

Medicinal Product Protocol Guidance and Template

FULL TITLE OF THE TRIAL

Colo-Pro Pilot: A pilot randomised controlled single blind trial to compare standard single dose antibiotic prophylaxis to antibiotic prophylaxis administered as a bolus-continuous infusion for the prevention of surgical site infections in adults undergoing colorectal surgery.

SHORT STUDY TITLE

Short title: Colo-Pro Pilot: A pilot study to compare standard single dose antibiotic prophylaxis to bolus-continuous infusion dosed antibiotic prophylaxis for the prevention of infections after colorectal surgery.

Lay title: Colo-Pro Pilot: A pilot study to compare standard single dose antibiotic prophylaxis to higher dose antibiotic prophylaxis for the prevention of infections after colorectal surgery.

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



Colo-Pro Pilot

RESEARCH REFERENCE NUMBERS

Leeds Teaching Hospitals Trust R&I number: MB15/130

The University of Leeds reference number: MB15/130

TRIAL REGISTRY NUMBER AND DATE

Clinical trials.gov: NCT02445859

PROTOCOL VERSION NUMBER AND DATE

Version 2.2. 10/10/2016

SPONSOR

The University of Leeds



RESEARCH REFERENCE NUMBERS

REC Reference: 15/YH/0260

Clinical trials.gov Number: NCT02445859

SPONSORS Number: MB15/130

FUNDERS Number: Department of Microbiology, Leeds Teaching Hospitals
NHS Trust.

Reference number: Not applicable



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 ICHGCP and research governance framework 2005

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

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

For and on behalf of the Study Sponsor

Signature:

Date:

...../...../.....

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Name:

Position:

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Chief Investigator

Signature:

Date:

...../...../.....

.....

Name: Andrew Kirby

Position: Associate clinical professor in microbiology



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Sponsor	The University of Leeds
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Clinical Trials Unit	None
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Statistician	Not applicable
Trials pharmacist	Not applicable
Committees	The Trial Steering group: This group will periodically review



	<p>safety data and liaise with the DMC regarding safety issues.</p> <p>Data (safety) monitoring group: This group will exist to ensure the trial protocol is followed and that any adverse events are investigated and reported</p> <p>Committees Contact</p> <p>Georgina Davis</p> <p>Old Medical School, Leeds General Infirmary, Leeds, LS1 3EX</p> <p>Tel: 0113 3926814</p> <p>Fax: 0113 3922696</p> <p>E-mail: georgina.davis@nhs.net</p>
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TRIAL SUMMARY

Trial Title	Colo-Pro Pilot: A pilot randomised controlled single blind trial to compare standard single dose antibiotic prophylaxis to antibiotic prophylaxis administered as a bolus-continuous infusion for the prevention of surgical site infections in adults undergoing colorectal surgery.	
Short title	Colo-Pro Pilot: A pilot study to compare standard single dose antibiotic prophylaxis to bolus-continuous infusion dosed antibiotic prophylaxis for the prevention of infections after colorectal surgery.	
Clinical Phase	Therapeutic exploratory trial including comparison with the standard treatment regimen (Phase II/III)	
Trial Design	A randomised controlled single blind parallel group trial.	
Trial Participants	<p>Adults (>18 years)</p> <p>Undergoing colorectal surgery (incision, excision or anastomosis of the large bowel, including anastomosis of small to large bowel).</p> <p>Cefuroxime and metronidazole are suitable prophylactic antibiotics</p> <p>Expected duration of surgery > 2 hours</p> <p>Creatinine clearance > 40 ml/min</p>	
Planned Sample Size	90	
Treatment duration	Duration of the surgical procedure up to 6 hours	
Follow up duration	30 days	
Planned Trial Period	12 months	
	Objectives	Outcome Measures



Primary	To reduce by 50% the rate of surgical site infections after colorectal surgery.	Surgical site infection within 30 days of operation.
Secondary	<p>To reduce the rate of all infections after colorectal surgery.</p> <p>To reduce antimicrobial consumption after colorectal surgery</p> <p>To reduce length of hospital stay after colorectal surgery</p> <p>To reduce mortality after colorectal surgery</p> <p>To reduce anastomotic leakage after colorectal surgery</p> <p>To improve quality of life after colorectal surgery</p> <p>To reduce the cost of healthcare treatment associated with colorectal surgery</p> <p>To investigate if pre-operative antibiotic resistance, as determined by antibiotic susceptibility testing of rectally colonising Enterobacteriaceae, is predictive of a patients risk of a post-operative surgical site infection.</p> <p>To investigate the exposure-response relationship for antibiotic prophylaxis in the prevention of surgical site infection prevention after colorectal surgery.</p>	<p>All infections within 30 days of operation.</p> <p>Antimicrobial consumption within 30 days of operation.</p> <p>Length of hospital stay after operation</p> <p>Mortality after operation at one year.</p> <p>Radiological or clinically diagnosed anastomotic leakage</p> <p>Quality of life scores pre-operatively and post operatively at 30 days.</p> <p>Cost of healthcare treatments after operation at 30 days.</p> <p>See Table 5</p> <p>See Table 5</p>



Medicinal Product	Cefuroxime 1.5g powder for solution for injection or infusion
Formulation, Dose, Route of Administration	<p><u>Formulation</u></p> <p>Cefuroxime: Each vial contains, as the active ingredient, cefuroxime sodium for injection 1578mg equivalent to 1500mg of cefuroxime respectively</p> <p><u>Dose</u></p> <p><u>Standard treatment</u></p> <ul style="list-style-type: none"> 1.5 grams 4 hourly. <p><u>Intervention treatment:</u></p> <ul style="list-style-type: none"> A maximum loading dose of cefuroxime 2332 mg A maximum hourly dose on continuous infusion of 1226 mg/hour. These doses will be administered for a maximum of 6 hours. <p><u>Route of administration</u></p> <p>Intravenous</p>



FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL AND NON FINANCIALSUPPORT GIVEN
The University of Leeds	Employment of Dr Andrew Kirby Employment of Mr Dermot Burke
Leeds Teaching Hospitals NHS Trust	Employment of Dr Andrew Kirby Employment of Mr Dermot Burke
Department of Microbiology, Leeds Teaching Hospitals NHS Trust	Facilities/Funding for microbiological/pharmacological testing Leeds Teaching Hospitals Charitable funding to support microbiological testing at £12, 000
Department of Surgery, Leeds Teaching Hospitals NHS Trust	Facilities for recruitment and intervention
The West Yorkshire Postgraduate Medical Deanery	Employment of Academic Foundation Year 2 doctor



ROLE OF STUDY SPONSOR AND FUNDER

Neither study sponsor or funder has had any direct or indirect input into the study design.

Neither study sponsor or funder will have any input into study conduct, data analysis or interpretation beyond ensuring governance arrangements for such procedures are appropriate.



ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITTEES/GROUPS & INDIVIDUALS

The Trial Steering group

This group will periodically review safety data and liaise with the DMC regarding safety issues.

Chair: Dr Andrew Kirby

Research doctor: Mr Dermot Burke

Research doctor: Rotational academic FY2 doctor

Administrator: Georgina Davis

The Trial data (safety) monitoring group

This group will exist to ensure the trial protocol is followed and that any adverse events are investigated and reported. The short nature of this pilot trial precludes the need for a committee only related to data monitoring or trial steering.

Independent Chair: Dr Jonathan Sandoe

Physician: Dr Damian Mawer

Physician: Dr Sarah Drake

Administrator: Georgina Davis



Protocol contributors

Dr Andrew Kirby

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

The protocol will be reviewed by service users through the Leeds Patient and Public Involvement in Research Group

KEY WORDS:

Antibiotic; Prophylaxis; Surgical site infection;
Pharmacodynamics.



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LIST OF ABBREVIATIONS

Define all unusual or 'technical' terms related to the trial. Add or delete as appropriate to your trial. Maintain alphabetical order for ease of reference.

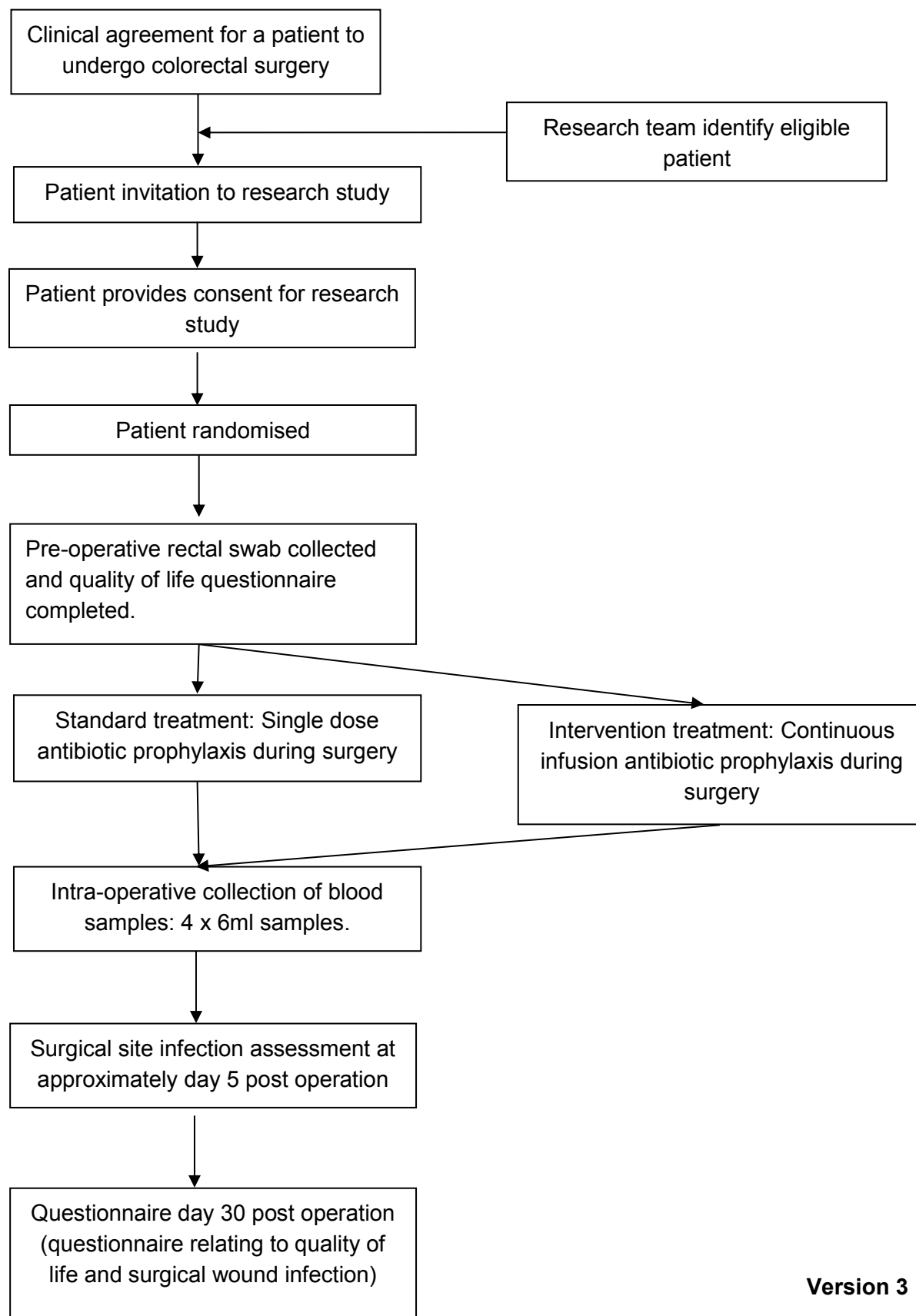
AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	European Commission
EMA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MP	Medicinal Product
MS	Member State



NHS R&D	National Health Service Research & Development
NIMP	Non-Investigational Medicinal Product
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File



TRIAL FLOW CHART



STUDY PROTOCOL

Title: Colo-Pro Pilot: A pilot randomised controlled single blind trial to compare standard single dose antibiotic prophylaxis to antibiotic prophylaxis administered as a bolus-continuous infusion for the prevention of surgical site infections in adults undergoing colorectal surgery

1 BACKGROUND

Review of published literature

Surgical site infection (SSI) following colorectal surgery

20,000 patients annually undergo elective colorectal surgery in England with approximately 22% developing a surgical site infection (SSI). SSIs after colorectal surgery have been associated with a 4.6% increase in 30 day mortality, increase hospital stay and cost £5000 per SSI (Jenks 2014).

Colorectal surgery is a common surgical procedure for conditions such as colonic cancer, ulcerative colitis and Crohn's disease. Following surgery, patients undergoing colorectal surgery have a high rate of surgical site infection (SSI), higher than all other types of surgery (Health Protection Agency 2014). SSIs include infections of the site site which encompasses infection of the skin and/or deep tissues (superficial and deep SSIs, as well as infections within the abdomen (organ space SSIs). For the purposes of this study we will refer to superficial and deep SSIs as SSIs (i.e. excluding organ space SSIs). Post operative SSIs in colorectal patients are associated with increased length of hospital stay, increased health care costs (£5000 per SSI) and in the case of organ space SSIs, are associated with an increase in post operative mortality (Coello, 2005, Kirby 2015a).

Antibiotic prophylaxis to prevent SSI – current practice and limitations.

In an attempt to prevent SSIs antibiotics are usually given just before an operation, this is called antibiotic prophylaxis. Antibiotic prophylaxis is effective. When initially introduced antibiotic prophylaxis reduced SSI rates from 40% to 10% (Nelson 2014). Currently, published evidence suggests SSI rates after elective colorectal surgery occur in over > 10% of patients (Kirby 2015a, Petrosillo 2008, Smith 2004, Tanner 2009, Wick 2008). The reasons for the higher rate of SSIs now are unclear, but it may represent different definitions (SSI includes organ space infections, SSI does not), more aggressive treatment e.g. pre-operative radiotherapy, or that antibiotic prophylaxis is less effective. In patients undergoing emergency procedures SSI rates are higher than for elective procedures (Morikane 2014). Most SSIs (90%) occur within 14 days of the operation (Kirby 2015a). These infections are commonly caused by bacteria that live in the human bowel. The types of bacteria from the bowel which are believed to cause SSIs are called Enterobacteriaceae, commonly referred to as “coliforms” (e.g. *E. coli*) and anaerobes.

Antibiotic prophylaxis is currently prescribed to patients at doses similar to those used to treat infections such as pneumonia. It is not known if these are the best doses to prevent infections after colorectal surgery. There has only been one study which compared different antibiotic doses for the



prevention of SSI after colorectal surgery. In this study two different-dosing regimens were compared (Gentamicin: 4.5mg/kg and 1.5 mg/kg) in 146 patients. The study determined that the higher dose regimen had a lower SSI rate (22%) than the low dose regimen (55%) (Zelenitsky 2000). Unfortunately other studies have not been completed to further investigate if new, non-treatment based dosing regimens, are better at preventing post-operative SSIs when compared to dosing used for the treatment of infections.

There is increasing concern over the efficacy of antibiotic prophylaxis in the United Kingdom, as well as internationally, because of increasing rates of resistance to antibiotics (McGregor 2013). Some clinical evidence suggests that pre-operative identification of antimicrobial resistant (AMR) coliforms in patients undergoing liver transplants and prostate biopsies is associated with an increased rate of post operative infections (Roberts 2014, Lübbert 2104). There is currently no evidence relating AMR to SSIs in colorectal surgery. In addition, increasing rates of obesity mean higher antibiotic doses are likely to be needed to obtain the same benefits; twenty five percent of adults are now obese, compared to 15% 20 years ago. Data have been reported which does show obesity (BMIs over 30) are associated with a higher SSI rates (Itani 2008). These concerns over the efficacy of antibiotic prophylaxis may be justified because a significant increasing trend of colorectal SSIs has been reported by Public Health England (2014). There is also evidence, based on pharmacological modelling, that suggests patients with good renal function, who excrete antibiotics quickly, are another risk group for SSIs (Asín-Prieto 2015).

Ways to improve prophylaxis

AMR bacteria are normally identified in patients with infection, and so resistance rates are reported for defined infections. Similar data are not available for patients who are about to undergo surgery as they are not normally sampled. To understand if patients admitted to the hospital for colorectal surgery were colonised with resistant bacteria pre-operatively we completed a feasibility study. In 63 patients due for colorectal surgery, rectal swabs were collected pre-operatively. Enterobacteriaceae (e.g. *E.coli*) underwent antimicrobial susceptibility testing. It was found that 18.2% of patients with Enterobacteriaceae cultured (10/55) were colonised with cefuroxime resistant Enterobacteriaceae (Kirby 2015b). The antibiotic susceptibilities of these Enterobacteriaceae are presented in Table 1 by MIC value. A Minimum Inhibitory Concentration (MIC) is the lowest concentration that inhibits the growth of a bacterium. MICs are used to define bacteria as sensitive or resistant to an antibiotic i.e. as likely to be effectively treated by an antibiotic or not. Cefuroxime resistance in Enterobacteriaceae is defined as an Enterobacteriaceae which requires >8mg/L to inhibit overnight growth.

Table 1: The Minimum Inhibitory Concentration of rectally colonising Enterobacteriaceae to cefuroxime in participants planned to undergo elective colorectal surgery (Kirby 2015b) (resistance highlighted in bold).

		Enterobacteriaceae MICs to cefuroxime (%)
MIC (mg/L)	<=2	7.3
	4	70.9



	8	3.6
	16	7.3
	>=32	10.9

It is not known how MICs relate to treatment outcome when using antibiotics for surgical prophylaxis. Expert publications have suggested that the time during the operation that the free (non protein bound) serum drug level is above the MIC is most likely to be predictive of treatment success (Moine 2013). By using clinical data on drug levels we can compare serum drug levels achieved throughout an operation in patients receiving standard doses of antibiotics to the antibiotic susceptibility of Enterobacteriaceae. A summary measure of Enterobacteriaceae susceptibility is the MIC90. The MIC90 is the MIC value which includes 90% of a bacterial population. For the data provided in Table 1 the MIC90 is 16mg/L. These data suggest that treatment doses of antibiotics commonly used an antibiotic prophylaxis for surgery, e.g. cefuroxime (1.5g), does not reach blood levels which would inhibit the growth of 90% of bacteria for much beyond one hour of an operation (Table 2). These data should also be considered in relation to the variation in drug levels seen in a population of patients. In pharmacological models which take account of this variation, in patients with normal renal function, less than 40% of patients are predicted to have free serum drug levels of 8mg/l at 4 hours of surgery (Asín-Prieto 2015).

Table 2: Known and estimated cefuroxime serum drug concentrations after intravenous administration in relation to *E. coli* MIC90.

Drug		Drug concentration at 1 hour time intervals (mg/L) after a single intravenous dose				Reference
		1hr	2hr	3hr	4hr	
Cefuroxime 1.5g	Free drug: 50% of total drug	21.5	12.15	7.8	4	Estimated from Kucers' 2010
Cefuroxime MIC90 (mg/L)		16				

Table 2 shows that many patients do not achieve drug levels throughout surgery that are predicted to prevent infections. One way of maintaining drug levels at desired concentrations is by dosing differently. Currently, single doses of antibiotic are administered pre-operatively. An alternative strategy is to dose continuously throughout surgery. Continuous infusion offers the opportunity to maintain targeted drug concentrations for the duration of an operation. This could also be achieved by administering antibiotics with long serum half lives, Table 3. The antibiotics with long serum half lives are ceftriaxone and ertapenem. Ceftriaxone has been assessed in relation to other cephalosporins with shorter half lives and been found to be more effective. For abdominal surgery ceftriaxone is more effective these other cephalosporins, having an odds ratio of 0.5 (Woodfield 2009). And ertapenem, when compared to ceftriaxone has been shown to be equally effective (Leng 2014). The disadvantages of these antibiotics are that they have been written out of antibiotic prophylaxis



guidelines by microbiologists due to concerns over antibiotic resistance and *Clostridium difficile* infection. Third generation cephalosporins (e.g. ceftriaxone) and carbapenems are antibiotics that are usually reserved for the treatment of antibiotic resistant infections in hospitalised patients. Widespread use for antibiotic prophylaxis would be a concern as antibiotic consumption is known to relate to antibiotic resistance. In addition, the use of antibiotics with a long half-life would expose bacteria to antibiotics over a relatively long period of time, and to relatively low concentrations of antibiotics for a long time (i.e. a long tail). Ceftriaxone use has been dramatically reduced in the UK given its association with *C. difficile* infection. Therefore it is unlikely a strategy of prophylaxis using ceftriaxone, despite its improved efficacy, would be accepted within the NHS.

Table 3: Ceftriaxone and ertapenem antibiotic serum drug concentrations after intravenous administration in relation to *E. coli* MIC90.

Drug		Drug concentration at 1 hour time intervals (mg/L) after a single intravenous dose				Reference
		1hr	2hrs	3hrs	4hrs	
Ceftriaxone 1g	Free drug: 27 %	1.74	1.3	0.98	0.73	Kucers'
Ceftriaxone MIC 90 mg/L		0.125				
Ertapenem 1g	Free drug: 10%	13.1	11.4	9.0	8.0	Kucers'
Ertapenem MIC 90 mg/L		0.25				

The problem of low drug levels when administering short half life antibiotics during surgery could be addressed by continuous infusion of these antibiotics. There is concern, and evidence (Zelenitsky 2000) that these low levels which can occur during surgery are associated with antibiotic prophylaxis failures. This strategy, continuous infusion of short half life antibiotics, limits the post operative antibiotic exposure and so potentially reduces risks of *C. difficile* infection and antibiotic resistance.

Antibiotic prophylaxis and pharmacodynamics

If it is accepted that maintaining the antibiotic levels above certain serum blood concentration targets (pharmacokinetic (PK) targets) is desirable during surgery, consideration is needed as to exactly what that target is. The desired PK target should take account of what antibiotic concentration profile is best able to prevent an infection (pharmacodynamic (PD) targets). PD targets are unfortunately unknown for prophylaxis. For treatment, the PD targets are most commonly the time unbound serum drug concentrations are above the MIC ($fT > MIC$), or the ratio of maximal serum concentration to MIC (C_{MAX}/MIC) (MacGowan 2011). There are reasons these relationships may not be applicable to prophylaxis. Firstly, there is clinical evidence: A study of gentamicin prophylaxis showed that serum concentrations at the end of surgery were associated with efficacy, whereas treatment success with gentamicin is predicted by C_{MAX}/MIC . In addition, serum drug levels below 3.5g/L were associated



with an increased SSI rate (Zelenitsky 2000). Given the MIC90 of gentamicin is 1-2mg/L (estimate based on EUCAST data (<http://www.eucast.org/>)) this would suggest the effectiveness of gentamicin prophylaxis was reduced below $ft > 2-4 \times MIC_{90}$. Theoretical reasons why treatment exposure-response relationships may not be relevant to prophylaxis include: The site of surgery does not have an established immune response as it would in an infection, so blood/drug flows and immune responses at the surgical site are reduced. The bacterial challenge is numerically higher: The load of bacteria within the gastrointestinal tract is likely to be different, and higher, to that identified in an infection. The surgical process is traumatic and likely to result in tissue with reduced blood flow via damaged blood vessels. Antibiotic penetration may be reduced. Tissue damage is likely to result in the release of cellular protein. Antibiotics bind to protein and so, especially for long acting (high protein binding) antibiotics, free/active drug concentrations may be lower than predicted. Antibiotic prophylaxis is single dose, acting over a short time period, compared to treatment which is multi-dose over a number of days. On this basis it is not possible to design antibiotic dosing regimens for antibiotic prophylaxis in colorectal surgery which are based on high quality evidence. The absence of data on which to design the dosing regimen for this study is the weakness of the study, but it also is the basis on which the study is required.

Free serum antibiotic concentrations vs tissue concentrations

Tissue antibiotic concentrations, in relation to antibiotic activity, have been suggested as an alternative marker of outcomes than serum antibiotic concentrations. As described by Mouton et al, tissue concentrations are difficult to measure. Tissue homogenates are often assessed for drug concentration but these levels may not reflect the drugs true location e.g. extracellular vs intracellular. In addition, the time profile of tissue concentrations is different to serum concentrations so multiple samples require testing (Mouton 2008). Enterobacteriaceae which are being studied in this research are extracellular pathogens, and the extracellular fluid rapidly equilibrates with the serum concentrations. On this basis serum antibiotic concentrations have been chosen as the preferred biomarker over tissue concentrations.

Systematic reviews

- Antibiotic resistance impact on SSIs

In 2015 Kirby & Santoni published a review of the impact of antibiotic resistant Enterobacteriaceae on the efficacy of antibiotic prophylaxis for surgical site infections in colorectal surgery (Kirby 2015c). No clinical research data was identified to inform clinical practice. One ongoing research project was identified. The study (R-GNOSIS) is investigating the use of a rapid molecular test for antibiotic resistance with modification of antibiotic prophylaxis when resistance genes are detected.

- CDC systematic review into the prevention of surgical site infections.



In 2014 the Centre for Disease Control (CDC) in the USA published a systematic review into the prevention of SSIs (CDC 2014). They addressed questions identified by experts as the most important for SSI prevention. Two of those questions are relevant to this research. They asked if there was evidence for dose modifications based on patient weight, and the need to achieve higher intra-operative antibiotic drug levels by intra-operative re-dosing. Both original articles were reviewed as well as clinical guidelines, so comparing evidence and practice recommendations.

Weight based dosing: CDC “did not identify any randomised controlled trial or systematic review that evaluated weight-adjusted antimicrobial prophylaxis dosing and its impact on the risk of SSI”. They reviewed clinical guidelines and found: “Clinical practice guidelines based on a review of the evidence and expert opinion recommend increasing the single preoperative prophylactic antimicrobial agent dose for select prophylactic antimicrobial agents in obese and morbidly obese patients”

Intraoperative redosing: Only one RCT was identified which compared single dose timentin (an antibiotic containing ticarcillin and clavulanic acid)) and timentin re-dosed at 2 hours after the first dose of antibiotic prophylaxis. No differences in outcomes were reported. CDC reports this trial to be at moderate risk of bias. It is noted the trial was reported in 1991, when antibiotic resistance and BMIs were lower. The results were not subject to multivariate analysis. The half life of timentin is approximately 1 hour. The review reports: “Clinical practice guidelines based on a review of the evidence and expert opinion recommend prophylactic antimicrobial agent redosing in cases of prolonged procedures (when the procedure exceeds the half-life of the prophylactic antimicrobial agent or is longer than 3-4 hours) and in patients with major blood loss (>1500 ml) or extensive burns. Redosing should also be performed at intervals of 1-2 times the prophylactic antimicrobial agent half-life, starting at the beginning of the pre-operative dose. No recommendations are provided for optimal prophylactic antimicrobial agent dosing in obese and morbidly obese patients when redosing.”

CDC Recommendations

No recommendation can be made regarding the safety and effectiveness of weight-adjusted dosing of parenteral prophylactic antimicrobial agents for the prevention of surgical site infection (No recommendation/unresolved issue) (Key Question 1C).

No recommendation can be made regarding the safety and effectiveness of intraoperative redosing of parenteral prophylactic antimicrobial agents for the prevention of surgical site infection (No recommendation/unresolved issue) (Key Question 1D).

- Cochrane review of antibiotic prophylaxis for colorectal surgery

In 2014 a Cochrane review of antibiotic prophylaxis in colorectal surgery determined that aerobic cover, in addition to anaerobic cover, reduced surgical site infection (SSI) rates (RR 0.44, 95% C.I. 0.29 to 0.68) (Nelson 2014). This benefit obtained by addition of aerobic cover is the potential for surgical efficacy to be reduced if Enterobacteriaceae (aerobe) resistance impacts on the efficacy of antibiotic prophylaxis. No recommendations are made on antibiotic dosing.



- Meta-analysis of ceftriaxone vs other antibiotics for antibiotic prophylaxis.

Ceftriaxone, an antibiotic with a long half life, has been assessed in relation to other cephalosporins with shorter half lives and been found to be more effective. For abdominal surgery it is more effective, having an odds ratio of 0.5 (Woodfield 2009).

Brief description of proposed study

We propose to randomise patients due to undergo colorectal surgery to standard antibiotic prophylaxis or an interventional antibiotic prophylaxis regimen and assess surgical site infection (SSI) rates. Standard antibiotic prophylaxis is a pre-operative injection of cefuroxime, repeated every 4 hours. The intervention regimen is a loading dose of cefuroxime followed by a continuous infusion of cefuroxime until the end of surgery. The intervention regimen dosing will be calculated using a patient's renal function. The intervention regimen will target a free serum drug concentration of 64mg/L. This serum level is 4x the MIC₉₀ for colonising Enterobacteriaceae. The rationale for this dosing regimen is summarised below. The primary objective of the study is to reduce by 50% the rate of surgical site infections after colorectal surgery.

The rationale for this study design is based on the following rationale. An expert assessment is that $ft > MIC$ is the measure most likely to be applicable to prophylaxis (Moine 2013). But as shown in table 2, this measure is not achieved by standard prophylaxis regimens. Neither do clinical data suggest this target achieves optimal prophylaxis. Therefore there is an opportunity to optimise antibiotic prophylaxis dosing. As the exposure response-relationship (pharmacodynamic target) is unknown we could either complete a number of studies exploring different relationships, or compare standard treatment to a single regimen which included a number of exposure-response relationships. The two most common exposure-response relationships are the C_{MAX}/MIC ratio and the $ft > MIC$. And it has been reported that killing, as opposed to inhibition used in MIC values, is optimised by achieving 4 times an MIC value (Macgowan). An antibiotic prophylaxis regimen which achieved drug concentrations of 4xMIC for the duration of surgery would therefore achieves a high C_{MAX}/MIC ratio, high $T > MIC$, and optimise bacterial killing. Therefore, standard dose antibiotic prophylaxis will be compared against a PD target dosed antibiotic prophylaxis regimen. The PD target will be a free serum antibiotic concentration of 4xMIC₉₀ for Enterobacteriaceae against cefuroxime. Bolus-Continuous infusion of antibiotic prophylaxis will ensure there is continuous targeting of this drug level throughout the operation.

2 RATIONALE



Research question: Does pharmacodynamic target (4x MIC90 free serum concentration) based continuous antibiotic dosing of antibiotic prophylaxis reduce the rate of surgical site infection after colorectal surgery when compared against standard antibiotic prophylaxis dosing regimens.

Research hypothesis: Pharmacodynamic target (4x MIC90 free serum concentration) based continuous antibiotic dosing of antibiotic prophylaxis reduces the rate of surgical site infections after colorectal surgery by 50% when compared against standard antibiotic prophylaxis dosing regimens.

Importance of research question

Surgical site infections after colorectal surgery are an important post-operative complication.

- 78,000 patients annually undergo elective colorectal surgery in England (Hospital Episode Statistics 2014) with approximately 22% (12%) developing an SSI. 9000 patients undergo emergency surgery, with approximately 30% developing an SSI.
- SSIs after colorectal surgery have been associated with an increased hospital stay (Kirby 2015a)
- SSIs are recognised as a patient safety issue: The National Patient Safety website and the Patient Safety First campaign highlight that prevention of SSIs is an NHS patient safety priority.
- On average each SSI is treated with 8 days of antibiotics. Antibiotic consumption is associated with antibiotic resistance.
- It is recognised that antibiotic resistance threatens the viability of surgical procedures. Sally Davies, England's Chief Medical Officer, has said "antibiotic resistance could routinely result in deaths from minor surgery". If new antibiotics are developed they are unlikely to be used for routine prophylaxis. We must therefore do better with the antibiotics we currently have.
- The English National Point Prevalence Survey of HCAs identified 13.2% of antibiotics prescribed in hospital each day were for surgical prophylaxis. This is therefore an important area to dose correctly.

Why closely related questions are not being answered

Weight based dosing/intra-operative re-dosing.

The CDC systematic review on the prevention of surgical site infections identified 10 key questions after consultation with expert sources. Five of these questions were related to antibiotic prophylaxis, three were answered with a recommendation, but two questions received no recommendation and were identified as an unresolved issue. These two questions relate to:

- 1- The safety and effectiveness of weight-adjusted dosing of parenteral prophylactic antimicrobial agents for the prevention of surgical site infection.
- 2- The safety and effectiveness of intraoperative redosing of parenteral prophylactic antimicrobial agents for the prevention of surgical site infection.

Both these questions are essentially asking if dosing of antibiotic prophylaxis can be optimised. The Colo-Pro study will address both these questions in a single study of optimised dosing of antibiotic prophylaxis. PK analysis has shown that weight is not an important variable in an optimised regimen, but renal function is. PD target dosing includes renal function within the dose calculation, which PK



analysis suggests is more important than weight, and the continuous infusion addresses the aim of re-dosing i.e. maintaining “therapeutic” drug levels through the operation.

Individualised antibiotic prophylaxis

An individual's antibiotic prophylaxis could be modified based on antibiotic resistance testing of colonising Enterobacteriaceae. The challenges to this approach are

- 1- Time delays involved in testing
- 2- No established or defined sensitive/resistance testing protocols. Sensitive resistance classifications used for treatment may not be relevant to the prophylaxis setting.
- 3- Logistics of individualising prophylaxis
- 4- Excludes emergency surgical patients
- 5- Excludes the possibility of reducing SSI rates in the majority of patients with sensitive Enterobacteriaceae (80%) who have a high rate of SSIs

Rapid molecular testing could be completed, as per the R-GNOSIS study, which is using a rapid molecular test. In the UK we have low rates of ESBL infections, and detection of a resistance mechanism may not be informative with regard the expression of the resistance mechanism. Despite the limitations of this approach it is a potential avenue of research. We would explore the testing aspects of this approach within the Colo-Pro study. Rectal swabs would be collected pre-operatively and various biomarkers with regard to colonising Enterobacteriaceae (Species, Concentration, Antimicrobial susceptibility testing) would be determined and related to outcomes. This will allow a greater understanding of resistance in the prophylaxis setting, and what the best test of resistance testing and individualising antibiotic prophylaxis would be.

Alternative antibiotic choice

Another strategy to reducing SSI rates could be to compare alternative antibiotics. There are some new antibiotics e.g. tigecycline, and old antibiotics e.g. fosfomycin, that could be used for antibiotic prophylaxis. The use of these antibiotics could potentially help mitigate some of the impact of antibiotic resistance. They may not though be expected to reduce SSI rates for the majority of patients who have susceptible Enterobacteriaceae and so not answer questions identified by the CDC experts relating to weight based dosing and re-dosing. Nor the question set by this study of PD target driven dosing. Alternative antibiotics may also have limitations e.g. tigecycline has no activity against *Morganella* or *Proteus* spp. In settings of high resistance we think a strategy of alternative antibiotics should be explored and we would consider investigating it once more fundamental principles of antibiotic dosing for surgical prophylaxis have been established in the Colo-Pro study.

Risk based approach to alternative regimens

Another strategy to avoid treating patients colonised with resistant Enterobacteriaceae with antibiotics they were resistant to would be to create an antibiotic resistance risk prediction rule. In our Leeds study (Kirby 2015b) there were no factors which predicted colonisation with a resistant Enterobacteriaceae.

Non absorbable oral antibiotics

The Cochrane review of antibiotic prophylaxis in colorectal surgery asked if oral (PO) non absorbable oral antibiotics given in addition to intravenous (IV) antibiotics for antibiotic prophylaxis were able to



reduce SSI risk. It was reported that combining these two regimens reduced SSI rates (RR 0.56 [0.43, 0.74]) compared to IV therapy alone. These trials were carried out in an era of pre-operative bowel cleaning preparation. Pre-operative bowel preparation has not been associated with clinical benefit so is now not recommended, and it is not known if this will reduce the efficacy of non absorbable oral antibiotic prophylaxis. A number of trials in this meta-analysis were limited by including systemically absorbed PO antibiotics. In addition the PO regimens included regimens given for a number of days, which may increase the opportunity for selection of antibiotic resistance. There are large trials not included in the Cochrane review which do not show a benefit of oral antibiotic prophylaxis (Kobayashi 2007). There is therefore clearly clinical equipoise in this area and it is suggested research is carried out. We suggest this should be carried out after the IV antibiotics have been assessed for optimisation given the increased chance of resistance associated with more prolonged courses of antibiotics.

Long half life antibiotics

See background section: Long half life antibiotics.

Available treatments and their limitations

In the UK three regimens are commonly recommended for antibiotic prophylaxis:

- 1- Co-amoxiclav 1.2g IV
- 2- Cefuroxime 1.5g IV and Metronidazole 400mg IV
- 3- Amoxicillin 1g IV, Gentamicin (various doses), and Metronidazole 400mg IV

There are a number of potential limitations to these treatments

- 1- Dosing is fixed. This may result in antibiotic drug levels which are lower than intended, with an increased risk of antibiotic prophylaxis failure.
- 2- Dosing is single dose, and the antibiotics have a short half-life, 1-2 hours. This can result in antibiotic drug levels which are lower than intended, with an increased risk of antibiotic prophylaxis failure.
- 3- The dosing of these antibiotics has not been optimised.
- 4- Antimicrobial resistance may be having an impact on the efficacy of prophylaxis
- 5- Increasing antibiotic MICs, even within the susceptible range, may be having an effect on the efficacy of prophylaxis.
- 6- If re-dosing is recommended, it is frequently forgotten by the surgical/anaesthetic team.

The potential improvement of the Investigational Medicinal product (IMP) over the standard treatments is:

- 1- Dosing is varied based on renal function, ensuring targeted drug levels are more likely to be achieved increasing the chance of antibiotic prophylaxis success.
- 2- Dosing is continuous, avoiding the risk of low levels during the procedure.
- 3- The dosing achieves MIC serum levels equal to 4x MIC90 throughout the operation, a level which will potentially provide an optimised antibiotic prophylaxis regimen.
- 4- A continuous infusion will remove the need for a surgeon/anaesthetist to remember to provide recommended re-dosing during an operation.



The minimum clinically important difference

From the patients perspective the receipt of antibiotic prophylaxis by single dose or continuous infusion is not important given they are anaesthetised for duration of antibiotic administration. And the dosing is not expected to increase the risk of side effects. Therefore any reduction in SSI rates will be acceptable to the patient. Though not expected, there are potential risks to patients e.g. increased risk of thrombophlebitis, vascular access related complications; larger overall doses of antibiotic may increase *C. difficile* risk and risk of antibiotic resistance. The alternative beta-lactam used in the UK for prophylaxis is co-amoxiclav. There is evidence that cefuroxime has a lower *C. difficile* infection risk than co-amoxiclav supporting the choice of cefuroxime (Slimings 2014).

The additional cost of a continuous infusion regimen is likely to be minimal for an individual patient. There will be no additional cost beyond those associated with the infusion equipment and additional antibiotic costs. These are likely to be small in relation to the cost of £5000 per SSI i.e. only a 1 or 2 percent reduction in SSI rates is likely to be cost effective.

The study will therefore not be powered based on a minimally clinically important difference but will consider expected reductions in SSI rates.

Justification for the dosage regimen and treatment duration

Antibiotic prophylaxis at treatment doses is the most effective intervention for the prevention of SSIs. Despite this effective intervention a significant minority of patients, >10%, still suffer SSIs. Therefore, if it is possible to improve the efficacy of prophylaxis it is likely, given the limited benefits of other interventions aimed at reducing SSI rates, that this intervention would offer the most rewards in terms of reducing SSIs. To improve the efficacy of an antibiotic intervention it would be normal practice to design a dosing regimen using the known exposure-response relationship. An exposure-response relationship would define the most effective dosing regimen. Different exposure-response relationships have been identified in the treatment of infections. For example, aminoglycoside dosing is optimised by getting a high ratio of peak drug concentration/MIC. For beta-lactams the time the serum level is above the MIC is important. The exposure-response for antibiotics used for prophylaxis is unknown.

We have therefore decided to investigate if a pharmacodynamic (PD) target based dosing approach, with a single target that covers a number of different exposure-response relationships, is more effective than standard antibiotic dosing regimens. The use of a PD target, as opposed to simply giving higher doses, means that we address issues highlighted as being important. These include obesity and the need to maintain antibiotic drug levels throughout the duration of surgery. A PD target of a free serum drug concentration of 4 x MIC 90 value has been chosen as up to this level bacterial killing is reported to increase (MacGowan 2011). This level equates to 64mg/L for and cefuroxime, which is below a level of 100mg/L. It has been suggested that a level of <100mg/L is a safe beta-lactam target to aim for (Moriyama 2010). This level will potentially increase the killing of bacteria including those that are resistant (MIC>8mg/L). The PD target chosen, 4xMIC90, therefore addresses concerns that antibiotic resistance is impacting on the efficacy on standard dosing of antibiotic prophylaxis.

Choice of control interventions:

Intravenous cefuroxime 1.5 grams pre-operatively, and repeated at 4 hours will be the standard treatment, in combination with intravenous metronidazole 500mg as a single pre-operative dose.

This equates to standard treatment.



2.1 Assessment and management of risk

Benefit analysis: The potential benefits from the IMP are a reduced SSI rate which is estimated to be in the order of a 50% reduction. SSIs are associated with increased length of hospital stay, increased cost and increased antibiotic consumption.

Risk analysis

Beta-lactam antibiotics are generally very well tolerated. The most serious potential risk is anaphylaxis which is reported in 1-5/10,000 doses. As per usual clinical practise, patients will have their allergy status checked pre-operatively and those with a known relevant allergy excluded from the trial. For those included, we have no reason to believe that continuous infusion is any more likely to result in an allergic reaction than bolus dose. The risk above standard treatment with in this study protocol is the higher dose of cefuroxime required to achieve the target a serum level of 64mg/L for the duration of surgery (53% <3 hours, 95% < 6 hours). Cefuroxime levels above 64mg/L are surpassed after bolus administration of intravenous therapy. But due to cefuroxime's short half life (1.5 hours) these levels normally fall over the following hours. Continuous infusions of beta-lactam antibiotics, in order to achieve continuously targeted serum concentrations of up to 100mg/L, have been administered for days of treatment without reported adverse events (Moriyama 2010). Other beta-lactams e.g. piperacillin, are given at 4g in a single dose (repeated 8 hourly). Cefuroxime can be dosed at higher doses (higher dose 3g 8 hourly, vs standard dose 1.5 g 8 hourly) for meningitis. This suggests targeting cefuroxime serum levels of 64mg/L for up to 6 hours is unlikely to result in dose related adverse events. See section 8.6 for full details of the study intervention dosing regimen.

An assessment of adverse events associated with cefuroxime is provided in the products SPC:
<https://www.medicines.org.uk/emc/medicine/16929>

This study has been reviewed by the MHRA and assessed as not being a CTIMP.

Risk minimisation/management

- Administration of doses: Anaesthetists/Research staff will administer antibiotics. They will use a programmable infusion pump to dose according to the protocol.
- Intravenous antibiotics can cause phlebitis, therefore antibiotic administration recommendations will be that where possible a 14G cannula/largest possible is used for administering antibiotic into a large peripheral vein.

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS



3.1 Primary objective

To determine if pharmacodynamic target (4xMIC90 free serum concentrations) based continuous antibiotic dosing of antibiotic prophylaxis reduces the rate of surgical site infections after colorectal surgery when compared against standard antibiotic prophylaxis dosing regimens.

3.2 Secondary objectives

To determine if pharmacodynamic target (4xMIC90 free serum concentrations) based continuous antibiotic dosing of antibiotic prophylaxis reduces the rate of all in-patient infections after colorectal surgery when compared against standard antibiotic prophylaxis dosing regimens.

To determine if pharmacodynamic target (4xMIC90 free serum concentrations) based continuous antibiotic dosing of antibiotic prophylaxis reduces the in-patient consumption of antibiotics after colorectal surgery when compared against standard antibiotic prophylaxis dosing regimens.

To determine if pharmacodynamic target (4xMIC90 free serum concentrations) based continuous antibiotic dosing of antibiotic prophylaxis reduces the length of hospital stay after colorectal surgery when compared against standard antibiotic prophylaxis dosing regimens.

To determine if pharmacodynamic target (4xMIC90 free serum concentrations) based continuous antibiotic dosing of antibiotic prophylaxis reduces mortality after colorectal surgery when compared against standard antibiotic prophylaxis dosing regimens.)

To determine if pharmacodynamic target (4xMIC90 free serum concentrations) based continuous antibiotic dosing of antibiotic prophylaxis reduces anastomotic leak after colorectal surgery when compared against standard antibiotic prophylaxis dosing regimens.

To determine if pharmacodynamic target (4xMIC90 free serum concentrations) based continuous antibiotic dosing of antibiotic prophylaxis improves quality of life after colorectal surgery when compared against standard antibiotic prophylaxis dosing regimens.

To determine if pharmacodynamic target (4xMIC90 free serum concentrations) based continuous antibiotic dosing of antibiotic prophylaxis reduces the cost of healthcare treatment after colorectal surgery when compared against standard antibiotic prophylaxis dosing regimens.

To determine if pre-operative antibiotic resistance, as determined by antibiotic susceptibility testing of rectally colonising Enterobacteriaceae, is predictive of a patients risk of a post-operative surgical site infection.



To determine the exposure-response relationship for antibiotic prophylaxis in the prevention of surgical site infection prevention after colorectal surgery.

3.3 Outcome measures/endpoints

3.4 Primary endpoint/outcome

Primary endpoint: Surgical site infection within 30 days of operation.

Endpoint aggregation by percent.

Timings of measurement: Day 5, Day 30.

Rationale for the choice of trial endpoint/outcome

The Centre for Disease Control's (CDCs) National Nosocomial Infections Surveillance (NNIS) criteria for defining SSIs, to be used in this study, have been widely applied to SSI research studies. Application of these criteria has been shown to differentiate the effectiveness of SSI interventions in a number of studies e.g. antibiotic prophylaxis and surgical skin preparation. Whilst these criteria do have some limitations, principally the application involves a subjective assessment of the wound, we have agreed access to a SSI assessment training package developed for the ROSSINI trial (NIHR RfPB funded) to help standardise SSI assessment.

3.5 Secondary endpoints/outcomes

- All in-patient infections within 30 days of operation
- All in-patient antimicrobial consumption within 30 days of operation.
- Length of hospital stay after operation
- Mortality after operation at one year.
- Anastomotic leak within 30 days of operation
- Quality of life scores pre-operatively and at 30 days.
- Cost of healthcare treatments after operation at 30 days.

3.6 Exploratory endpoints/outcomes

Table 5: Exploratory endpoints		
Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
To explore the impact of the antibiotic susceptibility of rectally colonising Enterobacteriaceae on the	Minimum Inhibitory Concentration of the Predominant Enterobacteriaceae	Pre-operative



efficacy of antibiotic prophylaxis in patients receiving standard antibiotic dosing, and in patients receiving PD target based dosing.	<p>Minimum Inhibitory Concentration of the most resistant Enterobacteriaceae</p> <p>Minimum Inhibitory Concentration of the predominant <i>E. coli</i>.</p> <p>Surgical site infection rate within 30 days of operation</p>	
To determine exposure response relationships within patients treated with standard antibiotic dosing.	<p>Free serum drug levels</p> <p>MICs of colonising Enterobacteriaceae</p> <p>Exposure response relationships including:</p> <p>fT>MIC</p> <p>C_{MAX}/MIC</p>	1,2,3 and 4 hours post initiation of antibiotic prophylaxis.

4 TRIAL DESIGN

Colo-Pro Pilot: A pilot randomised controlled single blind trial to compare standard single dose of antibiotic prophylaxis to antibiotic prophylaxis administered as a continuous infusion for the prevention of surgical site infections in adults undergoing colorectal surgery.

5 STUDY SETTING

- Leeds Teaching Hospitals NHS Trust
- Interventions will be carried out by the following staff
 - Recruitment and allocation: Research nurse or research doctor
 - Intervention: Anaesthetist and surgeon, supported by a research nurse or research doctor.
 - Sample collection: Rectal swab and blood samples: Research nurse or research doctor
 - Outcome data collection: Research nurse or research doctor.



6 ELIGIBILITY CRITERIA

This study is pragmatic as it is intended that the intervention would be applied to all patients undergoing colorectal surgery, emergency and elective, with varied indications for surgery, and varied risks of surgical site infections.

6.1 Inclusion criteria

- Undergoing colorectal surgery (incision, excision or anastomosis of the large bowel, including anastomosis of small to large bowel)
- Age >18.
- Expected duration of surgery > 2hours
- Creatinine clearance > 40 ml/min
- Cefuroxime/metronidazole are appropriate antibiotic prophylaxis regimens.
- Patient capable of giving informed consent
- Patients undergoing colorectal surgery plus additional surgery e.g. plastic surgery, urological surgery, gynaecological surgery.
- If it is not possible to obtain intra-operative blood samples e.g. difficult vascular access, or pre-operative swabs e.g. anatomy makes it difficult to obtain, patients will be included and this information treated as missing data. Patients on antibiotic treatment for an existing infection (except SSIs) can be included in the study

6.2 Exclusion criteria

- Unable to consent
- Pregnancy
- Expected duration of surgery <2hours
- Creatinine clearance <40ml/min
- Individual level microbiological advice for non cefuroxime based prophylaxis
- Cephalosporin allergy
- Penicillin allergy (hypersensitivity reaction only)
- Coumarin (warfarin and acenocoumarol) treatment
- Active blood borne virus infection e.g. HIV, hepatitis.
- Seizure history
- Concurrent use of probenecid
- Current participation in a research project aimed at reducing SSIs
- Antibiotics for treatment of a systemic Gram negative infection within 2 hours of initiation of surgery (Vancomycin, Teicoplanin, Daptomycin, Linezolid, Flucloxacillin. Nitrofurantoin and Clarithromycin would be permissible antibiotics without systemic Gram negative antibiotics).
- A current diagnosis of an SSI at the time of study entry.
- STARR procedures
- Weight <30kg or >110kg



Duration of the risk mitigation measures: 24 hours

MPs are not teratogenic

7 TRIAL PROCEDURES

Schedule of procedures: Appendix 4.

7.1 Recruitment

Participants who are screened for trial entry and are not randomised will have data collected for Consolidated Standards of Reporting Trials (CONSORT) reasons to allow reporting of the generalisability of the results. Anonymised information on participants who are not randomised for will include: Age, Gender, whether the patient is registered or not registered, the reason not eligible for trial participation, or if they are eligible but declined, the procedure they were due to undergo, if the procedure was elective or an emergency procedure and the ASA score.

7.1.1 Patient identification

Participant eligibility screening process

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

- Notification by a member of the patient's clinical team, to the research team, a patient is due to undergo colorectal surgery. This may happen after the patient has been seen:
 - o In the outpatient setting
 - o As a hospital in patient
- Identification by a member of the research team a patient is due to undergo colorectal surgery by screening of hospital surgical theatre lists.

Both the clinical team and the research staff will hold a contract, permanent or honorary, with their host hospital. All recruiting staff will therefore be part of the patient's normal clinical staff.

The research team will include medical and nursing staff. Eligibility will be confirmed by a medical practitioner.

7.1.2 Screening

- No diagnostic testing is required to confirm eligibility
- Penicillin/cephalosporin allergy will be assessed

7.2 Consent

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

Delegation of consent:



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

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

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

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

Translation:

To comply with the Welsh Language Act 1993, the Participant Information Sheets and Consent forms will be translated into Welsh or provided bilingually where this is requested by a participant at a research site.

The protocol will fully describe the process which typically involves:

Consenting protocol involved:

- Discussion between the potential participant or his/her legally acceptable representative and an individual knowledgeable about the research about the nature and objectives of the trial and possible risks associated with their participation
- The presentation of written material (Patient information leaflet and consent form, approved by the REC and in compliance with GCP, local regulatory requirements and legal requirements)
- The opportunity for potential participants to ask questions
- Assessment of capacity. Participants must be capable of giving consent for themselves. A capable person will:
 - understand the purpose and nature of the research
 - understand what the research involves, its benefits (or lack of benefits), risks and burdens
 - understand the alternatives to taking part
 - be able to retain the information long enough to make an effective decision.
 - be able to make a free choice
 - be capable of making this particular decision at the time it needs to be made (though their capacity may fluctuate, and they may be capable of making some decisions but not others depending on their complexity)
 - where participants are capable of consenting for themselves but are particularly susceptible to coercion, it is important to explain how their interests will be protected

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

7.2.1 Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable



- Data and biological specimens including bacteria from rectal swabs and blood samples for antibiotic drug concentrations will be acquired and stored during the trial.
- Participation in the ancillary research is required for participation in trial. A single consent will be obtained for the use of rectal swabs samples and blood samples for antibiotic drug concentrations in planned and future research related to the clinical condition under study only.

7.3 The randomisation scheme

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

7.3.1 Method of implementing the allocation sequence

The allocation sequence will involve:

- generation of an unpredictable allocation sequence
- concealment of that sequence until assignment irreversibly occurs.

The system to use be used a web based randomisation/treatment allocation system

Research nurses and research doctors recruiting patients will access this at the research

- The allocation system will provide sealed envelopes to be accessed upon a decision to allocate a participant to a treatment arm.
- Documentation of the randomisation arm will be added to the patient notes in a sealed document holder for access in case of medical need only.
- Documentation of the randomisation will be provided to a research database accessible to researchers.

7.4 Blinding

The trial design is a single blinded trial. The trial participants will be blinded to their treatment.

Staff present at the time of operation, and prophylaxis, will be unblinded.

Health care staff not present at the time of operation will be blinded to treatment.

Outcome assessors will be blinded to treatment.

Final unbinding of all trial participants will occur after the creation of a locked analysis data set.

Medical/Anaesthetic notes will not contain the patient's treatment arm to limit unbinding.

Blinding of all care providers is not possible because of logistics relating to the blinding of treatments at short notice for all trial participants e.g. emergency surgery participants.

7.5 Unblinding



The study code will only be broken for valid medical or safety reasons e.g. in the case of a severe adverse event where it is necessary for the investigator or treating health care professional to know which treatment the patient is receiving before the participant can be treated. Subject always to clinical need, where possible, members of the research team will remain blinded. Documentation of the blinding arm will remain in the patient's notes to allow access as needed. If this information is accessed the person accessing the arm will be notified to inform the principal investigator. The PI will notify the study sponsor and relevant authorities.

7.6 Baseline data

Data collection includes but is not limited to:

Pre-operative data

- Age
- Sex
- Height/Weight
- Co-morbidities
- Indication for surgery
- Pre-operative blood tests e.g. haemoglobin
- National Nosocomial Infection Score
- MRSA colonisation status
- Infection status. Defined by NNIS definitions
- Pre-operative radiotherapy
- Pre-operative chemotherapy
- Pre-operative bowel preparation

Intra-operative data:

- Surgical skin preparation
- Surgical procedure- Including OPSC code
- Surgical duration
- Surgical classification (Clean to dirty)
- Surgeon status
- Surgical drain use
- Colonic perforation noted.

Post-operative data

- Adverse events
- Infections: Defined by NNIS definitions
- Antibiotic consumption

7.7 Trial assessments

Pre-operative assessment-Visit 1

- Medical history
- Antibiotic history



- Rectal swab
- QoFL assessment

Intra-operative assessment-Visit 2

- Anaesthetic history
- Surgical history
- Antibiotic prophylaxis history
- Antibiotic blood concentrations

Post operative assessment-Visit 3, day 5 (approximately) post-operation, or day of discharge

- Medical history
- Antibiotic history
- Surgical site assessment: Where possible the surgical wound will be inspected and an SSI specific evaluation will be completed
- Infections assessed as per standard (HPA point prevalence survey) definitions

Post-operative assessments-Visit 4 (4A, 4B etc) (72 hourly post visit 3 while in-patient)

- Medical history
- Antibiotic history
- Surgical site assessment: Where possible the surgical wound will be inspected and an SSI specific evaluation will be completed
- Infections assessed as per standard (HPA point prevalence survey) definitions

Post-operative assessment-Visit 5, day 30-45 post-operation

- This will normally be completed by postal or telephone assessment though when possible the 30-day follow-up might be combined with a patients post-operative clinic follow-up.
- Surgical site infection questionnaire relating to outpatient SSIs
- Antibiotic history
- QoFL questionnaire

7.8 Long term follow-up assessments

Duration of follow-up period: 1 year

Assessments to be carried out: Mortality assessments at 1 year via electronic health records.

Patients will be identified as 'lost to follow-up if they are unable to be contacted or declined further follow up.

Measures taken to obtain the information if visits or data collection time-points are missed: Medical notes will be reviewed where appropriate, questionnaires sent to patients or telephone interviews conducted.

7.9 Withdrawal criteria



The intervention is a single intervention, so withdrawal criteria are not expected to result from issues of being in the trial over a long period of time.

An acute event associated with the MP would therefore be the main medical reason for removal from the trial. An anticipated acute event e.g. recognition of allergy after enrolment, would also lead to removal from the trial. These cases should be discussed with a microbiologist to decide upon appropriate antibiotic prophylaxis if the surgical procedure is performed as planned. A microbiologist will want to know how much antibiotic has been administered prior to the allergy being recognised, and the expected duration of the procedure.

If withdrawn in this setting the participant would be included in the trial assessments as part of obtaining a complete data set for an intention to treat analysis.

Documentation to be completed on subject withdrawal (including recording reasons for withdrawal and any follow-up information collected with timing).

Withdrawn subjects are not to be replaced

7.11 Storage and analysis of samples

Criteria for the collection, analysis, storage and destruction of biological samples

Rectal swab

- Testing location: Old Medical School, Leeds General Infirmary.
- Timings of testing: Pre-operative
- Shipping details: Clinical transport system
- Sample destruction: At the end of the laboratory studies have been completed, not expected to be > 1 year after date of the participant recruitment.
- Sample storage
 - o Conditions: 4 degrees Celsius +/- 5 degrees Celsius
 - o Duration: As sample destruction
 - o Location: as testing location
 - o Long term storage: None
- Laboratory manual: Available in the Old Medical School, Leeds General Infirmary

Blood samples for antibiotic drug concentrations

- Whole blood
- 6 ml
- Blood tube: Serum separator tube
- Testing location: Southmeads antimicrobial reference laboratory.



- Timings of testing: 4 samples taken intra-operatively. One sample will be collected at approximately 10 minutes after antibiotic infusion. One sample will be collected prior to closing the surgical wound. The other two samples will be taken after the surgery is approximately 1/3rd and 2/3rds complete. If a patient is re-dosed intra-operatively one of these two samples can be moved to be taken prior to the re-dosing.
- Shipping details: On ICE to Southmeads Antibiotic reference laboratory
- Sample destruction: As per Southmeads local guidelines (not more than 7 days of result)
- Sample storage
 - o Conditions: Freezer (-20 or -80 degrees)
 - o Duration: Until testing
 - o Location: Leeds and Southmeads
 - o Long term storage: None

Responsibilities of the trial site in regard to samples: The trial site to ensure that samples are appropriately labelled in accordance with the trial procedures to comply with the 1998 Data Protection Act. Biological samples collected from participants as part of this trial will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act.

7.12 End of trial

The date of the last visit/data item of the last patient undergoing the trial is the trial end definition

The study PI will notify REC of the end of the trial.

8 TRIAL MEDICATION

8.1 Name and description of medicinal product

Comparators

The comparator regimen is:

Cefuroxime

- Each vial contains, as the active ingredient, cefuroxime sodium for injection 1578mg equivalent to 1500mg of cefuroxime respectively

Metronidazole

- Metronidazole 5 mg/ml Solution

Medicinal Products

Cefuroxime



- Each vial contains, as the active ingredient, cefuroxime sodium for injection 1578mg equivalent to 1500mg of cefuroxime respectively

Metronidazole

- Metronidazole 5 mg/ml Solution

Route of administration

- Intravenous

8.2 Legal status of the drug

Cefuroxime

- Licensed at 1.5g 8 hourly dosing and 3g 8 hourly (meningitis)
- Indication: No BNF indication for surgical prophylaxis, although BNF provides dosing information for Surgical prophylaxis, 1.5 g by intravenous injection up to 30 minutes before the procedure.

8.3 Summary of Product Characteristics (SmPC)

A Summary of Product Characteristics (SmPC) will be used in this trial.

Updated versions will be incorporated into the trial after submission to the study sponsor, the National Research Ethics Committee (as appropriate).

8.4 Drug storage and supply

- The MPs will be supplied from normal hospital stock.
- The drug should be stored as per manufacturers guidelines

8.5 Preparation and labelling of Medicinal Product

Preparation: Cefuroxime sodium will be diluted in water for injection. A dose of 1.5 grams will be diluted in 50ml's of water for injection. Infusion will be according to Table 6 Labelling of infusion will be with infusion volume, drug concentration and infusion rate.

Of note: The NHS Injectable Medicines Guide Group (2015) state that there is evidence of Y-site compatibility for atracurium and cefuroxime (in glucose 5%). This information is reflected in the Handbook of Injectable Drugs by Trissel (2015).

8.6 Dosage schedules

Comparator

- Cefuroxime 1.5g 4 hourly throughout surgery. First dose given pre-operatively.

Intervention



The MPs are to be administered to achieve a steady state blood concentration of free serum concentrations of 4xMIC90 for the duration of an operation, up to a total duration of 6 hours.

In the intervention group, if surgery lasts for more than 6 hours, the infusion will be stopped and the dosing regimen will revert to 4-hourly bolus dose.

Antibiotics will be administered initially with a loading dose, intravenously as is standard practice for antibiotic prophylaxis, in order that drug concentrations can be reliably achieved for the start of an operation.

After the loading dose drug will be administered by continuous intravenous infusion.

Timing of each dose: Loading dose will be within the hour before surgery, with initiation of the continuous infusion before surgery.

To achieve this, the following calculations will be used to determine the bolus dose and the hourly dose.

Loading dose (mg) = $C_{peak}(mg/L) \times V_d(L/kg) \times \text{weight (kg)}$

Maintenance infusion rate (mg/h) = $C_{ss} (mg/L) \times Cl_{total} (L/h)$

Maintenance infusion rate in renal impairment (mg/h)

= maintenance infusion rate $\times (CrCl/100)$

$Cl_{total} (L/h) = K_e(h^{-1}) \times V_d(L/kg) \times \text{weight (kg)}$

$K_e(h^{-1}) = 0.693/t_{1/2}$

C_{peak} = target peak concentration

V_d = volume of distribution

C_{ss} = target mean steady state concentration

Cl_{total} = total body clearance

K_e = elimination rate constant

$t_{1/2}$ = half life

CrCl = Creatinine clearance

Cefuroxime dosing recommendations are provided below, Table 7.

Table 7: Cefuroxime dosing guidelines

Weight (kg)	Loading dose (mg)	Continuous infusion dose: Based on creatinine clearance (ml/min)					
		40-50	50-60	60-70	70-80	80-90	>90
30-40	617	128	157	185	214	242	285
40-50	793	165	202	238	275	312	367
50-60	970	202	246	291	336	381	448



60-70	1146	238	291	344	397	450	529
70-80	1322	275	336	397	458	519	611
80-90	1499	312	381	450	519	589	692
90-100	1675	348	426	503	580	658	774
100-110	1851	385	470	556	641	727	855

Maximum dosing

A maximum loading dose of cefuroxime 2332 mg

A maximum hourly dose of continuous infusion of 1226 mg/hour.

These doses will be administered for a maximum of 6 hours.

Route of administration: Intravenous

8.7 Dosage modifications

Dose modifications: Dosages will be modified according to renal function as described in section 8.6.

Stopping rules: Acute adverse event, duration of surgery 6 hours.

Procedures in the event of toxicity reactions: Antibiotic treatment will be stopped.

8.8 Known drug reactions and interaction with other therapies

The cefuroxime SPC reports: "Cephalosporin antibiotics at high dosage should be given with caution to patients receiving potent diuretics or aminoglycosides, as these combinations are suspected of adversely affecting renal function. Clinical experience has shown that this is not likely to be a problem at the recommended dose levels."

Given the short duration of treatment, and so low total drug amounts administered compared to daily treatment regimes, we will allow patients on diuretics (principally furosemide) and aminoglycosides to enter the study.

8.9 Concomitant medication

Predictable concomitant agents include the anaesthetic medication administered intra-operatively.

Anaesthetic medications: An exhaustive list of anaesthetic agents is not provided. Common anaesthetic agents are provided below:

Anaesthetic agent: Propofol

Analgesic/anaesthetics: Alfentanil, fentanyl, remifentanyl

Anaesthetic agents: Suxamethonium, atracurium, vecuronium, rocuronium



Analgesia: Morphine, tramadol, paracetamol, NSAID, oxycodone

Anti-emetics: Ondansetron, dexamethasone, cyclizine, metoclopramide

Vasoconstrictors: Metaraminol, ephedrine, noradrenaline

Cephalosporins are not recognised as interacting with any anaesthetic agents.

8.10 Trial restrictions

No contraindications whilst on the active phase of the trial.

Contraception needs not be used.

8.11 Assessment of compliance

Patient compliance is not applicable to this trial.

Drug administration will be documented on research forms.



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)	<p>An untoward and unintended response in a participant to an medicinal product which is related to any dose administered to that participant.</p> <p>The phrase "response to an 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.</p> <p>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.</p>
Serious Adverse Event (SAE)	<p>A serious adverse event is any untoward medical occurrence that:</p> <ul style="list-style-type: none"> • 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 <p>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.</p> <p>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.</p>
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)	<p>A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out:</p> <ul style="list-style-type: none"> • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product • in the case of any other medicinal product, in the investigator's brochure (IB) relating to the trial in question

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a



specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

9.2 Operational definitions for (S)AEs

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

9.3 Recording and reporting of SAEs AND SUSARs

The period of time over which AEs, ARs, SAEs, SARs and SUSARs are to be monitored start at and finish at:

- For AEs / SAEs – 1st MP dose to day 30 post operation
- For ARs / SARs and SUSARs – 1st MP dose to day 30 post operation

SAEs occurring in a research participant should be reported to the main REC/Sponsor where in the opinion of the Chief Investigator (CI) the event was:

- Related – that is, it resulted from administration of any of the research procedures, and
- Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence.

Adverse events which are expected occurrences and relevant to the study population includes but is not limited to (multiple post-operative complications occur routinely in this cohort undergoing extensive colorectal surgery):

- Those listed in the Summary of Product Characteristics
- Surgical site infections
- All other infections including respiratory, urinary and skin infections (including fungal infections).
- Vascular events e.g. emboli, thrombosis, haemorrhage
- Failure of the surgical procedure e.g. anastomotic breakdown, fistulation
- Procedures i.e. urinary catheterisation, venous access device.

SUSARs occurring from the time of **randomisation** until 30 days post cessation of trial treatment must be recorded on the AE form and faxed to the Sponsor within one working day of the research staff becoming aware of the event. Once all resulting queries have been resolved, the Sponsor will request the original form should also be posted to the Sponsor and a copy to be retained on site.

For each **SUSARs** the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome



- seriousness criteria
- causality (i.e. relatedness to trial drug / investigation), in the opinion of the investigator
- whether the event would be considered expected or unexpected.

Any change of condition or other follow-up information should be faxed to the Sponsor as soon as it is available or at least within one working day of the information becoming available.

SUSARs will be reported to the REC using the online reporting form within 15 days. Events will be followed up until the event has resolved or a final outcome has been reached, or 30 days have passed. The data monitoring committee will also be given a combined report of all the AEs, SAEs, ARs, SARs and SUSARs at the meeting. Any AEs with rates higher than expected will reported to the REC and sponsor.

All SUSARs will be subject to expedited reporting to the Medicines and Healthcare Products Regulatory Agency (MHRA). The PI or delegate will inform the MHRA, the REC and the Sponsor of SUSARs within the required expedited reporting timescales.

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.
2. Ensuring that all planned recording and reporting procedures for SAEs AND SUSARs as detailed in section 9.3 are adhered to. Ensuring that SUSARs are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.

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

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.
3. Using medical judgement in assigning expectedness.
4. Immediate review of all SUSARs.
5. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.

Trial Steering Committee (TSC):

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



Data Monitoring Committee (DMC):

In accordance with the Trial Terms of Reference for the DMC, periodically reviewing unblinded 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.



9.6 Pregnancy reporting

Pregnancy will not be reported in this trial

9.7 Overdose

Overdose will be reported by the anaesthetist as this person is the only person to be administering drug. The anaesthetist will be provided contact details for the PI to be notified. Any overdosed patients will be withdrawn from the trial

9.8 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 working days from the date the measures are taken, inform the relevant REC of the measures taken and the circumstances giving rise to those measures.

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

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

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

10 STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation

This study is a pilot study intending to recruit 90 patients. We require 60 patients with blood samples collected for pharmacokinetic analysis. In approximately 30% of patients it is not possible to obtain blood samples for intra-operative technical reasons.

The full study sample size will be based on the following data:

- Alternative hypothesis: Pharmacodynamic target (4xMIC90 free serum concentrations) based continuous antibiotic dosing of antibiotic prophylaxis reduces the rate of surgical site infection after colorectal surgery by 50% when compared against standard antibiotic prophylaxis dosing regimes.

Justification: Ceftriaxone reduces surgical site infection in colorectal surgery by 39% compared to other cephalosporin regimes (odds ratio 0.61). It is believed this benefit is achieved by obtaining optimal PD targets. The PD target approach to antibiotic prophylaxis investigated in this study is attempting to obtain an equivalent benefit seen from ceftriaxone, without using ceftriaxone. We expect this 39% benefit to be restricted to patients who have operations over 2 hours. As 73% of patients have operations over 2 hours we expect the reduction in SSIs to be 53% (39/73).

Treatment Effect or Alternative Hypothesis: is this the smallest size of effect that would be of clinical interest- how is this justified in the form of appropriate references, pilot data or clinical arguments.



- Null Hypothesis: Pharmacodynamic target (4xMIC90 free serum concentrations) based continuous antibiotic dosing of antibiotic prophylaxis does not reduce the rate of surgical site infection after colorectal surgery when compared against standard antibiotic prophylaxis dosing regimes i.e. there is an absolute difference in response rates between arms of zero.
- Significance level: 0.05.
- Power: 90%
- Adjustments to sample size based on interim analysis(es)
- SSI rate in standard treatment group (operations > 2 hours)
 - 16.5% (estimated from elective patients only)
- SSI rate in investigation group: 50% of standard group=8.25%

10.2 Planned recruitment rate

This pilot study plans to recruit 1 patient per week.

10.3 Statistical analysis plan

10.3.1 Summary of baseline data and flow of patients

- Variables to be used to assess baseline comparability of the randomised groups
 - Age
 - Sex
 - Smoker
 - BMI
 - Charlson Comorbidity Index
 - Respiratory tract disease
 - Urinary tract disease
 - Diabetes
 - Most recent colorectal surgery
 - Previous hospital stay
 - Indication for surgery
 - Haemoglobin
 - eGFR
 - Albumin
 - MRSA status
 - ASA score
 - NNIS score

A consort flow diagram (<http://www.consort-statement.org/>) will be produced, as per the figure below.

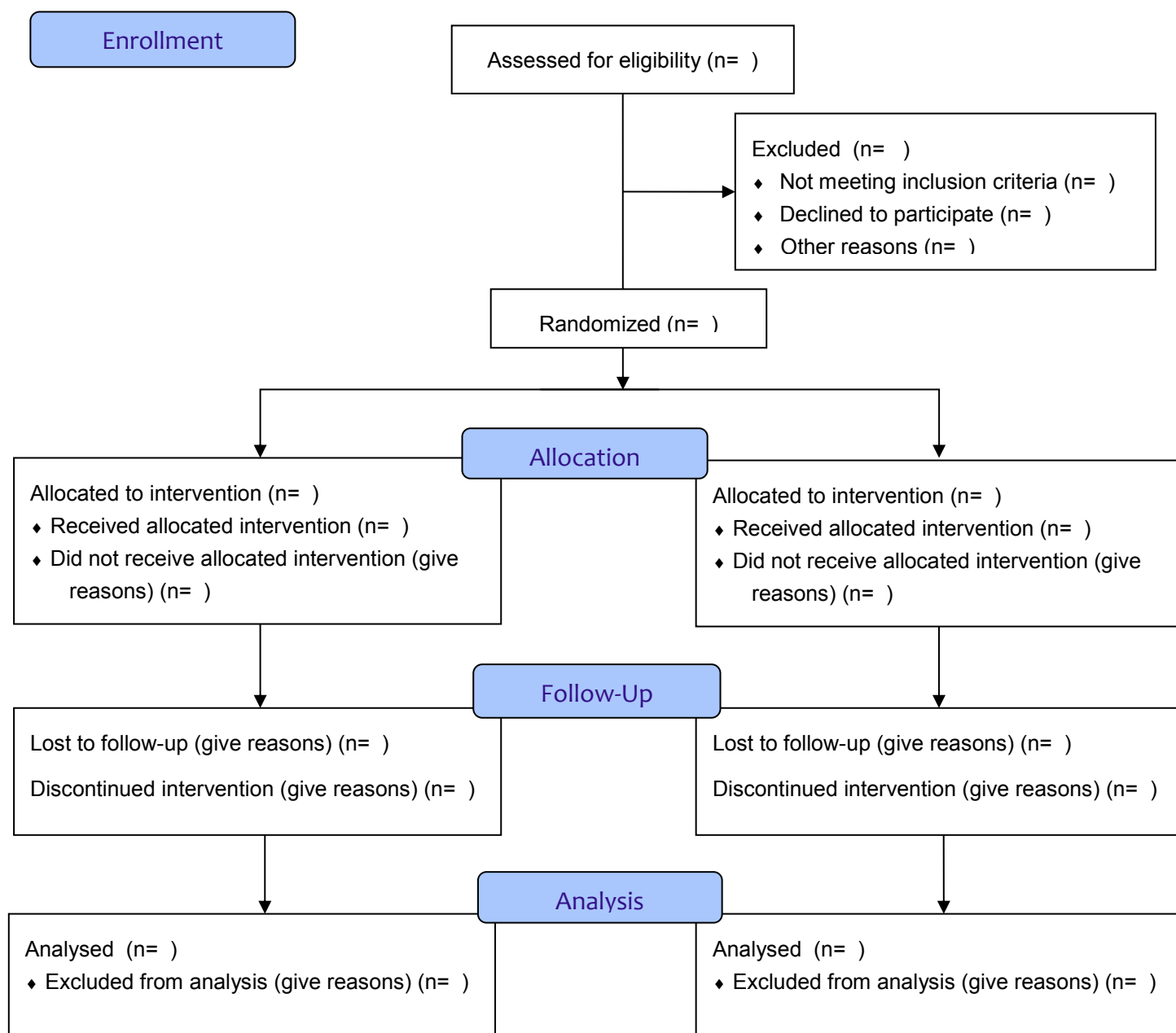




CONSORT

TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram



10.3.2 Primary outcome analysis

Statistical analyses of the primary outcome:

- Surgical site infection within 30 days of colorectal surgery will be analysed by comparing proportions.

10.3.3 Secondary outcome analysis

Secondary outcomes will be analysed by comparing proportions.

10.4 Subgroup analyses

Not applicable

10.5 Adjusted analysis

Not applicable

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

Not applicable

10.7 Subject population

Any subject randomised into the study that received at least one dose of study drug will be subjected to the study analysis.

10.8 Procedure(s) to account for missing or spurious data

Strategies to maximise follow-up will be employed including telephone follow up and postal follow up
No strategies are being planned for missing data.

10.9 Other statistical considerations.

None



10.11 Economic evaluation

None

11 DATA HANDLING

11.1 Data collection tools and source document identification

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

CRFs will be created to document

- Surgical history, including antibiotic prophylaxis and blood collection timings
- Day 5 surgical site infection assessment
- Post operative medical history including antibiotic consumption within 30 days of surgery, infection diagnoses and length of hospital stay
- End of study form including mortality data
- Quality of Life questionnaires (EQ5-D)
- Surgical site infection questionnaire.

Records of all participating patients (sufficient information to link records e.g., CRFs, hospital records and samples), all original signed informed consent forms and copies of the CRF pages will be kept.

Records will be stored in a locked room at the Old Medical School, Leeds General Infirmary, Leeds.

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

To maximise data collection, telephone assessments and postal questionnaires will be used where patients are unable to attend in person for assessments.

11.2 Data handling and record keeping

- Data entry: Data will be added to an excel database stored on Leeds Teaching Hospitals NHS Trust.
- Data quality audit will be completed at the end of the study.
- Data will be stored on paper and online.
- Data will be pseudonymised.
- Data entry will be by a clinical researcher (clinical research nurse or research doctor)
- The PI will be responsible for data entry, quality and analysis.
- Arrangements to pseudonymise the data: Samples and data (case report forms) will be given a study number at the time of collection. A database linking study numbers to patients will be created and be separate to the data and samples. Both paper and electronic records will be kept as part of a data disaster recovery 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.

11.4 Archiving

Archiving will be authorised by the Sponsor following submission of the end of study report

The research group will be responsible for archiving all research data collected.

Paper archiving will be for 5 years from the end of the study and be based in a locked room in the Old Medical School, Leeds General Infirmary.

12 MONITORING, AUDIT & INSPECTION

- A Trial Monitoring Plan will be developed and agreed by the Trial Management Group (TMG) and TSC based on the trial risk assessment which may include on site monitoring
- It is not anticipated this pilot study will be monitored or inspected.
- Any authorised body will be supported by the trial site to in monitoring the study. These may include hosting site visits, providing information for remote monitoring, or putting procedures in place to monitor the study internally

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Research Ethics Committee (REC) review& reports

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

13.2 Peer review



High quality peer review

Peer review has been completed by Dr Jon Sandoe, Consultant Microbiologist, Leeds Teaching Hospitals NHS Trust.

13.3 Public and Patient Involvement

The involvement of Patients and Public in the research includes

- A previous design of this study was presented to the Leeds Cancer PPIR group. This resulted in a recommendation for an interventional trial as per this study.
- This study design (Colo-Pro) is due to be presented to this group again in June 2015.

13.4 Protocol compliance

Accidental protocol deviations will be adequately documented on the relevant forms and reported to the sponsor immediately.

13.7 Data protection and patient confidentiality

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

This includes:

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

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

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

The PI is the data custodian

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

None to declare

13.9 Indemnity

The University of Leeds is providing

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

The NHS is providing



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

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

13.10 Amendments

Amendments will be agreed by the Trial management and data (safety) monitoring group. The Trial management and data (safety) monitoring group will decide if amendments are substantial.

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

HRA guidance on reporting of amendments (non CTIMP reporting) will be followed.

<http://www.hra.nhs.uk/resources/during-and-after-your-study/progress-and-safety-reporting/>



13.11 Post trial care

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

13.12 Access to the final trial dataset

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

14 DISSEMINATION POLICY

14.1 Dissemination policy

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

The data will be owned by The University of Leeds.

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

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

14.2 Authorship eligibility guidelines and any intended use of professional writers

Authorship will include

On the final trial report: The Trial Steering Committee

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



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16. APPENDICIES

16.1 Appendix 1-Risk

Risks associated with trial interventions

- ☒ LOW ≡ Comparable to the risk of standard medical care
- ☐ MODERATE ≡ Somewhat higher than the risk of standard medical care
- ☐ HIGH ≡ Markedly higher than the risk of standard medical care



Justification: Briefly justify the risk category selected and your conclusions below (where the table is completed in detail the detail need not be repeated, however a summary should be given):

The intervention antibiotic prophylaxis is an evidence based intervention.

The method of administering the intervention, continuous infusion, is an established method of intervention, and used routinely in many health care systems.

The maximum loading dose of cefuroxime recommended in this study, 2332 mg, is below the SPC single dose recommended for dosing cefuroxime of 3000mg.

The maximum total dose of cefuroxime recommended in this study, 9688mg over 6 hours, is comparable to that in the drug SPC for treating meningitis, 3000mg 8 hourly (6000mg infused in an 8 hour period).

Beta-lactam therapy is established as a safe treatment. High dose beta-lactam therapy is routinely administered e.g. 2400mg benzylpenicillin 4 hourly for treatment of endocarditis, amoxicillin 2000mg four hourly for endocarditis, flucloxacillin 2000mg 4 hourly for endocarditis, piperacillin 4000mg 8 hourly for severe infections.

What are the key risks related to therapeutic interventions you plan to monitor in this trial?

How will these risks be minimised?

MP/Intervention	Body system/Hazard	Activity	Frequency	Comments
Cefuroxime	Gastrointestinal tract/Clostridium difficile associated diarrhoea	Routine clinical assessment	Continuous while a hospital in-patient	
Cefuroxime	Hepatobiliary disorders	Liver function test (blood)	Clinically driven testing	
Cefuroxime	Blood and lymphatic system disorders	Full blood count	Clinically driven testing	
Cefuroxime	Skin and subcutaneous tissue disorders	Routine clinical assessment	Continuous in-patient assessment	
Cefuroxime	Renal and urinary disorders	Renal function monitoring (blood tests)	Clinically driven testing	
Cefuroxime	General disorders and administration site conditions	Injection site reactions which may include pain and thrombophlebitis	Routine clinical assessment	

Outline any other processes that have been put in place to mitigate risks to participant safety (e.g. DMC, independent data review, etc.)

MHRA assessment of the trial protocol

Trial oversight committees



Independent protocol review

National Research Ethics Committee

Maximum dosing levels defined

Exclusion of patients at risk of adverse events e.g. patients with known history of seizures.

Advice that cefuroxime may affect the gut flora (as with most antibiotics), leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.



16.2 Appendix 2 - Study management / responsibilities**16.2.1 Patient registration/randomisation procedure**

No part of the trial coordination is outsourced.

16.2.2 Data management

No outsourcing of data management is planned.

The PI is responsible for data management.

CRF will be data checked, and the online database will facilitate this process.

16.2.3 Preparation and submission of amendments

No part of the trial coordination is outsourced.

16.2.4 Preparation and submission of Annual Safety Report/Annual

No part of the trial coordination is outsourced.

16.2.5 Data protection/confidentiality

No part of the trial coordination is outsourced.

16.2.6 Trial documentation and archiving

No part of the trial coordination is outsourced.

16.3 Appendix 3 – Authorisation of participating sites

Not applicable: single site study.



16.4 Appendix 4 – Schedule of Procedures

Time (Specify months/ weeks/ days)		0	Day 5	Day 8-30		30 days	
	Preoperative/Pre-assessment clinic*	Surgery	Day 5 (+/- 48 hours) or earlier if discharge at less than 5 days.	72 hourly post initial assessment	Discharge	30 days post surgery/End of trial	Premature withdrawal
Informed consent	X						
Assessment of Eligibility Criteria	X						
Review of Medical History	X		X	X	X	X	
Review of Concomitant Medications	X						
Registration	X						
Physical Exam - Complete			No	No	No	No	
Physical Exam - Surgical site			X	No	No	No	
Documentation of surgical practices e.g. antibiotic prophylaxis		X					
Review of clinical notes including antibiotic prescribing	X		X	X	X	X	
Patient questionnaire	X		X			X	
Height	X						
Weight	X						
Heart rate, respiratory rate, blood pressure							
Rectal swab	X						
Wound swab							
Study intervention (antibiotics) and documentation of surgical practices		X					
Assessment of Adverse Events			X	X	X	X	X



16.6 Appendix 5 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	1.1			AE/SAE event reporting updated
2	2.1		AK	Dosing regimen updated
3	2.2	10/101/2016	AK	Dosing regimen returned to original regimen

Protocol amendments will be submitted to the Sponsor for approval prior to submission to the REC committee.

