrobacter, E.coli, Enterobacter, Klebsiella, Serratia), Enterococcus spp., Pseudomonas spp. and Streptococcus species.

3.5 Secondary endpoints/outcomes

Quality of life: Sepsis, such as can be caused by cIAI relapse, impacts quality of life over a prolonged period of time. The impacts of sepsis map closely onto the components of a quality of life measure e.g., the EQ-5D-5L. We will therefore measure the EQ-5D-5L multiple times over the 180 days following cIAI randomisation.

Desirability Of Outcome Ranking (DOOR) [25]: Patients will be categorised according to the worst outcome they experience over the six month follow up period using a four-level ordinal classification.

The four levels will be 1. No treatment failure, 2. Treatment failure (as for the primary outcome), 3. Treatment failure associated with sepsis (NEWS 6 in ward based patients and SOFA 2 in ICU based patients [22]). Treatment failure associated with death. Note, sepsis and death must occur within 5 days of antibiotic treatment starting or changing.

Other secondary outcome measures: time to treatment failure, number of episodes of treatment failure, number and type of source control procedures, relapse of cIAI, all-cause mortality (time to event), length of hospital stay, re-admission, C. difficile infection, anti-microbial resistant (AMR) infections within 180 days of antibiotic therapy, days of antibiotic therapy (in-patient and outpatient, including anti-fungal therapy), acute kidney injury, complications, days of ventilation and days of renal replacement therapy.

3.6. Outcome measurements

EQ-5D-5L: This questionnaire will have an initial measure taken at baseline, then follow-up questionnaires will be completed at 30, 90 and 180 days after randomisation. It will primarily be completed electronically although a paper version of the baseline questionnaire will be available for patients without access to an electronic portable device. Patients will be asked if they prefer to receive their follow-up questionnaires by email or by telephone. If they are in hospital and do not have access to a portable electronic device then a paper questionnaire will be provided. If at home, postal completion will be a back-up option. Values will be assigned by proxies for those unable to complete due to sedation or illness [23], unless they have a personal consultee (see section 7.2) who is willing to complete the questionnaire on their behalf.

Resource use questionnaire: This will collect resources used by patients when in-hospital or at home. We will include items such as, hospital stay, treating ward, hospital attendances, outpatient, GP and specialised nurse visits. We will also include items to identify use of social care resources such as social workers visits, meals on wheels or laundry services, among others. This questionnaire will be collected at the same time as the EQ-5D-5L (baseline, day 30, 90 and 180). We will aim to collect data electronically where possible and responses will be assigned by proxies for those unable to complete due to sedation or illness if necessary.

DOOR: Sepsis will be assessed daily as per standard practice on ICUs using the SOFA scoring system. On the ward a proxy of sepsis will be used, as SOFA scoring is not routinely completed. The proxy will be a NEWS, which is routinely recorded as part of clinical practice [22].

Number and type of source control procedures: In-patient operation notes and radiological reports will be monitored to determine the total number of source control procedures and their type (radiologically

guided (Ultrasound scan, CT) or surgical (open, laparoscopic)). The definition of source control used for this study is 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. Note, where the abdomen is left open following a surgical procedure a procedure to close the abdomen will be counted as a second and separate procedure,

Relapse of cIAI: In patients with an episode of treatment failure up to 180 days after randomisation, senior clinicians from the patient's primary care team will be asked to report if the patient had a relapse or not, and the date of the first relapse. .

Antimicrobial resistant (AMR) infection: When standard treatment fails in patients with cIAI, antibiotics are often escalated to one of the carbapenem class of antibiotics. We will therefore use rates of carbapenem prescribing as a surrogate for AMR infections. Whilst all surrogates of AMR infection have limitations, this measure is important to both patients and clinicians and should be an effective AMR surrogate measure across a large number of sites.

Further, we will complete passive surveillance of AMR infection across the six month follow up period. Susceptibility patterns of bacterial isolates identified as part of routine clinical practice will be collated from microbiology laboratories to identify AMR including MRSA, VRE, ESBL and CPE. Detection of any AMR infection (MRSA, VRE, ESBL and CPE) will be a secondary outcome. Also, antimicrobial treatments will be analysed for the number of antibiotic class switches. We do not consider it feasible to standardise the investigation of infections for patients with acute infections to allow active surveillance of AMR.

Days of prescribed antibiotic therapy: Electronic medical records will be accessed to determine antibiotic (anti-bacterial) prescriptions in hospital and in the community where available. This data will be supplemented with self-reported antibiotic use at day 30, 90 and 180. Data on anti-fungal treatment will be collected to assess rates of fungal infections e.g., vulvo-vaginal candidiasis.

Others: All-cause mortality, length of hospital stay; re-admission and *C. difficile* infection will be assessed at day 180 after randomisation by review of hospital, medical records and interview with participants.

An episode of Acute Kidney Injury (Y/N): Increase in serum creatinine by ≥ 0.3 mg/dl (≥ 26.5 µmol/l) within 48 hours; or increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume < 0.5 ml/kg/h for 6 hours (KDIGO Clinical Practice Guideline for Acute Kidney Injury).

4 TRIAL DESIGN

A multicentre, open label, two-arm, parallel group, pragmatic, randomised controlled superiority trial with internal pilot. A total of 1166 consenting patients with cIAI will be recruited over 3 years and randomised on a 1:1 basis. Patients will be recruited from ICUs and hospital in-patient wards across 30 sites.

4.1. Internal pilot

The EXTEND trial will incorporate a 12-month internal pilot phase which will assess setup and recruitment rates and monitor adherence with allocated antibiotic treatment durations. Site setup and recruitment will be assessed against the criteria given in the Table below (percentages indicate proportions recruited out of the end of pilot target). The thresholds in the “Green” column are based on reaching our recruitment target of 1166 in 36 months, assuming 30 sites are opened in a staggered manner over the first 24 months of the recruitment period. This projected recruitment profile is illustrated in the Figure below. The thresholds in the “Red” column are based on the minimum values of these metrics for which (under certain assumptions) recruitment could still plausibly be completed in 36 months. Findings from the pilot phase will be used to remodel the projected recruitment trajectory for the main phase of the trial and, together with input from the trial oversight committees, inform any amendments necessary to achieve this trajectory. The trial team and oversight committees will also closely monitor the durations of antibiotics prescribed in each arm during the internal pilot phase. This will enable a proactive approach to managing and retraining sites where departures from the randomised allocations (as relates to antibiotic treatment durations) are identified and thereby ensure adequate separation of the two treatment groups. At the end of the internal pilot phase, the trial oversight committees and funder will review all elements of the pilot progression criteria, as well as data relating to adherence. They will advise whether the trial should; continue as planned or continue with minor or major amendments or enhanced monitoring/training, prior to making any recommendation on whether recruitment should be terminated early, if there is substantial evidence that the full trial is not feasible. Adherence to randomised allocation (standard and fixed-extended-duration antibiotic treatments) will be measured throughout the trial including in the internal pilot. Adherence rates will be reviewed at the end of the pilot phase.

Pilot progression criteria

	Red	Amber	Green
Recruitment rate (patients/site/month)	< 1.08	1.08 to 1.49	≥ 1.5
Number of sites opened	< 13 (< 65%)	13 to 20 (65% to 100%)	≥ 20 (≥ 100%)
Total number of participants recruited	< 144 (< 64%)	144 to 224 (64% to 100%)	≥ 225 (≥ 100%)
Separation (in days) between the average antibiotic durations in treatment arms.	< 5 days	5 to 10 days	> 10 days

4.2 Study within a trial (SWAT)

We recognise the need to broaden participation in trials. We have experience within the team of developing illustrated narratives (picture story books) as a means of communicating messages around infection. We will conduct a SWAT to evaluate whether presentation of the study to potential participants using this re-designed, illustrated, narrative based PIS leads to an increased recruitment rate compared with presentation of the study using a standard PIS. We will work with the established team which includes a writer (Lynda Waterhouse) and illustrator (Imogen Fancourt), alongside our patient representatives, to co-design and study the " Effects of including a Picture Book with the Participant Information Sheet on trial recruitment and retention" (SWAT <<insert ref number>>: MRC SWAT Repository Store). The SWAT will be cluster randomised at the site level to avoid contamination. Sites will be randomised 1:1 to either an enhanced PIS arm (Illustrated, narrative PIS + standard PIS) or standard PIS only arm. The allocation sequence will be generated by a researcher not involved in the recruitment of participants at sites. As is usual for embedded trials, no formal power analysis or sample size calculation was undertaken as the available sample size is dictated by the number of participants who are approached for consent. The primary outcome for this embedded trial is randomisation into the host trial. This outcome will be analysed at the individual level using a population averaged logit-binomial model (fit by generalised estimating equations) with a single binary indicator for SWAT allocation, and an exchangeable working correlation structure. The odds ratio for allocation will be reported together with a 95% confidence interval and p-value obtained using an appropriate small-sample adjustment. Further exploratory analyses will look at differences in retention between SWAT groups among those patients who are randomised into the host trial. The findings of the SWAT will be made publicly available as soon as possible after the end of the recruitment period. We will also collaborate with York Trials Unit who have completed a similar SWAT to ensure the data collected will facilitate future meta-analysis [24].

5 TRIAL SETTING

A list of the participating sites can be found at:
https://www.york.ac.uk/healthsciences/research/trials/research/trials/extend/

Eligibility criteria for trial centres: Trial centres must be UK based hospitals whose patient population includes adults and have general or specialist abdominal surgical services on site.

Eligibility for individuals who will perform the interventions: All clinical staff involved in patient's recruitment, randomisation and follow up must have current Good Clinical Practice training. They must also complete study specific training and the HRA eLearning module "Research involving participants lacking mental capacity."

6 PARTICIPANT ELIGIBILITY CRITERIA

6.1 Inclusion criteria

- Adults (≥ 16 years) with cIAI (see cIAI definition)
- Being treated with antibiotics until the point of randomisation, but within 10 days of initiation of antibiotic treatment for cIAI
- Ability to provide informed consent by the patient or their consultee.
- More than 72 hours of further active in-patient management for the patients cIAI is required
- In the event that the patient is re-admitted to hospital during the trial period, they will likely to be admitted to a hospital participating in the EXTEND trial

Patients will be included in the trial whether or not they undergo surgical or radiological source control procedures.

*cIAI is defined by the following case definition:

- A clinical presentation consistent with cIAI, plus
- Fever (temperature of ≥ 37.8°C) and/or a neutrophilia (> 7.5×10^9/L) and/or neutropaenia (<1.8x109/L) and/or intestinal pathogens cultured from sterile sites (closed peritoneum or blood), plus
- Evidence of pathologic findings on radiologic examination, or
- Evidence of pathologic findings at operation

6.2 Exclusion criteria

- Perforated gastric ulcer or duodenal ulcer treated within 24 hours of the onset of symptoms.
- Traumatic injury to the bowel (including iatrogenic or intra-operative) treated within 12 hours of injury.
- Uncomplicated diverticulitis defined as an episode with a short history and with clinical signs of diverticulitis, with an increased body temperature and inflammatory parameters, verified by computed tomography (CT), and without any sign of complications such as abscess, free air or fistula.
- Non-perforated, non-gangrenous appendicitis (Grade 4 and below of the 2017 American Association for the Surgery on Trauma Grading System) or cholecystitis.
- Ischemic or necrotic intestine without perforation
- Uterine perforation following uterine surgery treated <six hours following injury.
- cIAIs with a low risk of complications who may receive more than 72 hours antibiotics are not intended to be included, such as those listed above. Clinician assessment on the eligibility of patients receiving more than 72 hours of in-patient surgical care and antibiotics for their cIAI may be required in patients who have clinically improved at this point and do not require active surgical care but remain in hospital and on antibiotics.
- Current enrolment in another trial dictating antibiotic treatment duration.
- Previous *Clostridium difficile* infection
- Infected necrotic pancreatitis
- Concomitant infection requiring ≥4 weeks antibiotic therapy including Intra-hepatic abscess/es planned to be treated with fixed-extended-duration antibiotics of 4 to 6 weeks antibiotics, osteomyelitis, and endocarditis.
- Peritoneal dialysis
- Previously recruited for the EXTEND trial
- Treatment with Interleukin-6 Inhibitors
- High likelihood of death within 72 hours of randomisation in the opinion of the local Investigator
- Limitations in treatment decided before inclusion
- Patient with persistent cIAI of more than 6 months duration
- A maximum of 20% of participants entering the trial can have a source of cIAI as the appendix. If 230 patients with appendix as the source are recruited, this will become an exclusion criteria for subsequent patients.

7 TRIAL PROCEDURES

7.1 Identification

Screening/Identification methods: The hospital research team or treating clinician will identify potentially eligible patients from intensive care units, surgical wards, radiology reports and infection service consultations. This will be done by reviewing patient records daily as a collaboration between research nurses and local investigators, including associate Principal Investigators. Site teams will be encouraged to setup groups on approved platforms to communicate between themselves to facilitate participant identification. The research team will work closely with clinicians at each site to optimise screening and recruitment procedures for their local circumstances. Routine imaging and surgical findings will be used to inform eligibility. A clinician delegated to perform this task will confirm eligibility. Screening forms will be completed at all participating sites and will be used to capture numbers of ineligible or non-consenting patients at each site. High level data (age, sex, ethnicity and post-code) will be collected for those eligible but who do not participate to assess how representative the recruited trial population is, including to monitor equality and diversity. NIHR guidance on Equality, Diversity and Inclusion for study participants will be promoted.

7.1.1 Payment

Payments, rewards and recognition for study participants: Participants will be given an unconditional £20 voucher as a goodwill gesture with each follow-up questionnaire at 30, 90 and 180 days.

7.1.2 Quality control/assurance procedures

YTU will be responsible for the quality control/ assurance procedures.

7.2 Recruitment/Consent

Patient identification will be as close to cIAI diagnosis as possible to limit recruitment bias. However, randomisation will take place after eligibility is confirmed as per the trial inclusion criteria (see 6.1). A clinician or a member of the research team will invite the eligible patient to consider joining the study. The patient will be provided with an invitation letter and a detailed participant information sheet (PIS) which will explain the risks and benefits of trial participation clearly in text form. Potential participants will be given a contact phone number, so they can ask questions of clinical staff and to discuss the trial with friends/family prior to agreement to take part. Sufficient time (within the time available prior to patient randomisation being required) will be given to patients to consider their participation in the trial. Research staff will obtain written informed consent by an appropriately trained research clinician or research nursing staff. If any eligible participant agrees to participate specific consent will be sought to enable the sharing

of identifiable data with York Trials Unit (YTU) as part of the study in order to facilitate the collection of outcome data.

A proportion of potential participants may be sedated and therefore lack capacity to make an informed decision about their participation in the research project. The clinical and/or research team will assess capacity as per their usual procedures for receiving consent for a trial and decide as to whether the participant has capacity to consent prospectively or if a consultee agreement should be sought. In these instances, consent may be obtained at sites in England, Wales and Northern Ireland via a Personal Consultee (an individual who has a personal relationship with the patient; for example, relatives, carers or friends) or Nominated Consultee (a professional who is independent of the study). Appropriate (Good Clinical Practice trained and independent of the research team) Nominated Consultees will be identified at all of these sites for instances where a Personal Consultee is not available or decides they are unable to act in this capacity; in line with national guidance, as it applies to regions of the UK e.g. Mental Capacity Act (Department of Health, 2005) and Department of Health guidance (Department of Health, 2008). At sites in Scotland, consent may be obtained from a welfare guardian, welfare attorney or if neither of those is available a close relative; in line with the Adults Incapacity Act (Scotland, 2000). The person providing consent will be provided with all study information and given the opportunity to ask questions and discuss the study before making a decision on whether they think the patient would want to take part and if it is in their best interest to do so. If they agree, their written agreement for the patients' inclusion into the trial will be recorded. Written consent to continue in the study will be sought from the participant at the first appropriate opportunity once they regain capacity. In the interim, efforts will be made to involve participants who, temporarily or permanently, lack the capacity to decide to be involved in the study. Appropriate information will be communicated to the participant and updated as their understanding changes. At all times the study team will act in accordance with the participant's best interests. On rare occasions, participants who have lacked capacity to consent may be discharged prior to providing written consent themselves. Should this situation arise, the trial team will make every effort to discuss the trial with the patient and the patient's clinical care team at the earliest opportunity.

7.3 The randomisation scheme

Participants will be individually randomised 1:1 between 28-days antibiotics and standard care antibiotic duration using stratified block randomisation with randomly varying block sizes. Stratification will be by: Post-operative cIAI vs. non post-operative cIAI, surgical source control procedure vs. no surgical source control procedure and ICU stay vs. no ICU stay within 10 days of randomisation.

7.3.1 Method of implementing the randomisation/allocation sequence

Randomisation will occur within the first 10 days of antibiotic treatment for cIAI, and will be implemented using a web-based system designed and developed by the data management team at YTU. This system will be accessed by clinical research staff involved in patient recruitment at recruiting sites (as detailed in the site delegation log) and will be accessible 24 hours a day and 7 days a week. Prior to randomisation, research staff at recruiting sites will be required to enter the following key information; participant identification number, date of birth, participant contact details (to facilitate follow up), confirmation that the participant meets each of the eligibility criteria and the information required for stratification. The allocation sequences (one for each stratum) will be designed by the trial statistician. The actual sequences embedded in the randomisation system will be generated by a separate YTU statistician independent of the Trial Management Group, using a random number seed that will be concealed from all members of the trial team for the duration of the trial. Following randomisation, the research team at the site where the randomisation took place (including the PI, research nurses and pharmacists) will be notified of the treatment allocation by email. Each time a patient is randomised, the chief investigator and central trial management team at YTU will also be notified by email, but the assigned allocation will not be disclosed.

7.4 Blinding

This is an unblinded trial with both treating clinicians and participants aware of treatment allocations.

7.5 Emergency Unblinding

Not applicable

7.6 Baseline data

Data required prior to being eligible for study entry include:

- Full blood count demonstrating the patient has elevated or low neutrophils.
- Radiological investigation (e.g., CT scan/ultrasound scan/X-ray) consistent with a cIAI.

These will be undertaken as part of routine clinical practice and are not therefore trial specific procedures.

A full breakdown of data which will be collected at baseline is provided in Appendix 3.

7.7 Trial assessments

See Appendix 4.

7.8 Long term follow-up assessments

No long term follow-up beyond the initial 6 month follow-up period is planned.

7.9 Withdrawals

Patients are free to withdraw from the trial without reason at any time. Unless the participant specifically withdraws consent for their data to be stored, all data collected from them will continue to be stored as per the original patient consent. At a participant's request, their data collected up to the point of withdrawal can however be withdrawn from the trial and will not be used in the final analysis. Participants withdrawing from the trial will not be replaced. Patient's may also withdraw from specific aspects of the trial data collection e.g., completion of questionnaires, but provide consent for collection of data from their research their medical notes to be allowed to continue.

On participant withdrawal, data will be collected recording reasons for withdrawal (as far as possible). During the trial, the DMEC will review rates of withdrawals of different type, as well as the available reasons for these, and make recommendations regarding amendments to trial procedures, or re-training/discussion with trial investigators at any sites where these issues are most prevalent.

7.10 Departures from randomised treatment (non-adherence)

Clinicians/Investigators are free to deviate from a patient's assigned treatment allocation if clinically indicated. Where patients depart from their randomised treatment due to an error, efforts will be made to re-instigate their correct treatment allocation if possible, within 5 days of the change. Changes to the randomised treatment do not need to be reported to YTU as protocol deviations. Patients' data will continue to be collected regardless of any departures from the allocated treatment strategy to help facilitate an intention-to treat analysis. During the trial, the DMEC will review data relating to adherence, and make recommendations regarding amendments to trial procedures as necessary.

7.11 End of trial

Relevant bodies including the trial sponsor and the Health Research Authority will be notified by YTU that the trial has ceased. The end of trial is the date of the last patient last visit (LPLV). This is defined as:
a. Completion of 6 month follow up assessments by the last randomised patient, or
b. Withdrawal of the last randomised patient from planned follow up data collection

8 TRIAL STRATEGIES

This trial is comparing two antibiotic treatment duration strategies for the treatment of complicated intra-abdominal infection.

8.1 Intervention: A fixed-extended-antibiotic duration of 28-days effective therapy for patients with cIAI. Effective antibiotic therapy is defined as therapy not limited by proven antimicrobial resistance according to standard laboratory criteria.

8.2 Detailed specification of the intervention: The intervention is a strategy of a fixed-extended-duration antibiotic treatment of 28-days. The start of antibiotic therapy is the first day of active therapy for cIAI treatment, which will generally occur before randomisation, but could be following randomisation if antibiotics given prior to randomisation are ineffective/inactive. The start date of antibiotic treatment will be determined by the patient's clinical team or clinical research team. Examples of antibiotic therapy that are not therapy for cIAI include antibiotic prophylaxis, or treatment for other infections e.g., cystitis. All treatment will be considered active unless antimicrobial resistance is identified on clinical samples collected before randomisation and that resistance is believed to be clinically relevant i.e., antibiotic treatment is changed based on the microbiological evidence of antibiotic resistance. The start date of fixed-extended-duration antibiotic treatment of 28-days will be re-set to day 0 where antibiotic treatment is changed based on pre-randomisation detection of antibiotic resistance. The strategy relates to the fixed-extended-duration treatment only, and the date of randomisation is not changed.. The choice of antibiotic and route of administration are therefore selected by the treating clinician. Source control procedures (surgical and radiological) will be carried out as per standard practice.

8.3 Comparator: Standard care antibiotic duration. We describe standard care as being based on clinician judgment. Clinicians use the clinical progress of the patient in combination with inflammatory blood markers, surgical and radiological findings to guide standard treatment antibiotic durations. Standard care antibiotic durations do not dictate the choice or route of antibiotics; as per the intervention arm standard care refers to antibiotic durations only. Source control procedures (surgical and radiological) will be carried out as per standard practice. The start of antibiotic therapy is the first day of effective therapy. When antimicrobial resistance is identified and believed to be clinically relevant i.e., antibiotic treatment is changed based on microbiological results, the start of antibiotic therapy will be re-set to day 0 if this occurs within the first 10 days of treatment. The end

date for standard antibiotic duration is defined by the first 48 hour period without antibiotic therapy. The end date is the first date within this 48 hour period.

8.4 Assessment of adherence with treatment: Monitoring adherence to antibiotics prescribed while an in-patient will be carried out by monitoring patient's prescription charts. An amount of antibiotics prescribed orally may be consumed while an out-patient. We recognise the importance of adherence to ensure separation between the trial arms in terms of the intervention durations. We therefore need to review outpatient adherence within our internal pilot. We will do this by means of a modified Brief Adherence Rating Scale [25] in the 1 month participant questionnaire. There will be no process of formally assessing if antibiotic treatment is adherent to the protocol in those treated with standard care antibiotic treatment. In participants receiving a fixed extended-duration antibiotic treatment of 28 days, this will be considered protocol adherent where the overall treatment duration is within 5 days of this duration.

9 PHARMACOVIGILANCE

9.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in the SmPC. It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative aetiology that would explain the event.

Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening* • 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 reference safety information: • in the case of a product with a marketing authorisation, this could be in the summary of product characteristics (SmPC) for that product, so long as it is being used within its licence. If it is being used off label an assessment of the SmPCs suitability will need to be undertaken. • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question

9.2 Operational definitions for (S)AEs

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

9.3 Recording and reporting of SAEs, SARs AND SUSARs

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

Non-serious AEs will not be reported to YTU and will not be recorded on case report forms.

SAEs/SARs will be reported to YTU, except for exemptions detailed below, via e-mail using a form provided by YTU within 24 hours of the research team becoming aware of the event. SAEs which are exempt from reporting to YTU are those which occur commonly in this patient population, as follows:

- Infections including surgical wound infections, respiratory, urinary and skin infections (including fungal infections).
- Surgical complications such as failure of a surgical procedure (specifically anastomotic breakdown or development of a fistula) or bowel obstruction. 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.
- A full list of specific SAEs which do not need to be reported is available in Appendix 6

Non-serious ARs will not be reported to YTU and will not be recorded on case report forms.

SARs will be reported to YTU, except for specific exemptions, via e-mail using a form provided by YTU within 24 hours of the research team becoming aware of the event. SARs exempt from reporting to YTU are those where 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 YTU via e-mail using a form provided by YTU within 24 hours of the research team becoming aware of the event. All SAEs assigned by the PI or delegate (or following central review) as both suspected to be related to IMP-treatment and unexpected will be classified as SUSARs and will be reported by YTU to the Medicines and Healthcare Products Regulatory Agency (MHRA) via the yellow card scheme within 1 working day.

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

- full details of the event
- seriousness criteria
- event duration (start and end dates, if applicable)

- outcome
- action taken
- 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 e-mailed to YTU as soon as it is available on a follow-up report form provided by YTU, or at least within one working day of the information becoming available. Events will be followed up until resolved or a final outcome reached.

YTU will be responsible for reviewing all reported **SAEs / SARs / SUSARs.** Where they are to be reported to the sponsor, YTU will email reports to governance-ethics@leeds.ac.uk within 1 working day of becoming aware of the event.

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 drug's SmPC.
2. Report SAEs and SARs to YTU within 24 hours.

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. Clinical review of a line listing of all life threatening or SAEs resulting in death within 1 week of their occurrence.
5. Clinical review of a line listing of all other SAEs on a monthly basis (for lower risk trial).
6. Immediate review of all SUSARs.

Sponsor responsibilities (delegated to the York Trials Unit)

1. Central data collection and verification of SAEs, SARs and SUSARs according to the trial protocol onto a database.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
3. Ensuring that where relevant SAEs and SARs (including SUSARs) are recorded and reported to the sponsor within 1 working day of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that reported SAEs and SARs (including SUSARs) are chased with Sponsor if a record of receipt is not received within 3 working days of initial reporting.
4. Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring and Ethics Committee (DMEC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
5. Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines.
6. Notifying Investigators of SUSARs that occur within the trial.

Trial Steering Committee (TSC):

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMEC regarding safety issues.

Data monitoring and Ethics Committee (DMEC):

In accordance with the Trial Terms of Reference for the DMEC, periodically reviewing overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

9.5 Notification of deaths

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

9.6 Pregnancy reporting

Pregnancy is not considered an AE and will not be reported.

9.7 Reporting urgent safety measures

An “urgent safety measure” is a procedure which is not defined by the protocol that can be put in place with immediate effect without needing to gain prior authorisation by the REC (and MHRA where applicable), in order to protect clinical trial participants from any immediate hazard to their health and safety.

If any urgent safety measures are taken by an investigator, these must be reported to YTU within 24 hours. YTU will take responsibility for reporting of urgent safety measures to the Sponsor (if not already aware), MHRA (if applicable) and the relevant REC if required.

10 STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation

The primary outcome for this study is treatment failure. Using an estimated proportion of treatment failure in the standard treatment group of ≥ 50% over the 180 days of follow up, an effective sample size of 1048 patients (524 per arm) obtains 90% power to detect a 10% (absolute) reduction in incidence of the clinical outcome in a two-sided test of size 5%. Assuming 10% attrition 1166 patients (583 per arm) are required. The sample size calculation was carried out using Stata version 16.0.

10.3 Statistical analysis plan

10.3.1 Statistical analysis overview, principles and procedures

Analyses will be conducted following intention-to-treat principles and will follow a detailed pre-specified statistical analysis plan (SAP) completed and approved during the internal pilot phase, and prior to any review of the outcome data. All analyses will be conducted just once at the end of the trial, with no modification of trial processes (including termination) being made based on interim comparisons of accumulating outcome data (hence no stopping rules/monitoring boundaries are specified). Any deviations from the pre-specified analyses in the SAP will be detailed according to YTU’s standard operating procedures.

The flow of patients through the trial will be reported in a CONSORT diagram, including the number of patients screened (and reasons for ineligibility), the number approached for consent (and reasons for non-consent), the number randomised, adherence to allocated treatment, follow-up data completeness and the number of participants included in the analyses. Descriptive summaries of continuous data (or discrete numerical data with many distinct values) will be given in terms of the non-missing sample size, arithmetic mean, standard deviation, median, inter-quartile range, minimum and maximum. Descriptive summaries of categorical data (or discrete numerical data with few distinct values) will be given in terms of frequencies and proportions.

All analysis models used to compare treatment strategies will include all randomised participants with data available for the relevant outcome in the groups to which they were allocated (unless explicitly stated otherwise). For binary outcomes, differences between randomised groups will be estimated on the log odds scale, conditional on informative baseline covariates (including the randomisation stratification factors) unless otherwise stated. Point and interval estimates of conditional odds ratios will be reported. Point and interval estimates of relative risk (cases/non-cases) and absolute risk reduction based on estimated marginal effects from these models will also be reported. For ordinal categorical outcomes, differences between randomised groups will be estimated on the log odds scale, conditional on informative baseline covariates (including the randomisation stratification factors), using appropriate ordinal logit models (unless otherwise stated). Point and interval estimates of the conditional odds ratios obtained from the fitted models will be reported. For continuous and count outcomes, differences between groups will be estimated using appropriate generalised linear models, with the differences between groups (absolute or relative) obtained from the fitted models being reported on the scale of the original measurements, unless stated otherwise.

10.3.2 Baseline data

Baseline data will be collected immediately prior to randomisation and will include the variables described in Section 7.6. These data will be reported by group (and overall), as randomised (i.e. including baseline data from all randomised patients) and as included in the primary analysis (i.e. including baseline data from all participants with non-missing primary outcome data). Reporting of these data will be descriptive (see detailed specification of statistics reported in Section 10.3.1), with no interval estimation or testing of differences in baseline characteristics being conducted or reported. In addition to the tabular summaries described above, plots of the distribution of key baseline characteristics will also be generated.

10.3.3 Primary outcome analysis

The primary clinical outcome is treatment failure (Failure vs No failure) within 180 days of randomisation, as defined in Section 3.4. The number and proportion of participants experiencing treatment failure will be reported by randomised group and overall, as will the number of participants with complete outcome and covariate data. The primary analysis will model the log odds of treatment failure using a mixed effect logistic regression model, with randomised treatment group, the stratification factors (Post-operative vs Non post-operative cIAI, Source control vs No source control, ICU care vs No ICU care), and other pre-specified prognostic baseline covariates included as fixed effects, and random intercepts for recruitment site/hospital. All participants with non-missing primary outcome data will be included in this model, with any missing baseline covariate data being imputed using an appropriate method prior to model fitting. Inference concerning the effectiveness of the intervention will be primarily based on the estimated conditional odds ratio, two-sided 95% confidence interval and p-value for allocation from the fitted primary analysis model. To aid interpretability, point estimates and appropriate two-sided 95% confidence intervals for the relative risk (cases/non-cases) and absolute risk reduction (based on the fitted primary analysis model) will be reported, with the fixed effect covariates in the model set to various representative values (i.e. marginal risk ratio and risk difference at representative values). Average marginal effects on both the risk ratio and risk difference scales will also be reported with appropriate two-sided 95% confidence intervals.

Several pre-specified sensitivity analyses of the primary outcome will be conducted to investigate the possible influence of non-adherence (via the estimation of alternative estimands that aim to account for non-adherence), and different assumptions about the missing outcome data (via analysis of data multiply imputed assuming outcome data are missing at random (MAR) and assuming various systematic departures from MAR).

10.3.4 Secondary outcome analysis

Secondary outcomes will be analysed following the principles outlined in Section 10.3.1 (unless otherwise stated). Brief details of the analyses of the secondary outcomes are given below. Detailed specification these analyses will be given in the SAP.

<u>Desirability of Outcome Ranking (DOOR)</u>

Patients will be categorised according to the worst outcome they experience over the 6 months follow up period using a four-level ordinal classification. The four levels will be C_1 = No treatment failure, C_2 = Treatment failure (as for the primary outcome), C_3 = Treatment failure associated with sepsis and C_4 = Treatment failure associated with death.

The DOOR will be analysed using a mixed effect proportional odds model with group allocation, the stratification factors and other prognostic baseline covariates included as fixed effects, with random intercepts for recruitment site. The estimated conditional odds ratio for allocation and two-sided 95% CI and p-value from this model will be reported. For i = 2, 3 and 4, risk ratios ($Pr(Y \geq C_i \mid Z = Intervention, X)/Pr(Y \geq C_i \mid Z = Control, X)$) and absolute risk reductions ($Pr(Y \geq C_i \mid Z = Intervention, X) - Pr(Y \geq C_i \mid Z = Control, X)$) based on the fitted model, will also be reported (with appropriate 95% confidence intervals) at various representative covariate patterns X (i.e. marginal effects at representative values). The fitted model will also be used to compute average marginal effects of allocation on both the risk ratio and risk difference scales.

The extent to which the effect of allocation meets the proportional odds assumption will be assessed using both Brant and likelihood ratio tests (the likelihood ratio test will compare a proportional odds model with a less restrictive partial proportional odds model that allows the effect of allocation to differ across each of the three possible binary groupings of the outcome). If either of these tests suggest the effect of allocation deviates substantially from the proportional odds assumption, then the partial proportional odds model will be fitted (with cluster robust standard errors), and the three estimated odds ratios for allocation (one for each of the three possible binary groupings of the outcome) will be reported together with appropriate 95% confidence intervals and p-values [27].

EQ-5D-5L

Participants will complete the EQ-5D-5L at baseline, and at days 30, 90 and 180 post-randomisation. Analysis of EQ-5D data will be part of the health economics analysis and will be described in the Health Economics Analysis Plan (HEAP). For the statistical analysis, descriptive summaries of the EQ-5D data at each time point will be given by randomised group and overall.

Time to treatment failure

Time to initial treatment failure will be analysed using both cause specific, and sub-distribution hazards models, with fixed effects for allocation, the stratification factors and other prognostic baseline covariates, and shared frailties for study recruitment site. Inclusion of time varying effects of treatment will be considered if there is evidence of non-proportional hazards. The cause specific hazards model(s) will be used to estimate the effect of the intervention on the instantaneous rate of treatment

failure among those that are event free, and the latter to estimate the effect of the intervention on the cumulative incidence of treatment failure (conditional on pre-specified values of interest for the fixed effect covariates).

Source Control Procedures

The number, incidence and type of source control procedures occurring over the 180 days following randomisation will be reported descriptively by randomised group. The total number of source control procedures of different types (radiological, surgical) and source control procedures of any type occurring in each randomised group will be compared using a proportional odds model, with fixed effects for allocation, the stratification factors and other prognostic baseline covariates, and random intercepts for study recruitment site. This model will be used to derive the difference in mean number of source control procedures in each group, conditional on pre-specified representative values of the fixed effect covariates, as well marginal effects (on both the risk ratio and risk difference scales) conditional on pre-specified representative values of the fixed effect covariates (e.g. Pr(Y > 0 | Intervention, X)/Pr(Y > 0 | Control, X) for covariates X). Average marginal effects (on both the risk ratio and risk difference scales) will also be reported together with appropriate 95% confidence intervals for various relevant outcomes/cut-offs.

Length of Hospital Stay

The length of initial hospital stay (i.e. time to first discharge following randomisation) will be analysed using competing risk regression methods. For this analysis, the day of randomisation will be treated as day zero and the day of discharge will be the event of primary interest, with death treated as a competing event. Both discharge and death will be considered absorbing states. Time to discharge will be analysed using both cause specific, and sub-distribution hazards models, with fixed effects for allocation, the stratification factors and other prognostic baseline covariates, and shared frailties for study recruitment site. The former will be used to estimate the effect of the intervention on the instantaneous rate of discharge among those that are event free, and the latter to estimate the effect of the intervention on the cumulative incidence of discharge (conditional on pre-specified values of interest for the fixed effect covariates).

Days/Nights in Hospital

The total number of nights spent in hospital during the 180 days following randomisation, proportion of total follow up time in hospital and mortality will be reported descriptively by randomised group and overall. For analysis, death within 180 days following randomisation will be coded as the "worst"/"highest" outcome (i.e. death will be ranked worse than any number of nights in hospital without death). This outcome and its empirical cumulative distribution function will be plotted by randomised group and overall. Total number of nights in hospital (with death coded as the worst/highest outcome) will be compared using a proportional odds model, with fixed effects for allocation, the stratification factors and other prognostic baseline covariates, and random intercepts for study recruitment site. This model will be used to derive marginal effects (on both the risk ratio and risk difference scales) conditional on pre-specified representative values of the fixed effect covariates (e.g. Pr(Y > 28 | Intervention, X)/Pr(Y > 28 | Control, X) for covariates X). Average marginal effects (on both the risk ratio and risk difference scales) will also be reported together with appropriate 95% confidence intervals for various relevant outcomes/cut-offs.

Days of Anti-microbial Therapy

The total number of days of anti-microbial therapy (inpatient, outpatient and overall) during the 180 days following randomisation, proportion of total follow up time on anti-microbial therapy, and mortality will be reported descriptively by randomised group and overall. For analysis, death whilst still receiving antibiotics will be coded as the "worst"/"highest" outcome (i.e. death will be ranked worse than any number of days of antimicrobial therapy without death). This outcome and its empirical cumulative distribution function will be plotted by randomised group and overall. Total number of days on anti-microbial therapy (with death coded as the worst/highest outcome) will be compared using a proportional odds model, with fixed effects for allocation, the stratification factors and other prognostic baseline covariates, and random intercepts for study recruitment site. This model will be used to derive marginal effects (on both the risk ratio and risk difference scales) conditional on pre-specified representative values of the fixed effect covariates (e.g. Pr(Y > 28 | Intervention, X)/Pr(Y > 28 | Control, X) for covariates X). Average marginal effects (on both the risk ratio and risk difference scales) will also be reported together with appropriate 95% confidence intervals for various relevant outcomes/cut-offs.

Complications

Complications (i.e. any untoward medical event that occurs during the patient's illness/follow-up) will be reported and assigned a grade according to the Clavien-Dindo classification (slightly modified to allow for complications that are not post-operative in nature) [REF]. The assigned grades will be reported descriptively by randomised group and overall and will also be used to generate a

Comprehensive Complications Index (CCI) score [REF] for the 180 days following randomisation. The worst complication experienced (i.e. the complication with the highest grade assigned) during the 180 day follow-up period will be analysed using an ordinal regression model with fixed effects for allocation, the stratification factors and other relevant baseline covariates, and random intercepts for recruitment site. This model will be used to derive marginal effects (on both the risk ratio and risk difference scales) conditional on pre-specified representative values of the fixed effect covariates (e.g. Pr(Y > 1 | Intervention, X)/Pr(Y > 1 | Control, X) for covariates X). Average marginal effects (on both the risk ratio and risk difference scales) will also be reported together with appropriate 95% confidence intervals for various relevant outcomes/cut-offs. The CCI will be analysed using a Gaussian family generalised linear mixed model, with an appropriate link function. This model will include fixed effects for allocation, the stratification factors and other relevant baseline covariates, and random intercepts for recruitment site. This model will be used to derive between group differences in expected CCI score with an appropriate 95% confidence interval and p-value.

Relapse of cIAI

The proportion of patients that experience a relapse of cIAI during the 180 days following randomisation will be reported by randomised group. This outcome will be modelled using a mixed effect logistic regression model with fixed effects for allocation, the stratification factors and other prognostic baseline covariates, and random intercepts for study recruitment site. The estimated conditional odds ratio for allocation, 95% confidence interval and p-value will be reported. To aid interpretability, point estimates and appropriate two-sided 95% confidence for the relative risk (cases/non-cases) and absolute risk reduction (based on the fitted model) will be reported, with the fixed effect covariates in the model set to various representative values (i.e. marginal risk ratios and risk differences at representative values). Average marginal effects on both the risk ratio and risk difference scales will also be reported with appropriate two-sided 95% confidence intervals.

Number of episodes of treatment failure

The total number of episodes of treatment failure during the 180 days following randomisation will be reported descriptively by randomised group and overall. For analysis, death within 180 days following randomisation will be coded as the “worst”/”highest” outcome (i.e. death will be ranked worse than any number of treatment failure episodes without death). This outcome and its empirical cumulative distribution function will be plotted by randomised group and overall. Total number of episodes of treatment failure (with death coded as the worst/highest outcome) will be compared using a proportional odds model, with fixed effects for allocation, the stratification factors and other prognostic

baseline covariates, and random intercepts for study recruitment site. This model will be used to derive marginal effects (on both the risk ratio and risk difference scales) conditional on pre-specified values of interest for the fixed effect covariates (e.g. Pr(Y > 1 | Intervention, X)/Pr(Y > 1 | Control, X) for covariates X). Average marginal effects (on both the risk ratio and risk difference scales) will also be reported together with appropriate 95% confidence intervals for various relevant outcomes/cut-offs.

Re-admissions

The proportion of participants who are re-admitted to hospital during the 180 days following randomisation, and number of re-admissions per participant will be reported descriptively by randomised group and overall. The number of re-admissions per participant and empirical cumulative distribution function will also be plotted by randomised group and overall. The binary re-admission outcome (re-admitted vs not re-admitted during 180 days post-randomisation) will be modelled using a mixed effect logistic regression with fixed effects for allocation, the stratification factors and other prognostic baseline covariates, and random intercepts for study recruitment site. The estimated conditional odds ratio for allocation, 95% confidence interval and p-value will be reported. To aid interpretability, point estimates and appropriate two-sided 95% confidence intervals for the relative risk (cases/non-cases) and absolute risk reduction (based on the fitted model) will be reported, with the fixed effect covariates in the model set to various representative values (i.e. marginal risk ratios and risk differences at representative values). Average marginal effects on both the risk ratio and risk difference scales will also be reported with two-sided appropriate 95% confidence intervals. The count re-admission outcome (number of re-admissions during 180 days post-randomisation) will be analysed using a proportional odds model, with fixed effects for allocation, the stratification factors and other prognostic baseline covariates, and random intercepts for study recruitment site. This model will be used to derive the difference in mean number of readmissions in each group, conditional on pre-specified representative values of the fixed effect covariates, as well marginal effects (on both the risk ratio and risk difference scales) conditional on pre-specified representative values of the fixed effect covariates (e.g. Pr(Y > 0 | Intervention, X)/Pr(Y > 0 | Control, X) for covariates X). Average marginal effects (on both the risk ratio and risk difference scales) will also be reported together with appropriate 95% confidence intervals for various relevant outcomes/cut-offs.

All-cause Mortality

Brief summaries of the total time at risk and number/proportion of participants who died will be presented by randomised group and overall. The number and proportion of participants who are lost to follow up or reach 180 days post-randomisation without experiencing an event, will be reported by

group. Survival times will be illustrated using Kaplan-Meier cumulative incidence curves stratified by randomised group (without adjustment for any baseline covariates). Hazards will be compared using a proportional hazards model, with fixed effects for allocation and the stratification factors and shared frailties for recruitment site. The hazard ratio for allocation and appropriate two-sided 95% confidence interval and p-value will be reported. This model will be used to derive the estimated difference in median survival time, and an appropriate two-sided 95% confidence interval. A model including a treatment by time interaction will also be fitted to explore the presence and nature of any time-varying treatment effects.

C. difficile infection

The proportion of patients that experience C. difficile infection during the 180 days following randomisation will be reported by randomised group. This outcome will be modelled using a mixed effect logistic regression model with fixed effects for allocation, the stratification factors and other prognostic baseline covariates, and random intercepts for study recruitment site. The estimated conditional odds ratio for allocation, 95% confidence interval and p-value will be reported. To aid interpretability, point estimates and appropriate two-sided 95% confidence intervals for the relative risk (cases/non-cases) and absolute risk reduction (based on the fitted model) will be reported, with the fixed effect covariates in the model set to various representative values (i.e. marginal risk ratios and risk differences at representative values). Average marginal effects on both the risk ratio and risk difference scales will also be reported with appropriate two-sided 95% confidence intervals.

Anti-microbial resistant infections

Participants will undergo passive surveillance for antimicrobial resistant infections (including MRSA, VRE, ESBL and CPE) during the 180 days following randomisation. The proportion of patients that experience each type of antimicrobial infection, number of days receiving carbapenem class antibiotics and the number of antibiotic class switches will be reported descriptively by randomised group and overall. Incidence of any antimicrobial resistant infection will be analysed using a mixed effect logistic regression model with fixed effects for allocation, the stratification factors and other prognostic baseline covariates, and random intercepts for study recruitment site. The estimated conditional odds ratio for allocation, 95% confidence interval and p-value will be reported. Point estimates and appropriate two-sided 95% confidence intervals for the relative risk (cases/non-cases) and absolute risk reduction (based on the fitted model) will be reported, with fixed effect covariates held at representative values. Average marginal effects on both the risk ratio and risk difference scales will also be reported with appropriate two-sided 95% confidence intervals. The number of days

receiving carbapenem class antibiotics and the number of antibiotic class switches will be modelled using a proportional odds model, with fixed effects for allocation, the stratification factors and other prognostic baseline covariates, and random intercepts for study recruitment site. This model will be used to derive the difference in mean number of class switches and days receiving carbapenem, conditional on pre-specified representative values of the fixed effect covariates, as well marginal effects (on both the risk ratio and risk difference scales) conditional on pre-specified representative values of the fixed effect covariates (e.g. Pr(Y > 0 | Intervention, X)/Pr(Y > 0 | Control, X) for covariates X). Average marginal effects (on both the risk ratio and risk difference scales) will also be reported together with appropriate 95% confidence intervals for various relevant outcomes/cut-offs. Data on antimicrobial resistance will be used, in conjunction with antibiotic prescribing data, to assess the appropriateness of antibiotic therapy. Appropriateness will be assessed by a blinded clinician, and will be assigned as inappropriate, appropriate, or not determined.

Acute Kidney Injury (AKI)

The proportion of patients that experience AKI (as defined in Section 3.6) during the 180 days following randomisation will be reported by randomised group. This outcome will be modelled using a mixed effect logistic regression model with fixed effects for allocation, the stratification factors and other prognostic baseline covariates, and random intercepts for study recruitment site. The estimated conditional odds ratio for allocation, 95% confidence interval and p-value will be reported. To aid interpretability, point estimates and appropriate two-sided 95% confidence for the relative risk (cases/non-cases) and absolute risk reduction (based on the fitted model) will be reported, with the fixed effect covariates in the model set to various representative values (i.e. marginal risk ratios and risk differences at representative values). Average marginal effects on both the risk ratio and risk difference scales will also be reported with appropriate two-sided 95% confidence intervals.

Days of ventilation

Days of ventilation during the 180 days following randomisation will be calculated as the number of days of intubation between randomisation and the final successful extubation. Successful extubation is defined as extubation and survival for at least 72 hours. Raw summaries of the number of days of ventilation between randomisation and 180 days post-randomisation will be reported by randomised group, both overall and by survival status. Death during intubation, or death during the 72 hours immediately following extubation will be ranked as worse than any number of days of ventilation without death. The empirical cumulative distribution function for this outcome will be plotted stratified

by randomised group. This outcome will be analysed using a proportional odds model with fixed effects for allocation, the stratification factors and other prognostic baseline covariates and random intercepts for recruitment site. This model will be used to derive marginal effects (on both the risk ratio and risk difference scales) conditional on pre-specified representative values of the fixed effect covariates (e.g. Pr(Y > 5 | Intervention, X)/Pr(Y > 5 | Control, X) for covariates X). Average marginal effects (on both the risk ratio and risk difference scales) will also be reported together with appropriate 95% confidence intervals for various relevant outcomes/cut-offs.

Days of renal replacement therapy

The number of days patients receive renal replacement therapy during the 180 days post randomisation will be reported by group, both overall and by survival status. For the purposes of analysis, death while receiving renal replacement therapy, or during the 72 hours following termination of renal replacement therapy will be ranked as worse than any number of days of renal replacement therapy without death. The empirical cumulative distribution function for this outcome will be plotted stratified by randomised group. This outcome will be analysed using a proportional odds model with fixed effects for allocation, the stratification factors and other prognostic baseline covariates and random intercepts for recruitment site. This model will be used to derive marginal effects (on both the risk ratio and risk difference scales) conditional on pre-specified representative values of the fixed effect covariates (e.g. Pr(Y > 0 | Intervention, X)/Pr(Y > 0 | Control, X) for covariates X). Average marginal effects (on both the risk ratio and risk difference scales) will also be reported together with appropriate 95% confidence intervals for various relevant outcomes/cut-offs.

10.4 Subgroup analyses

Three pre-specified exploratory subgroup analyses of the primary outcome will be conducted to investigate the consistency of treatment effect across different participant baseline characteristics (ICU admission vs no ICU admission, post-operative cIAI vs no post-operative cIAI and source control procedure vs no source control procedure) via addition of interactions between these characteristics and treatment group in the primary analysis model. The fit of the model including interactions will be compared with the fit of the primary analysis model using a likelihood ratio test. Estimates of the conditional odds ratios for allocation (and two-sided Wald method 95% confidence intervals) from the model including interactions will be reported for each level of the baseline characteristic of interest. Point estimates and appropriate two-sided 95% confidence intervals for the relative risk (cases/non-cases) and absolute risk reduction (based on the fitted model) will be reported, with fixed effect

covariates held at representative values. Average marginal effects on both the risk ratio and risk difference scales will also be reported with appropriate two-sided 95% confidence intervals.

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

Prior to the SAP being finalised, the trial statistician will provide descriptive summaries of recruitment figures, baseline data, primary outcome data and safety data to the DMEC blind to allocation. Once the SAP has been approved, the DMEC may request to see data by randomised group, in which case summaries will be presented with open labels (i.e., Intervention vs Control). After each meeting/review, the DMEC will make a recommendation to the TSC regarding continuation, and any safety concerns or modifications to trial processes that might need to be implemented to facilitate recruitment or improve adherence etc. The TSC in turn will report recommendations and/or concerns to the funder.

10.6 Economic evaluation

Health economics analysis: The analysis will follow a detail pre-specified health economic analysis plan (HEAP). The analysis will estimate the cost-effectiveness of a fixed-extended-duration antibiotic strategy vs. standard practice in patients with cIAI. This analysis will be aimed at evaluating the cost-effectiveness of the intervention at the end of the treatment phase (180 days) and via a long-term cost-effectiveness model aimed at capturing the potential life-time effects of re-infections and complications (e.g., operations). We will include an analysis of affordability from an NHS perspective. We will include indirect costs to patients, family members and caregivers. We will include a subsection in the resource use questionnaire to capture out-of-pocket and indirect costs incurred by patients and their families or caregivers, such as loss of income due to childcare, short or long term disability.

Resource use questionnaire: This will collect resources used by patients when in-hospital or at home. We will include items such as, hospital stay, treating ward, hospital attendances, outpatient, GP and specialised nurse visits. We will also include items to identify use of social care resources such as social workers visits, meals on wheels or laundry services among others. This questionnaire will be collected at the same time as the EQ-5D-5L (baseline, day 30, 90 and 180). Similarly, it will be completed in person for in-patients and remotely for outpatients in either written or electronic form and assigned by proxies for those unable to complete due to sedation or illness if necessary.

Health economics analysis: We will estimate the cost-effectiveness of a fixed-extended-duration antibiotic strategy vs. standard practice in patients with cIAI. This analysis will be aimed at evaluating

the cost-effectiveness of the intervention at the end of the treatment phase (180 days) and via a long-term cost-effectiveness model aimed at capturing the potential life-time effects of re-infections and complications (e.g., operations).

Within-trial analysis: The analysis will follow the health and social care perspective and use QALYs as an outcome measure (collected via the EQ-5D-5L questionnaire). Costs will be collected via a resource use questionnaire (see 5.12). The base case will be an ITT analysis, handling missing data using multiple imputation (assumption relaxed for the sensitivity analysis), adjusting for baseline imbalances and using seemingly unrelated regression to account for cost/outcome correlations.

Long-term model: This will follow patients through their lifetime. We intend the model will follow a Markov structure primarily populated from the collected data. We will, however, evaluate the heterogeneity of the patient population and if necessary, we will use a methodology that will allow us to account for specific patient characteristics or health status such as the ones descried in section 10.4 (subgroup analysis). This will likely involve an individual level model to. If data allows it, we will aim to extrapolate the effect of the intervention via survival analysis and complemented with a systematic review of the literature and expert opinion where necessary.

Base case scenario: The scenario for both models will use QALYs derived from the mapped 3L version as per NICE recommendations. Secondary analyses will be performed using QALYs derived from the 5L version (both models). Costs and outcomes will be discounted where necessary at a 3.5% discount rate [31]. Our results will be presented in cost-per-QALY via a deterministic and probabilistic cost-effectiveness analysis. We will estimate incremental cost-effectiveness ratios, net monetary benefit and determine cost-effectiveness using the NICE recommended threshold of £20,000 per QALY gained. We will perform one-way and scenario sensitivity analysis. Analyses will follow NICE guidelines and CHEERS reporting standards [31,32, 33].

11 DATA MANAGEMENT

11.1 Data collection tools and source document identification

All data management procedures (e.g., source data verification, data validation, archiving etc.) will be conducted in accordance with the trial data management plan which will be generated during the trial set-up phase. YTU will develop this plan and be responsible for all aspects of data management throughout the trial.

Source documents are original documents, data, and records from which participants' trial data are obtained. These include, but are not limited to, hospital records, clinical and office charts, laboratory and pharmacy records, radiographs, correspondence, completed scales and quality of life questionnaires. The trial team and site investigators will ensure that all source data for the trial is kept in a secure location.

Most trial data can be obtained from routinely collected clinical information recorded in patients' medical records (e.g., routine observations, blood tests and prescription charts). No medical procedures (e.g., blood tests) are required for the specific purpose of trial data collection but may be completed as part of standard care. Trial data will be collected from medical records using electronic case report forms (eCRFs) designed by the trial team at York Trials Unit (trial manager, trial coordinator, trial statistician) in conjunction with the chief investigator and clinical co-applicants. Data entered by site staff/investigators using these eCRFs will be entered directly onto the trial database, with "soft" validation implemented during data entry to help improve the completeness and consistency of the entered data. The remaining data (that cannot be obtained from patient medical records) will be captured on participant completed questionnaires. This will include a quality of life questionnaire (EQ-5D-5L), and a trial specific brief outpatient medication adherence questionnaire. It is anticipated that these questionnaires will generally be completed electronically by participants, with direct entry of these data onto the study database, and "soft" validation implemented during data entry. A paper version of the baseline questionnaire will be available for patients without access to an electronic portable device while in hospital. Follow-up questionnaires will be sent by email. If patients do not have an email, YTU will call to obtain the data by telephone. If patients do not respond within 5 days, a text message will be sent. Postal completion will be a back-up option and will be coordinated by YTU. Data on paper questionnaires will be transcribed to eCRFs by YTU. The trial database and the eCRFs will be hosted by York Trials Unit using REDCap (Research Electronic Data Capture) software.

11.2 Data handling and record keeping

This information will be detailed in the trial data management plan.

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- in line with participant consent. Following completion of the trial analyses, the final trial dataset(s) will be held by YTU. These datasets will be accessible via completion of a YTU data request form. The final analysis sets will be

stored as Stata.dta files on YTU's servers at the University of York, and can be converted to different formats for sharing as required.

11.4 Archiving

Once sites have completed a close out report and this is approved by the Sponsor, they will be instructed to archive their site file and trial data according to their local SOPs.

Archiving of the TMF and full dataset will be authorised by the Sponsor following submission of the end of trial report. York Trials Unit will complete this task as per their SOP. Documents/data will be stored for a minimum of 5 years after trial completion. No archived documents/data will be destroyed without authorisation from the Sponsor.

Essential documents will initially be stored in the YTU archive room. Once regular access is no longer required, they will be relocated to the YTU approved off-site archive provider, DeepStore Ltd. Permission from the lead statistician will be needed to request access. Electronic records will be stored on an electronic archive drive only accessible by named people.

12 MONITORING, AUDIT & INSPECTION

A Trial Monitoring Plan will be developed and agreed by the Trial Management Group (TMG), TSC and CI based on the trial risk assessment.No on-site monitoring will take place, however regular central monitoring will be performed according to ICH GCP and the EXTEND Monitoring Plan. Data will be evaluated for compliance with the protocol and GCP and the applicable regulatory requirements.

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 trial
- 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 endedIt is the responsibility of YTU to produce the annual reports as required.

- YTU will notify the REC of the end of the trial
- If the trial is ended prematurely, YTU will notify the REC, including the reasons for the premature termination
- Within one year after the end of the trial, YTU 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 independent (external to the investigators' host institution and not involved in the trial in any way), expert (qualifications) reviewers Robert G. Sawyer, MD, FACS, FIDSA, FCCM. Professor of Surgery and Medical Engineering Chair, Department of Surgery Western Michigan University Homer Stryker MD School of Medicine and Philippe Montravers, Département d'Anesthésie-Réanimation, CHU Bichat Claude Bernard, Paris, France.

13.3 Regulatory Compliance

- 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 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)

13.4 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 YTU immediately. YTU will be responsible for reviewing protocol deviations and reporting to the TSC/DMEC.

13.5 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.

7. Serious breaches should be reported to YTU within 24 hours of the breach. If the CI confirms this is a serious breach, YTU will report to the sponsor and the REC within 1 working day.

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

13.6 Data protection and patient confidentiality

The trial staff will ensure that the participants’ anonymity is maintained. The participants will be identified only by a participant ID number on the eCRF and trial other documents (exceptions below). All documents will be stored securely and only accessible by trial staff and authorised personnel. The study staffs, (all investigators and trial site staff) will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

Exceptions: The consent form will contain the patients’ initials and signature to ensure consent was given. The patient details form will contain the patients’ name, address and contact details so that they can be contacted for the purpose of requesting questionnaire completion. These documents will be sent to YTU electronically using a reliable encryption method and stored in a secure electronic location only accessible by members of the central trial management team.

The University of Leeds and University of York will be joint data controllers. Documents/data will be stored for a minimum of 5 years after trial completion. Further details will be within a data management plan

13.7 Financial and other competing interests for the chief investigator, PIs at each site and

None to declare

13.8 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.

13.9 Amendments

Once the TMG have agreed that an amendment is necessary, the amendments will be made to the required documentation and the HRA amendment tool completed. This tool will confirm the category of the amendment. Once Sponsor authorisation has been confirmed, YTU will submit and, where necessary, obtain approval from the Research Ethics Committee (REC), Health Regulatory Authority (HRA) and host institution(s) for approval of all substantial amendments to the original approved documents. Once approvals are received, the new documents/versions will be shared with sites and the study version control log will be updated for sites to check they are using only the most recent versions of trial documents.

13.10 Post trial care

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

13.11 Access to the final trial dataset

The lead statistician will have access to the final dataset. No other researchers will have access until the main results have been published. Following publication formal requests for access to trial datasets can be made.

14 DISSEMINIATION POLICY

14.1 Dissemination policy

Publications arising from the trial will be carried out with reference to the Consort Guidance. Data from the trial will be owned by the key research contributors as per this research protocol. Participating investigators will not have rights to publish any of the trial data until the full trial has been published and in agreement with the key research contributors. The NIHR will be acknowledged as the research funder. The trial protocol, full trial report, anonymised participant level dataset, and statistical code for generating the results will be made publicly available on reasonable request.

14.2 Authorship eligibility guidelines and any intended use of professional writers

Authors for any publications deriving from this protocol will be required to meet The International Committee of Medical Journal Editors (IJCMJE) has defined authorship criteria for manuscripts submitted for publication. All key protocol contributors will be provided the opportunity to fulfil IJCMJE author criteria.

Details of planned publications and requirements for authorship are detailed in the publication plan.

15 REFERENCES

1. Wenzel RP, et al. Antibiotics for abdominal sepsis. *N Engl J Med*. 2015;372(21): 2062-3.
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16. APPENDICIES

Appendix 1 - Trial management / responsibilities

The trial will be sponsored by the University of Leeds and hosted by York Trials Unit (YTU), University of York. YTU will manage the study and also quality assure trial processes. The institutions have an established track record of working together and running large clinical trials. The MHRA has provided a response that our planned investigation will not be considered a CTIMP. A Trial Management Group (TMG) will monitor ongoing management of the trial including the detailed design, set-up, initiation and supervision of the study. This will comprise the Chief Investigator (CI), all co-applicants, administrative trial team at YTU, trial statisticians, and trial health economist. The group will meet monthly from the start of the study to the end of the pilot phase and quarterly thereafter to manage the detailed design,

set-up, initiation and supervision of the study. YTU will work closely with the lead applicants, who will assume the role of PIs, during setup and during the internal pilot of the study, including regular teleconferences to ensure that all aspects of preparation of study material, study site set-up and the start of recruitment progress smoothly. They will keep in close contact via email, virtual meetings and telephone throughout. This will include all PPI/PAG activities on the project. The trial manager at YTU will assume responsibility for all aspects of trial management. They will be supported by a trial coordinator, who will be responsible for the day-to-day support of trial sites, data handling, and the management of the administrative trial team. The team at YTU will meet on a weekly basis during the study. There will be a Trial Steering Committee (TSC) to monitor progress and provide independent advice. An independent Data Monitoring and Ethics Committee (DMEC) will monitor the data arising from the study and recommend whether there are any ethical or safety reasons why the trial should not continue. The TSC and DMEC will comprise independent clinicians and health service researchers with appropriate expertise and will also be attended by the trial statisticians. There will also be independent public members on the TSC. Both the TSC and DMEC will meet at regular intervals to provide project oversight to the trial. The project will also be monitored by the sponsor for whom a representative will be invited to attend the TMG/TSC meetings, and we will submit required progress reports to the NIHR. Each site will have a site Principal Investigator (PI) who will be responsible locally for the trial. Consultant colorectal surgeons, anaesthetists or microbiologists will assume the role of site PIs. They will have oversight for a local site team including specialist trainees and research nurses. All trial staff will have current GCP certification and will be trained in trial procedures by YTU during site set-up, thereby meeting the sponsors and NIHR standards. The NIHR Associate PI scheme will be adopted to enable trainees to participate in the trial and support PIs. Both consultants and trainees will be responsible for the identification and recruitment of eligible patients. The research team has ensured trainee networking across relevant specialities is represented in the TMG to maximise the use of the associate PI scheme. Dr Ahmed is funded to support and co-ordinate trainee recruitment across the surgical, intensive care and microbiology specialties. Investigator meetings will be held annually, including one before recruitment commences. These meetings will help to further enhance the fostering of networks and engagement that improve local patient assessment and recruitment, adherence to the proposed intervention, and continue to develop knowledge and share experience. Outcomes from these meetings will be considered by the TMG and if appropriate the TSC and DMEC.

Appendix 2 - Principal Investigator responsibilities

The PI's legal responsibilities include: Attendance at initiation meeting/teleconference, training of new members of the trial team in the protocol and its procedures, ensuring that the site file is accurately maintained, dissemination of important safety or trial related information to all stakeholders within their site and safety reporting within the timelines.

Appendix 3 – Data collected at baseline

Variable	Options	Person completing data point	Rules/References/Calculation	Form for analysis and how will be reported (continuous, categorical, ordinal)
Age	Years	RN		Continuous
Sex	Male/Female	RN	Sex as recorded in a patient's medical notes	Categorical
Race/Ethnicity	Standard option set	RN		Categorical
Centre	Name of site	RN		Categorical
Height/weight/body mass index	Centimetres/Kg/Ratio	RN	The measurements closest to the time of recruitment. Where data is missing state data missing	Continuous
Co-morbidities	Charlson score	RN	This data will be collected prospectively based on case note review and patient responses.	Continuous/ ordinal
cIAI severity	NEWS2/SOFA	RN		Continuous/ ordinal
Organ associated with the infection	Abdominal wall Appendix Biliary tract Gallbladder Large bowel Meckel's diverticulum Oesophagus Pancreas Reproductive tract Rectum Small bowel Stomach Urinary tract No specific organ identified Unknown	RN/Clinician	List all organs associated with the cIAI based on Ct or surgical findings.	Categorical
Underlying pathology	Adnexal abscess communicating with peritoneal cavity Anastomotic leak Appendicitis Complicated cholecystitis (perforation or extra-biliary abscess): calculous Complicated cholecystitis: acalculous Cancer-Appendix Cancer-Bowel Cancer-Gall bladder Cancer-Gynaecological	RN/Clinician		Categorical

	Cancer-Other Chemo-radiotherapy in last 12 months Clostridium difficile colitis Crohn's disease Diverticular disease Drug reaction Fistula: Colo-urinary, Colo-intra-abdominal, Colo-cutaneous or Colo-vaginal Ischaemic bowel Immunosuppression Pancreatitis Perforated peptic ulcer Perforated small bowel Perforated large bowel Pelvic inflammatory disease Post-operative complication (< 90 days) Ulcerative colitis Spontaneous Volvulus Unknown Other (please state)			
Surgical or radiological interventions	Radiological (CT guided) percutaneous drainage (+/- drain insertion) Radiological (U/S guided) percutaneous drainage (+/- drain insertion) Surgical: Resection and anastomosis (+/- drain insertion) (+/-washout) Surgical: Drainage only (+/- drain insertion) (+/-washout) Surgical: Resection and proximal diversion (+/-washout) Surgical: Closure of perforation only (+/- drain insertion) (+/-washout) Surgical: Drainage and diversion (+/- drain insertion) (+/-washout) Surgical: Excision of damaged organ e.g gallbladder (+/- drain insertion) (+/-washout) Surgical: Washout only (+/- drain insertion) .None of the above: Hepatobiliary surgery None of the above: Pancreatic surgery None of the above: Colorectal surgery None of the above: Radiological procedure None of the above: Other The patient has had no surgical or radiological procedures to remove the infection	RN/Clinician		Categorical
Radiological findings when available	Collection (Y/N) Single collection (Y/N) Multiple collections (Y/N) Maximum depth of collection (cm) Evidence of anastomotic leak	RN/Clinician		Categorical Categorical Categorical Continuous Categorical

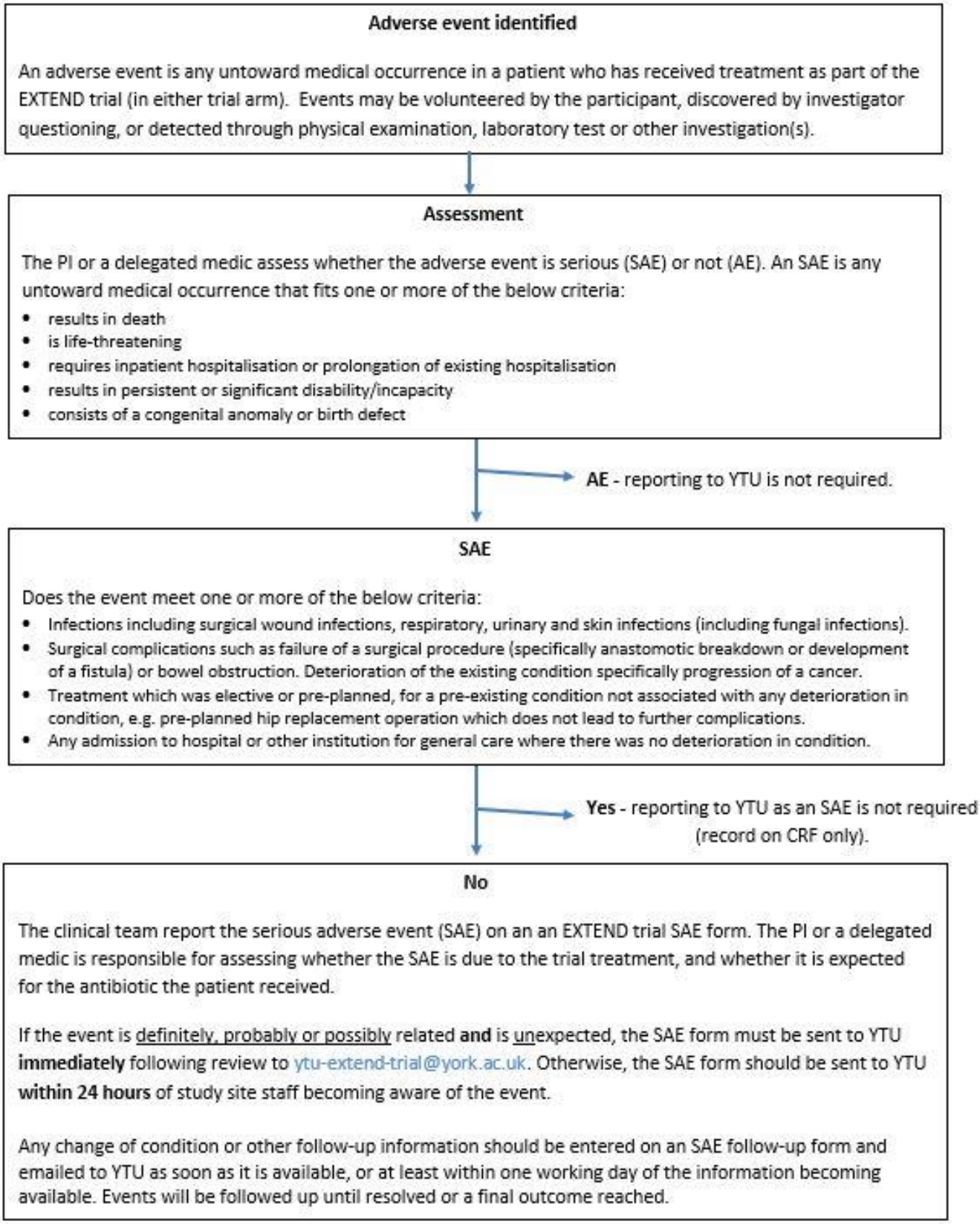
	(Y/N) Evidence of fistulation (Y/N)			Categorical Categorical
Antibiotic treatment	Antibiotic/Start date/End date/Dose/Frequency	RN		Categorical
Other infection	Clinical assessment	RN		Categorical
AMR infection	Microbiological results MRSA/ESBL/AMPC/CPE/VRE	RN		Categorical
ICU stay in the 30 days before randomisation	Number of days	RN		Categorical
Ventilation in the 10 days before randomisation	Number of days	RN		Categorical
Renal replacement therapy in the 10 days before randomisation	Number of days	RN		Categorical

Appendix 4 – Schedule of Procedures

	Routine care	Baseline	Day 30[1]	Day 90[1]	Day 180[1]
Medical assessments	X				
Blood tests (as part of routine care)	X				
Source control procedure	X				
C. difficile faeces testing	X				
In patient antibiotic prescriptions	X				
Microbiological sampling	X				
Informed consent		X			
Eligibility assessment and randomisation		X			
Medical history and Demographics		X			
EQ-5D-5L questionnaire		X	X	X	X
Resource use questionnaires			X	X	X
Outpatient antibiotic use Questionnaires			X	X	X
Adherence questionnaires			X		
Source control/source of infection assessment		X			
Objective data -Antibiotic prescriptions -Antimicrobial resistance -Inflammatory markers -Mechanical ventilation -Readmission -Renal function -Vasoactive agent use			X	X	X
Objective data -C. difficile results -Renal replacement					x

[1] +/- 7 days

Appendix 5 – Safety Reporting Flow Chart



Appendix 6 – A full list of specific SAEs which do not need to be reported

CARDIAC
Arrhythmia
Cardiac arrest
Myocardial Infarction or ischaemia

GASTROINTESTINAL (GI)
Anastomotic leak
Gastro-intestinal bleed
Post-operative haemorrhage
Bowel infarction
Perforated viscus

Ileus
Gastrointestinal Obstruction
Gastrointestinal ischaemia/necrosis
Gastrointestinal perforation
Pancreatitis
Development of a fistula

INFECTION
Skin and soft tissue infection
Bone and joint infection
Urinary tract infection
Vascular System infection
Reproductive tract infection
GI tract infection
Respiratory tract infection
Ear/nose/throat infection
CNS infection
Sepsis
Pyrexia of unknown cause

NEUROLOGICAL
Stroke
Acute psychosis or delirium

RENAL
Acute Renal Failure / Acute kidney injury

RESPIRATORY
Respiratory failure/Acute Respiratory Distress
Pulmonary oedema
Pulmonary embolism (PE)/DVT
Endotracheal re-intubation
Aspiration pneumonitis/Aspiration Pneumonia
Bronchospasm
Atelectasis
Cardiac Failure
Pneumothorax

SKIN AND SOFT TISSUE
Wound Dehiscence

UROLOGICAL
Urinary tract obstruction

VASCULAR
Pulmonary embolism (PE)/DVT

OTHER
Allergy
Expected drug reaction
Surgical complication
Progression of underlying condition including cancer
Treatment which was elective or pre-planned for a pre-existing condition