Comparison of intravenous versus combined oral and intravenous antimicrobial prophylaxis (COMBINE) for the prevention of surgical site infection in elective colorectal surgery: study protocol for a multicentre, double-blind, randomised controlled clinical trial.

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Comparison of intravenous versus combined oral and intravenous antimicrobial prophylaxis (COMBINE) for the prevention of surgical site infection in elective colorectal surgery: study protocol for a multicentre, double-blind, randomised controlled clinical trial

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ABSTRACT

Introduction Surgical site infections (SSIs) account for 30% of all healthcare-associated infections, with reported rates ranging from 8% and 30% after colorectal surgery and are associated with increased morbidity and mortality rates, length of hospital stay and costs in healthcare. Administration of systemic antimicrobial prophylaxis before surgery is recommended to reduce the risk of SSI, but the optimal regimen remains unclear. We aim to evaluate whether a combined oral and intravenous antimicrobial prophylaxis could be more effective to reduce the incidence of SSI after colorectal surgery, as compared with the standard practice of intravenous antimicrobial prophylaxis alone.

Methods and analysis Comparison of intravenous versus combined oral and intravenous antimicrobial prophylaxis (COMBINE) trial is a randomised, placebo-controlled, parallel, double-blind, multicentre study of 960 patients undergoing elective colorectal surgery. Patients will be randomly allocated in a 1:1 ratio to receive either combined oral and intravenous antimicrobial prophylaxis or intravenous antibiotic prophylaxis alone, stratified by centre, the surgical procedure (laparoscopic or open surgery) and according to the surgical skin antisepsis (chlorexidine–alcohol or povidone-iodine alcoholic solution). The primary endpoint is the rate of SSI by day 30 following surgery, with SSI defined by the criteria developed by the Centers for Disease Control and Prevention. Data will be analysed on the intention-to-treat principle and a per-protocol basis.

Ethics and dissemination COMBINE trial has been approved by an independent ethics committee for all study centres. Participant recruitment began in May 2016. Results will be published in international peer-reviewed medical journals.

- Comparison of intravenous versus combined oral and intravenous antimicrobial prophylaxis (COMBINE) trial is the first randomised, placebo-controlled, double-blind study evaluating the effect of combined oral and intravenous antimicrobial prophylaxis in colorectal surgery.
- The multicentre design, broad inclusion criteria, large sample size (960 patients) and follow-up will support external validity.
- The primary endpoint is defined according to well-defined and internationally validated criteria.
- Unknown whether results can be extrapolated to other patients, especially those with inflammatory bowel disease or obesity.

BACKGROUND

Surgical site infections (SSIs) account for 30% of all healthcare-associated infections among hospitalised patients, and up to 5% of surgical patients.[1 2] SSIs are a particularly significant problem in colorectal surgery, with reported rates between 8% and 30%.[3–6] SSIs are associated with a longer hospital stay, a fivefold likelihood of postoperative readmission after hospital discharge and a twofold to threefold increase in costs of care,[6–9] and

are an independent predictor of mortality in surgical patients.[10]

As reiterated by the 2016 WHO guidelines,[11] administration of systemic antimicrobial prophylaxis before surgical incision, aimed at reducing the bacterial load at a level that is no longer sufficient to establish an infection, is recommended to reduce the risk of SSI.[11] The antibiotic specificity and appropriate timing of administration have been identified as key factors for improving the efficacy of antimicriobial prophylaxis.[12] In elective colorectal surgery, a spectrum of coverage of both aerobic and anaerobic species is recommended.[13] Finally, antibiotics with the narrowest possible spectrum should be used to produce as little collateral damage as possible to the endogenous microflora,[14] which provides a natural colonisation resistance, to reduce the emergence of resistant organisms and to spare broader drugs for treatment of infections. Single-shot first-generation or second-generation cephalosporins initiated within 2 hours of skin incision are currently recommended as the drug of choice for routine antimicrobial prophylaxis in colorectal surgery.[15] However, recent data have shown that, despite an increase in compliance with antimicrobial prophylaxis and adherence to preventive measures, the prevalence of SSI remains high in elective colorectal surgery.[16 17]

Data from large retrospective analyses[18–20] and two randomised clinical trials (RCTs)[21 22] suggested that the use of oral antibiotic prophylaxis, in addition to conventional intravenous antimicrobial prophylaxis, could reduce the incidence of SSI in elective colorectal surgery. In a recent multicentre, open-label randomised controlled trial of 579 patients undergoing laparoscopic colorectal surgery, Hata and colleagues[21] found that, compared with intravenous antimicrobial prophylaxis alone, a combination of oral antibiotic (the day before surgery) and intravenous systemic antibiotic administration during surgery significantly reduced the risk of SSI (OR 0.536, 95% CI 0.305 to 0.940). Previous meta-analyses also suggested a significant benefit of oral antibiotic administration in patients undergoing colorectal surgery.[23–25] In the Cochrane review published in 2014, including data from 15 RCTs published between 1979 and 2007, the authors found that combined oral and intravenous antibiotic prophylaxis could reduce the risk of SSI by as much as 75% (relative risk 0.55 (95% CI 0.43 to 0.71)) compared with intravenous antibiotic administration alone. However, previous studies have several limitations precluding extrapolation of data into routine care, including (1) the use of more than a single preoperative dose in some studies, which is no longer recommended in elective surgery and may increase the risk of development of resistant bacteria and *Clostridium difficile* colitis[26 27]; (2) the use of antibiotics for oral prophylaxis that are no longer available; (3) only a few studies focused specifically on colorectal surgery; (4) only few data are available regarding the difference in incidence of SSI between laparoscopy, whose frequency of use is increasing in colorectal surgery, and open surgery; and (5) most studies did not include enhanced recovery after surgery (ERAS) programme, which was found to reduce the incidence of postoperative infection as compared with standard practice. Finally, and importantly, most available evidence on the benefit of combined oral and intravenous antimicrobial prophylaxis was obtained from studies in which mechanical bowel preparation was performed before surgery. Since most recent trials[28] and meta-analyses[29 30] have challenged the efficacy and safety of mechanical bowel cleansing before colonic surgery, related principally to septic risk after surgery, it is not known whether oral antibiotics would still be effective when the colon is not empty.

Given the high prevalence and the financial burden of SSI, the increasing number of colorectal surgery that are performed annually worldwide justifies a large randomised controlled trial to answer this question. The aim of the comparison of intravenous versus combined oral and intravenous antimicrobial prophylaxis (COMBINE) trial is to assess the effects of a combined oral and intravenous antimicrobial prophylaxis with that of intravenous antimicrobial prophylaxis alone (standard of care) in adult patients undergoing elective colorectal surgery. We hypothesise that a combined oral and intravenous antimicrobial prophylaxis could be more effective than intravenous antimicrobial prophylaxis alone at reducing the incidence of SSI within 30 days after elective colorectal surgery.

METHODS AND ANALYSIS

Trial design and setting

COMBINE (intravenous versus combined oral and intravenous antimicrobial prophylaxis for the prevention of SSI in elective colorectal surgery) study is an investigator initiated, national, multicentre, randomised, double-blinded, placebo-controlled, stratified, parallel group clinical trial with concealed allocation of patients scheduled to undergo elective colorectal surgery 1:1 to combined oral and intravenous antimicrobial prophylaxis or intravenous antimicrobial prophylaxis alone (figure 1). The Standard Protocol Items: Recommendations for Interventional Trials 2013 Checklist was used to ensure that recommended items in a clinical trial were addressed.[31] The trial will take place at 14 universitary and non-universitary centres. All participating centres perform more than 200 colorectal surgical procedures per year.

Participant eligibility and consent

Trial site investigators will identify consecutive eligible patients from the listed criteria. Eligible patients will receive written and oral information and will be included after investigators have obtained informed written consent.

Inclusion criteria

1. adult (18 years or older) patients admitted to the participating centre

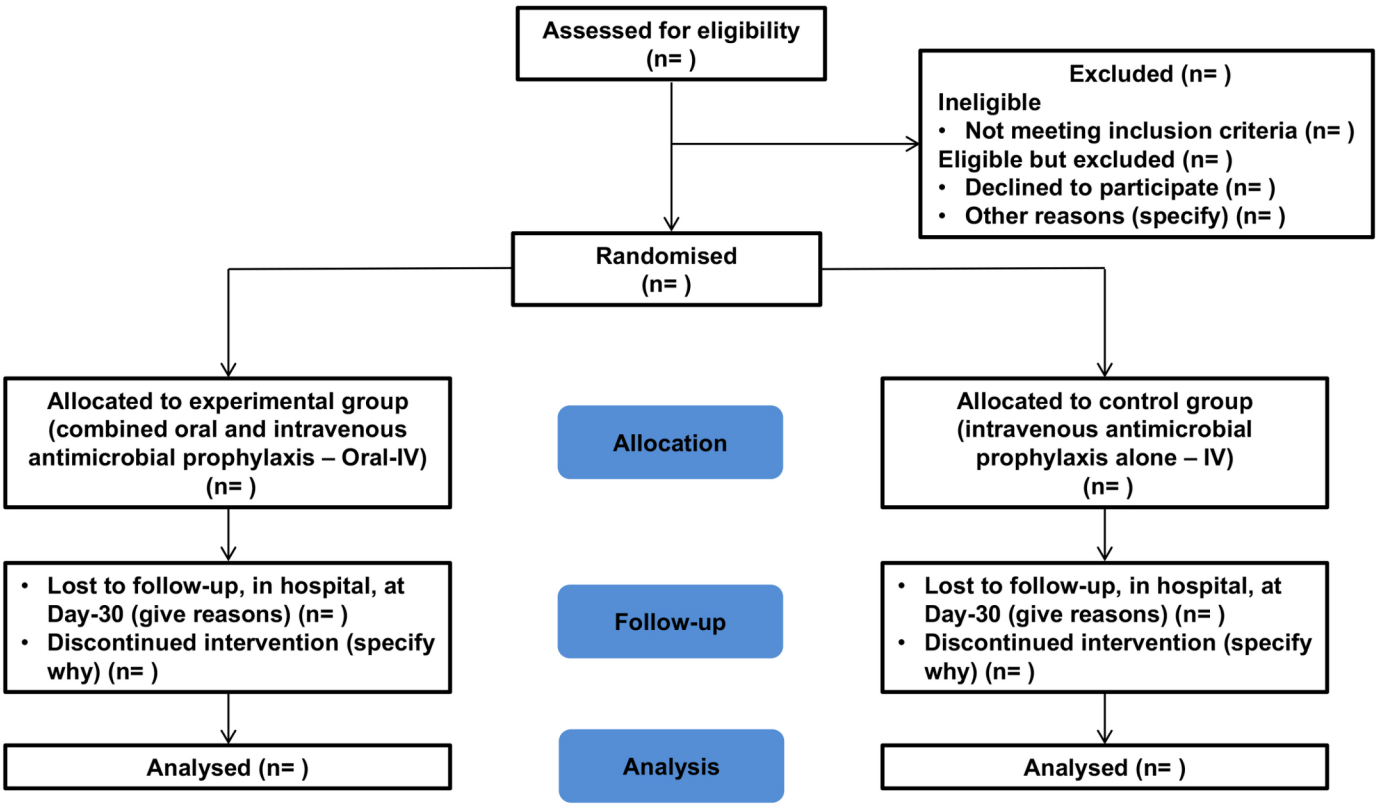

Figure 1 Flow diagram of the COMBINE trial. IV, intravenous.

2. scheduled to undergo laparoscopic or open elective colorectal surgery
3. From whom written informed consent is obtainable.

Exclusion criteria

Patients presenting with one of the following criteria will not be included in the trial:

1. non-elective colorectal surgery (emergent surgery and/or reintervention or revision of a previous colorectal procedure
2. relevant concomitant surgical procedure (eg, liver resection)
3. active bacterial infection at the time of surgery or recent antimicrobial therapy (up to 2 weeks before surgery)
4. inflammatory bowel disease
5. severe obesity (defined by a body mass index greater than 35 kg/m^2)
6. known history of hypersensitivity to β-lactams and imidazoles
7. preoperative severe impairment in renal function (defined by a glomerular filration rate (Modification of Diet in Renal Disease) lower than 30 mL/min/1.73 m^2)
8. patients with known infection or colonisation by multidrug-resistant digestive bacteria, especially multidrug-resistant Gram-negative bacteria
9. known allergy to lactose, galactose intolerance, lactase deficit or glucose and/or galactose malabsorption
10. pregnant women, breastfeeding women and childbearing potential women without effective contraceptive
11. protected major (guardianship)
12. refusal to participate or inability to provide informed consent.

Assignment of interventions

Randomisation

After patient informed consent is obtained, enrolled patients will be randomly allocated to receive either combined oral and intravenous antimicrobial prophylaxis or intravenous antibiotic prophylaxis alone in a 1:1 ratio. Randomisation will be conducted over a dedicated, password-protected, SSL-encrypted website (CSOnline, Clinsight) to allow concealed allocation. Each patient will be given a unique patient number and randomisation number. The allocation sequence will be generated with the use of a minimisation algorithm stratified according to centre, the surgical technique (laparoscopic or open surgery) and according to the preoperative skin antisepsis (chlorexidine–alcohol or povidione-iodine alcoholic solution). The participant allocation will be carried out by local investigators who will log into the randomisation system using a personal ID code and will enter any relevant information.

Blinding

Participants will be given blinded medication. Trial medication (ornidazole and placebo) are visually identical and will

be packaged into opaque and indistinguishable blister packs by the pharmacist of the coordinating centre and delivered to each specific study site. Only the pharmacy of the study coordinating centre will be aware of the blister composition (coding list). The receipt, storage and dispensing of the blinded trial medication will be conduced by the pharmacy department in each individual study site. The allocation of trial medication will be determined by the web-based randomisation system. Each study site will have sufficient blister packs to be allocated to patients included. This will ensure that the patient will receive only the antimicrobial prophylaxis that he or she was randomised to receive. The allocated trial medication will be blinded to the patient, the clinical staff caring for the patient, the investigators, the outcome assessors, the data manager, and the statistician conducting the analyses.

At each participating centre, data will be collected and entered into the web-based electronic case report form (eCRF) by trial or clinical trained personal (clinical research associate), blinded to the allocation group, under the supervision of the trial site investigators.

Study intervention

All included patients will be allocated to one of the following two study groups (figure 1):

- *Combined oral and intravenous antimicrobial prophylaxis (intervention group):* patients will receive a single oral dose of 1 g ornidazole at 12 hours before surgery in combination with intravenous dose of 2 g cefoxitin at least 30 min before surgical incision.
- *Intravenous antimicrobial prophylaxis (control group):* patients will receive a single oral dose of placebo at 12 hours before surgery in combination with intravenous dose of 2 g cefoxitin at least 30 min before surgical incision.

In each group, an additional dose of 1 g cefoxitin will be given every 2 hours during surgery. After surgery, no additional antibiotic doses will be given to either of the groups.

Decisions about all other aspects of patient care during the intraoperative and postoperative periods (especially general anaesthesia, postoperative pain management and physiotherapeutic procedures) will be performed according to the expertise of the staff at each centre and to routine clinical practice to minimise interference with the trial intervention. Nevertheless, to avoid extremes of clinical practice, trial investigators will be strongly encouraged to apply the ERAS programme, which was found to improve postoperative outcome of patients undergoing colorectal surgery.[32 33] In addition, recommendation is made not to perform preoperative mechanical bowel preparation for colonic surgery, which is no longer recommended in most recent guidelines, and left at the discretion of the surgical staff for rectum surgery for which there remains uncertainty.[29 34] Patients will be able to receive oral laxative (1 or 2 packages of X-PREP powder diluted in a glass of water) and retrograde rectal enema the day before surgery, as used previously.[34]

Outcome measures

Primary outcome measure

The primary outcome measure is the proportion of patients with any SSI within 30 days after surgery. SSI are classified as being superficial, deep and/or organ–space infection on the basis of validated and well-defined criteria developed by the Centers for Disease Control and Prevention.[35]

Secondary outcomes measures

- proportion of patient with each type of SSI (superficial, deep and/or organ–space infection) within 30 days after surgery
- proportion of patients with postoperative complication according to the Dindo and Clavien classification[36]
- proportion of patients with one or more of the following complications within 30 days after surgery (definitions of postoperative complications are listed in online supplementary file 1):
  - infectious complications: postoperative syndrome of systemic inflammatory response,[37] sepsis and septic shock[38]
  - cardiovascular complications: arrhythmia, myocardial infarction and acute cardiac failure
  - respiratory complications: pneumonia and need for postoperative reventilation (intubation and/or non-invasive mechanical ventilation)
  - renal dysfunction (defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) classification[39])
  - surgical complications: anastomotic leakage and the need for abdominal reoperation and/or radiological intervention for any reason.
- time to initiation of adjuvant chemotherapy
- need for hospital readmission
- unexpected admission to intensive care unit (ICU)
- duration of hospital stay (including hospital stay of patients who are readmitted after surgery)
- hospital free days (censored at 30 days following surgery)
- all-cause mortality at 30 and 90 days following surgery.

Statistics

Sample size estimation

Assuming a 15% rate of SSI in the control group (intravenous antimicrobial prophylaxis alone),[3 17 25 40] 2×460 patients will be needed to have 80% power to show a relative between-group difference of 40% (15%–9%)%) in the primary outcome measure at a two-sided alpha level of 0.05. Assuming lost to follow-up of 5%, 960 patients will be needed for the study.

Statistical analysis

All analyses will be conducted before the breaking of the randomisation code, in line with the International Conference on Harmonization Good Clinical Practice guidelines. The primary analysis will be conducted, first, on data from the modified intention-to-treat (ITT) population and, second, in the per-protocol population comparing

the rate of SSI 30 days after randomisation in the two groups with the use of unadjusted χ^2 test (or Fisher's exact test, as appropriate) (the statistical analysis plan is attached as a online supplementary file 2). Adjusted analysis will be conducted with the use of robust random-effects Poisson generalised linear regression (1) to take into account adjustment on possible confounding covariates selected according to clinical relevance and stratification variables and (2) to consider within and between centre variability. Data will be presented as relative risks and 95% CIs. Multiple logistic regression analysis will be used to identify relevant baseline covariates in the modified ITT population associated with the primary outcome (criterion for entering variables will be P<0.10), in addition to the stratification variables (centre, skin preparation and surgical technique). A χ^2 test (or Fisher's exact test, as appropriate) will be used for secondary binary outcomes. Adjusted analyses will be performed with the use of robust random-effects Poisson generalized linear model regression and will be presented as relative risks and 95% CIs. The Hochberg procedure will be used to adjust for multiple testing of components of the composite primary outcome. Continuous variables will be presented as mean and SDs (as median and quartiles, otherwise) and will be compared with the use of the unpaired t test or the Mann-Whitney U test as appropriate. The Shapiro-Wilk test will be used to assess normality and the Fisher-Snedecor test to assess homoscedasticity. Adjusted analyses, using multiple linear regression, will be conducted using the same adjustment variables. Time-to-event curves will be calculated with the use of the Kaplan-Meier method in univariable analysis. For multivariable analysis, marginal Cox proportional hazards model (with centre as random effect) will be performed with results reported as HRs with 95% CIs, and proportional hazard assumption verified using the Schoenfeld test and plotting residuals. Subgroup analyses will be done to explore potential influence of mechanical bowel preparation and the type of surgery (colonic and rectal resection) on the incidence of the primary outcome.

All analyses will be conducted with the use of Stata software (V.13). A two-sided p value of less than 0.05 will be considered for statistical significance.

Interim analysis

An interim analysis will be performed after 460 patients using the Lan and DeMets method (East software, Cytel, Cambridge, Massachusetts, USA). The Data Monitoring and Safety Committee (DSMC) may recommend that the trial should be stopped if it finds that the continued conduct of the trial clearly compromises patient safety (in case of serious adverse reactions (SARs) or suspected unexpected serious adverse reaction (SUSARs)). The steering committee (SC) will be responsible to continue, hold or stop the study based on the data monitoring and safety committee (DMSC) recommendations.

Missing values

The prevalence and pattern of missing values, if any, will collected and analysed. If the frequency of missing data is >5%, additional analyses will be performed using the multiple imputation method.[41]

Data registration

Data will be entered into the web-based eCRF (CSOnline, Clinsight) by trial or clinical personnel under the supervision of the trial site investigators at each participating centre. From the eCRF, the trial database will be established. Paper case report form will be used in case of technical difficulties with the eCRF. Data collection will be monitored by trained research coordinators.

The following data will be registered:

Prerandomisation and baseline characteristics

Demographic data (age, height, weight, gender and body mass index); American Society of Anesthesiologists physical status; comorbidities (hypertension: Y/N, diabetes mellitus: Y/N, active smoking: Y/N, alcohol abuse: Y/N, malnutrition: Y/N and chronic use of corticosteroid: Y/N); cancer: Y/N; preoperative chemotherapy or radiotherapy: Y/N; preoperative nutritional support: Y/N; preoperative mechanical bowel preparation: Y/N; and results of blood samples (standard lab values).

At randomisation

Type of surgical procedure (laparoscopy: Y/N and open laparotomy: Y/N) (stratification variable) and antiseptic skin preparation (chlorhexidine–alcohol solution: Y/N, povidone-iodine alcoholic solution: Y/N) (stratification variable).

Intraoperative data

Date and hour of trial medication (ornidazole or placebo) administration; date and hour of intravenous antimicrobial prophylaxis; need for additional dose of antibiotic doses: Y/N; type of surgery (colonic: Y/N and rectal: Y/N); type of surgical procedure if modified (conversion from laparoscopy to open): Y/N; stoma (Y/N and type); type of anastomosis (mechanical: Y/N and manual: Y/N); duration of surgery; surgical complication: Y/N; anaesthetic data (type of anaesthesia (epidural analgesia: Y/N, inhaled anaesthetic: Y/N, intravenous anaesthetic: Y/N and nitrous oxide: Y/N)), type (sufentanil: Y/N and remifentanil: Y/N) and dose of opioids, intravenous lidocaine: Y/N, corticosteroids (Y/N and type), type (crystalloids and colloids) and volume of fluids, total volume of blood losses, total number of blood products, stroke volume and/or cardiac output monitoring: Y/N and temperature monitoring: Y/N and inspired oxygen concentration (inspired oxygen fraction (FiO_2)).

Postoperative data (until hospital discharge)

Patients will be assessed once daily during the entire hospital stay (until hospital discharge) and at the time of follow-up evaluation (30 days after surgery). In case of patient's discharge from hospital prior to day 30 after surgery, trial or clinical research staff members will call the patients, using a dedicated questionnaire (online supplementary file 3), once a week during the 30-day follow-up period and will

arrange for prompt clinical evaluation in case of suspected infection. Whenever infection will be suspected or diagnosed, site investigators unaware of the patients' group assignments will assess the seriousness of all events, and all clinically relevant microbiological samples will be cultured.

The following data will be collected:

- postoperative care pathway (surgical ward: Y/N, high dependency unit: Y/N and ICU: Y/N)
- ERAS items (epidural analgesia: Y/N, nasogastric tube: Y/N, urinary catheter: Y/N, mobilisation: Y/N, laxative: Y/N and flatus/stool: Y/N)
- daily lowest and highest values for temperature
- results of blood sample for creatinine, C reactive protein, platelets, haemoglobin and leukocytes
- blood glucose level
- SS: Y/N (type: superficial: Y/N, deep: Y/N, organ–space: Y/N) and date and hour of SSI diagnosis: local incisional pain/tenderness: Y/N, localised redness, heat or swelling: Y/N, purulent drainage from the superficial incision: Y/N, superficial/deep incision spontaneously or deliberately opened by the surgeon: Y/N, bacteriological sample (fluid/tissue): Y/N and organisms isolated: Y/N (if yes, bacteriological identification)
- postoperative surgical complications: Y/N (anastomotic leakage: Y/N, reintervention: Y/N and radiological/endoscopic drainage: Y/N)
- postoperative non-surgical complications (Y/N, type and date of diagnosis)
- allergy to trial drugs: Y/N
- unexpected ICU admission: Y/N
- duration of stay in high dependency unit (HDU), ICU and surgical ward
- date of hospital discharge
- survival status (if the patient is deceased, date of death).

Weakly after hospital discharge (until 30 days following surgery)

- phone contact (Y/N, date)
- planned or unplanned surgical consultation Y/N
- SSI (Y/N, date of diagnosis).

Thirty days after surgery

- SSI (Y/N, date of diagnosis)
- type of SSI (superficial: Y/N, deep: Y/N, organ/space: Y/N)
- need for hospital readmission: Y/N
- total duration of hospital stay
- total hospital-free days
- survical status (if the patient is deceased, date of death).

Ninety days after surgery

- survival status (if the patient is deceased, date of death).

Patient withdrawal

Trial medications are to be used only during the preoperative period. Nevertheless, a participant who no longer agrees to participate in the clinical trial can withdraw the informed consent at any time without need of further explanation.

Participants who will withdraw from the study will be followed up until hospital discharge, according to routine clinical practice in each participating centre. In order to conduct ITT analyses with as little missing data as possible, it is in the interest of the trial to collect as much data from each participant as possible. Therefore, the investigator may ask the participant which aspects of the trial he or she wishes to withdraw from (participation in the remaining follow-up assessments and use of already collected data) and, whenever possible, will be asked for permission to obtain data for the primary outcome measure. If this is achieved, the participant will be included in the final analyses. If the participant declines, all data from that patient will be destroyed, and a new patient will be randomised to obtain the full sample size. All randomised patients will be reported, and all data available with consent will be used in the analyses. If appropriate, missing data will be handled in accordance with multiple imputation procedures if missing data are greater than 5%.

Safety

All adverse events thought to be related to the trial medication will be reported to the trial coordinating centre. According to the French Public Health Code, all suspected unexpected serious adverse events will be reported to the Agence National de Securite du Medicament (ANSM). In addition, this information will be submitted to the DMSC. The DMSC is independent of the trial investigators and will perform an ongoing review of safety parameters and overall study conduct. The DMSC is composed of two independent clinicians (a surgeon and an anaesthesiologist), a physician bacteriologist and a biostatistician, who have experience in the management of surgical patients, specific expertise in hospital-acquired infection and in the conduct, monitoring and analysis of RCTs.

The DMSC will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial and for monitoring the overall conduct of the clinical trial. To contribute to enhancing the integrity of the trial, the DMSC may also formulate recommendations relating to the recruitment/retention of participants, their management, improving adherence to protocol-specified regimens and retention of participants and the procedures for data management and quality control. No formal criteria are set for stopping the study. Nevertheless, recommendations for pausing or stopping the study will be made by the DMSC in case of SARs and SUSAR. Most adverse reactions are specified in the product characteristics of ornidazole. The SC will be responsible to continue, hold or stop the study based on the DMSC recommendations.

The DMSC will be advisory to the SC. The SC will be responsible for promptly reviewing the DMSC recommendations, to decide whether to continue or terminate

the trial, and to determine whether amendments to the protocol or changes in trial conduct are required.

Data handling and retention

Data will be entered into an web-based eCRF by trial personnel. Each site will only have access to site-specific data. Each patient will receive a unique trial identification number. Only the investigators and research team will have access to any protected health information of study participants and any study data. Data will be handled according to the French law. All original records (including consent forms, reports of SUSARs and relevant correspondences) will be archived at trial sites for 15 years. The clean trial database file will be anonymised and maintained for 15 years. Only the principal investigators and the statistician will have access to the final data set.

Ethics and dissemination

COMBINE trial is approved by the Institutional Review Board of the University Hospital of Clermont-Ferrand (France). COMBINE trial is registered in the European Clinical Trials Database (EudraCT 2015-002559-84) and at ClinicalTrials.gov with the trial identification number NCT02618720. Trial methods and results will be reported according to the Consolidated Standards of Reporting Trials 2010 guidelines.[42]

Enrolment and timeline

The patients are expected to be included from 14 French university and non-university hospitals during a 2-year period starting in May 2016.

- 2014–2016: protocol, approvals from ethics committee and trial tool development (eCRF and randomisation system).
- 2016 to 2018: inclusion of patients.
- 2018: cleaning and closure of the database.
- Early 2019: data analyses and writing of the manuscript and submission for publication.

Trial status

The current protocol is version 5.0. The randomised trial, which commenced in May 2016, is currently in the phase of participant enrolment and follow-up. To date (30 January 2018), 530 patients have been randomised in this study.

Publication plan

On trial completion, the main manuscript will be submitted to one of the major clinical journals regardless of the results. All trial sites will be acknowledged, and all investigators at these sites will appear with their names under 'the COMBINE investigators' in an appendix to the final manuscript. COMBINE study SC will grant authorship depending on personal input according to the Vancouver guidelines. If a trial site investigator is to gain authorship, the site has to include 50 patients or more. If the site includes 100 patients or more, two authorships will be granted. A writing committee will be composed of members of the SC and investigators to define the order of authors of any publications.

DISCUSSION

COMBINE trial is to allow us to evaluate whether a combined oral and intravenous antimicrobial prophylaxis given to patients undergoing elective colorectal surgery is related to a significantly lower incidence of SSIs. SSIs are a particularly significant problem following elective colorectal surgery, which is one of the most common surgeries performed worldwide. The reduction of SSI has become a major target of quality improvement projects.[43 44] Although some guidelines have been issued, providing evidence-based recommendations for the prevention of SSI, the prevalance of SSI remains high in elective colorectal surgery. Surgical antimicrobial prophylaxis is highly recommended to reduce the risk of SSI. Recent RCTs[21 22] and meta-analyses[23 25] have reported interesting findings regarding the effect of oral antibiotics in addition to intravenous antimicrobial prophylaxis. However, most of these studies have limitations, making the extrapolation of data into routine care challenging.

Among the strengths of the trial are the multicentre and double-blind design with the use of a placebo as compared with previous RCTs. In order to standardise practices as possible, we decided to limit the number of participating study centres to 14 centres, all of which performing at least 200 colorectal surgical procedures per year.

Stratified randomisation protects against bias from variability of practice and imbalance between treatment groups for skin antiseptic preparation and the surgical technique, which may both influence the outcome. We decided not to stratify according to the use of mechanical bowel preparation since most available evidence do not support bowel preparation alone before colonic surgery. However, in order to minimise interference with the trial intervention, decision to perform bowel preparation before rectal surgery will be carried out according to the expertise of the staff and to routine clinical practice at each centre.

In conclusion, this trial is the first multicentre randomised controlled double-blinded study adequately powered to evaluate whether combined oral and intravenous antimicrobial prophylaxis could reduce the incidence of SSI compared with intravenous antimicrobial prophylaxis alone. If COMBINE yields positive results, this can have significant clinical and public health implications.

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Contributors CP-B, KS, SJ, J-CL, YP and EF are members of COMBINE trial scientific committee and contributed to the conception and design of the research protocol. MV and MG provided critical input pertaining to the design of the trial interventions and procedures. MV and JB wrote the first draft of the protocol and this manuscript. BP and DM designed the statistical analysis plan. All authors critically revised the protocol for intellectual content and approved the final version to be published.

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Competing interests EF reports personal fees from Drager, personal fees from Edwards Lifesciences, personal fees from General Electric Healthcare, personal fees from Fresenius Kabi, personal fees from Fisher and Paykel Healthcare, outside the submitted work.

Patient consent Obtained.

Ethics approval By 3 July 2015, the study has been approved for all centres by a central ethics committee (Comité de Protection des Personnes Sud-Est VI, Clermont-Ferrand, France) (ref: AU1204).

REFERENCES

1. Bratzler DW. The surgical infection prevention and surgical care improvement projects: promises and pitfalls. *Am Surg* 2006;72:1010–6. discussion 21-30, 133-48.
2. Magill SS, Hellinger W, Cohen J, *et al*. Prevalence of healthcare-associated infections in acute care hospitals in Jacksonville, Florida. *Infect Control Hosp Epidemiol* 2012;33:283–91.
3. Hübner M, Diana M, Zanetti G, *et al*. Surgical site infections in colon surgery: the patient, the procedure, the hospital, and the surgeon. *Arch Surg* 2011;146:1240–5.
4. Keenan JE, Speicher PJ, Thacker JK, *et al*. The preventive surgical site infection bundle in colorectal surgery: an effective approach to surgical site infection reduction and health care cost savings. *JAMA Surg* 2014;149:1045–52.
5. Aimaq R, Akopian G, Kaufman HS. Surgical site infection rates in laparoscopic versus open colorectal surgery. *Am Surg* 2011;77:1290–4.
6. Smith RL, Bohl JK, McElearney ST, *et al*. Wound infection after elective colorectal resection. *Ann Surg* 2004;239:599–607. discussion 05-7.
7. Leaper DJ, van Goor H, Reilly J, *et al*. Surgical site infection - a European perspective of incidence and economic burden. *Int Wound J* 2004;1:247–73.
8. Weber WP, Zwahlen M, Reck S, *et al*. Economic burden of surgical site infections at a European university hospital. *Infect Control Hosp Epidemiol* 2008;29:623–9.
9. Wick EC, Shore AD, Hirose K, *et al*. Readmission rates and cost following colorectal surgery. *Dis Colon Rectum* 2011;54:1475–9.
10. Astagneau P, Rioux C, Golliot F, *et al*. Morbidity and mortality associated with surgical site infections: results from the 1997-1999 INCISO surveillance. *J Hosp Infect* 2001;48:267–74.
11. Allegranzi B, Zayed B, Bischoff P, *et al*. New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: an evidence-based global perspective. *Lancet Infect Dis* 2016;16:e288–e303.
12. European Centre for Disease Prevention and Control. Systematic review and evidence-based guidance on perioperative antibiotic prophylaxis. 2013 http://www.ecdc.europa.eu/en/publications/Publications/Perioperative%20antibiotic%20prophylaxis%20-%20June%202013.pdf.
13. Bowater RJ, Stirling SA, Lilford RJ. Is antibiotic prophylaxis in surgery a generally effective intervention? Testing a generic hypothesis over a set of meta-analyses. *Ann Surg* 2009;249:551–6.
14. Bratzler DW, Dellinger EP, Olsen KM, *et al*. Clinical practice guidelines for antimicrobial prophylaxis in surgery. *Am J Health Syst Pharm* 2013;70:195–283.
15. Bratzler DW, Houck PM, *et al*. Surgical Infection Prevention Guidelines Writers Workgroup. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. *Clin Infect Dis* 2004;38:1706–15.
16. Pastor C, Artinyan A, Varma MG, *et al*. An increase in compliance with the Surgical Care Improvement Project measures does not prevent surgical site infection in colorectal surgery. *Dis Colon Rectum* 2010;53:24–30.
17. Serra-Aracil X, García-Domingo MI, Parés D, *et al*. Surgical site infection in elective operations for colorectal cancer after the application of preventive measures. *Arch Surg* 2011;146:606–12.
18. Cannon JA, Altom LK, Deierhoi RJ, *et al*. Preoperative oral antibiotics reduce surgical site infection following elective colorectal resections. *Dis Colon Rectum* 2012;55:1160–6.
19. Morris MS, Graham LA, Chu DI, *et al*. Oral antibiotic bowel preparation significantly reduces surgical site infection rates and readmission rates in elective colorectal surgery. *Ann Surg* 2015;261:1034–40.
20. Kiran RP, Murray AC, Chiuzan C, *et al*. Combined preoperative mechanical bowel preparation with oral antibiotics significantly reduces surgical site infection, anastomotic leak, and ileus after colorectal surgery. *Ann Surg* 2015;262:416–25. discussion 23-5.
21. Hata H, Yamaguchi T, Hasegawa S, *et al*. Oral and parenteral versus parenteral antibiotic prophylaxis in elective laparoscopic colorectal surgery (JMTO PREV 07-01): a phase 3, multicenter, open-label, randomized trial. *Ann Surg* 2016;263:1085–91.
22. Ikeda A, Konishi T, Ueno M, *et al*. Randomized clinical trial of oral and intravenous versus intravenous antibiotic prophylaxis for laparoscopic colorectal resection. *Br J Surg* 2016;103:1608–15.
23. Nelson RL, Glenny AM, Song F. Antimicrobial prophylaxis for colorectal surgery. *Cochrane Database Syst Rev* 2009:CD001181.
24. Roos D, Dijksman LM, Tijssen JG, *et al*. Systematic review of perioperative selective decontamination of the digestive tract in elective gastrointestinal surgery. *Br J Surg* 2013;100:1579–88.
25. Nelson RL, Gladman E, Barbateskovic M. Antimicrobial prophylaxis for colorectal surgery. *Cochrane Database Syst Rev* 2014:CD001181.
26. Nelson RL, Kelsey P, Leeman H, *et al*. Antibiotic treatment for Clostridium difficile-associated diarrhea in adults. *Cochrane Database Syst Rev* 2011:CD004610.
27. Itani KM, Wilson SE, Awad SS, *et al*. Ertapenem versus cefotetan prophylaxis in elective colorectal surgery. *N Engl J Med* 2006;355:2640–51.
28. Contant CM, Hop WC, van't Sant HP, *et al*. Mechanical bowel preparation for elective colorectal surgery: a multicentre randomised trial. *Lancet* 2007;370:2112–7.
29. Slim K, Vicaut E, Launay-Savary MV, *et al*. Updated systematic review and meta-analysis of randomized clinical trials on the role of mechanical bowel preparation before colorectal surgery. *Ann Surg* 2009;249:203–9.

30. Güenaga KF, Matos D, Wille-Jørgensen P. Mechanical bowel preparation for elective colorectal surgery. *Cochrane Database Syst Rev* 2011:CD001544.
31. Chan AW, Tetzlaff JM, Gøtzsche PC, *et al*. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
32. Gustafsson UO, Scott MJ, Schwenk W, *et al*. Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS(®)) Society recommendations. *World J Surg* 2013;37:259–84.
33. Nygren J, Thacker J, Carli F, *et al*. Guidelines for perioperative care in elective rectal/pelvic surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations. *Clin Nutr* 2012;31:801–16.
34. Bretagnol F, Panis Y, Rullier E, *et al*. Rectal cancer surgery with or without bowel preparation: The French GRECCAR III multicenter single-blinded randomized trial. *Ann Surg* 2010;252:863–8.
35. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008;36:309–32.
36. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;240:205–13.
37. Bone RC, Sibbald WJ, Sprung CL. The ACCP-SCCM consensus conference on sepsis and organ failure. *Chest* 1992;101:1481–3.
38. Levy MM, Fink MP, Marshall JC, *et al*. SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Intensive Care Med* 2001;2003:530–8.
39. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* 2012;120:c179–c184.
40. Bennett-Guerrero E, Pappas TN, Koltun WA, *et al*. Gentamicin-collagen sponge for infection prophylaxis in colorectal surgery. *N Engl J Med* 2010;363:1038–49.
41. Royston P. Multiple imputation of missing values. *Stata Journal* 2004;4:227–41.
42. Schulz KF, Altman DG, Moher D, *et al*. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.
43. Arriaga AF, Lancaster RT, Berry WR, *et al*. The better colectomy project: association of evidence-based best-practice adherence rates to outcomes in colorectal surgery. *Ann Surg* 2009;250:507–13.
44. Bratzler DW, Hunt DR. The surgical infection prevention and surgical care improvement projects: national initiatives to improve outcomes for patients having surgery. *Clin Infect Dis* 2006;43:322–30.