Circular pOlyethylene drape in preVEntion of suRgical site infection (COVER Trial): Study protocol of a randomized controlled trial

Ri Na Yoo
St. Vincent's Hospital College of Medicine The Catholic University of Korea
Hyung Jin Kim
St. Vincent's Hospital College of Medicine The Catholic University of Korea
Jae Im Lee
Uijeongbu St. Mary's Hospital The Catholic University of Korea
Won-Kyung Kang
Yeouido St. Mary's Hospital The Catholic University of Korea
Bong-Hyeon Kye
Seoul St. Mary's Hospital The Catholic University of Korea
Chang Woo Kim
Kyung Hee University Hospital at Gangdong Kyung Hee University School of Medicine
Sung Uk Bae
School of Medicine Keimyung University and Dongsan Medical Center
Joong Ho Lee
National Health Insurance Service Ilsan Hospital
Byung Mo Kang (kbm0728@yahoo.co.kr)
Chuncheon Sacred Heart Hospital Hallym University College of Medicine https://orcid.org/0000-0003-0900-094X

Method Article

Keywords: Circular polyethylene drape, Abdominal surgery, Gastrointestinal tract, Surgical site infection, Randomized controlled trial

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Abstract

Background: Surgical site infection (SSI) after abdominal surgery is still a significant morbidity associated with an increased socioeconomic burden and poor quality of life. SSI prevalence rates as high as 40% in cases of fecal contamination have been reported; however, current methods to reduce SSI are limited to elective abdominal surgery. Further evaluation of preventive measures for reducing SSI is necessary.

Methods/design: The COVER trial investigates whether the application of a dual-ring circular plastic wound protector reduces the rate of SSI in patients undergoing open abdominal surgery related to the gastrointestinal (GI) tract, regardless of the type of wound classified by the Center for Disease Control (CDC). The COVER trial is a multicenter, randomized controlled clinical trial with two parallel arms – one using a wound protector and the other using conventional surgical dressing gauze. The primary outcome will measure the rate of SSI in two groups. Statistical analysis of the primary end point will be based on the intention-to-treat population. The sample size is determined to achieve a study power of 80% at 95% 2-sided confidence limits. Considering a dropout rate of up to 5%, a total of 458 patients, 229 patients in each group, will be enrolled in this study.

Discussion: The COVER trial will provide high-quality evidence for using a circular polyethylene drape in open abdominal surgery for the GI tract in all types of wound. The design of the trial will deliver high external validity and clinical significance.

Trial registration: The trial protocol was registered at ClinicalTrials.gov (NCT 03170843) on May 31, 2017. https://clinicaltrials.gov/ct2/show/NCT03170843?term=NCT+03170843&rank=1

Keywords: Circular polyethylene drape, Abdominal surgery, Gastrointestinal tract, Surgical site infection, Randomized controlled trial

Background

Rationale for the trial

Surgical site infection (SSI) is a common postoperative complication that is associated not only with considerable morbidity and mortality but also significant socioeconomic burden [1-3]. The rate of SSI is estimated to range from approximately 10% to 30% in elective abdominal surgery, depending on the presence of risk factors, type of procedure, and degree of endogenous contaminant [4,5,1]. In cases of fecal peritonitis, the SSI rate may reach up to 35~40% [6,7]. Despite organizational, systematic approaches for preventing SSI based on evidence, such as preoperative antibiotic prophylaxis and antiseptic skin cleansing, SSI is still a major problem associated with increased hospital cost, prolonged hospital stay, and unsatisfactory quality of life [8].

The main cause of postoperative SSI is speculated to be the endogenous flora residing in the host, mostly in the skin, mucous membranes, and hollow viscera [9,10]. When normal tissue is disrupted by surgical manipulation, toxins or other substances that normal flora may innately contain or produce possibly begin to damage or injure host tissue or signal to express their virulence. Pathogens may also arise from preoperative infection sites, even sites remotely located from the actual operative site [11]. In addition, exogenous pathogens from the surgical instruments, operating theater, and even surgical team members give rise to SSI during surgical procedures [11].

The pathogenesis of SSI is directly associated with the dose of bacterial contamination, following the equation: Dose of bacterial contamination x virulence / resistance of the host = SSI [4]. Thus, the risk of developing SSI will absolutely increase when the surgical incision site is exposed to loads of virulent bacteria in the contaminated surgical field. This risk leads to the idea of developing a physical barrier for the wound edge that can hinder direct exposure of the surgical incision edges to the contaminated field. Several devices purposed for wound edge protection and with the similar design of a flexible plastic wound cover placed into the laparotomy site are currently on the market. Prospective studies and randomized clinical trials (RCTs) have been conducted to evaluate the effectiveness of the plastic wound protector to reduce the incidence of SSI. However, the effect of the wound protector in abdominal surgery is still controversial and remains to be elucidated.

Previous trials

The largest RCT evaluating the effectiveness of wound protectors in reducing SSI is the ROSSINI trial, with 760 patients undergoing laparotomy at 21 different hospitals in the UK [8]. In this study, the drape design of the wound protector was compared to standard intraoperative care. The result showed that the use of a wound edge protector during open abdominal surgery did not reduce the rate of SSI. Similarly, RCTs using a drape type of wound protector applied in colorectal surgery reported no benefit of the wound protector in reducing SSI [12,13]. However, several other studies have claimed contrasting results. The BaFO trial, with 608 patients undergoing laparotomy at 16 different medical centers in Germany, demonstrated that the patients who used wound protection drape devices experienced SSI at a lower rate than those who did not [14]. A Japanese single-centered RCT with 221 patients enrolled for investigating the effect of a double-ring, circular wound protector applied in nontraumatic gastrointestinal surgery also showed that the rate of SSI was significantly lower in the experimental group than in the control group [15]. Two other single-centered RCTs similar to the Japanese trial evaluating the double-ring, circular wound protector in elective colorectal surgery reported a reduction in SSI [16,17].

This variation in study results may be interpreted by different trial designs, including sample size, the number of participating surgeons and centers, the method of randomization, adaptation of a standardized study protocol, and varying definitions of surgical wound infection. Moreover, according to a recent meta-analysis reporting that the dual-ring wound protector is effective in reducing SSI, the design of the device appears to affect the study outcome. A well-designed, multicentered, RCT evaluating the

effect of the dual-ring type of wound protector used in open laparotomy, particularly for contaminated or dirty infected wounds, has not yet been conducted.

Objective

The COVER trial aims to investigate the effect of a dual-ring, plastic wound protector in open gastrointestinal surgery. It is designed to test whether the device helps to reduce the overall rate of SSI development within 30 days postoperatively by 40% compared with the control group. The COVER trial particularly includes patients undergoing emergency laparotomy for contaminated or dirty infected wounds caused by bowel perforation, which allows the thorough investigation of its effect according to the degree of contamination.

Methods

Trial sites

Initially, eight sites of secondary or tertiary hospitals in South Korea have begun this trial. All participating investigators have been adequately trained and prepared according to the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use – good clinical practice (GCP) rules for taking part in this trial. This trial is still open for recruitment at participating centers.

Trial population and eligibility

All gastrointestinal surgical patients undergoing open abdominal surgery, either elective or emergent, will be screened for eligibility. Patients who satisfy the following criteria will be included: 1) patients must be in between the ages of 18 to 75; 2) open laparotomy; and 3) surgery for stomach, small intestine, or colon and rectum. Patients with any of the following will be excluded: 1) presence of concurrent infection in the abdominal wall; 2) open conversion from laparoscopic surgery; 3) presence of poor nutritional status indicated by a nutrition risk screening (NRS) 2002 score greater than 3; 4) patients undergoing combined hepatobiliary surgery; 5) pregnant or breast-feeding women; 6) moderate to severe immunosuppression state, defined as previous organ or bone marrow transplantation, concurrent steroid administration (more than 10 mg prednisolone daily or an equivalent dose of any other steroid), or concurrent administration of other immunosuppressive or chemotherapeutic agents within the last 2 weeks prior to trial intervention. Once an investigator explains the extent and nature of the COVER trial to an eligible patient, informed consent will be obtained.

Sample size

A total of 434 patients will be analyzed, considering an estimated dropout rate of approximately 5%. A total of 458 patients will be recruited, and 229 patients will be randomly assigned to each group. The trial flow is outlined in Figure 1.

Trial type

This clinical trial is a prospective, multicentered, patient-blinded, randomized controlled trial with two parallel comparison arms.

Recruitment and trial timeline

The eight centers of secondary or tertiary hospitals in South Korea have been actively conducting the trial since June 2017. Since then, 4 other centers have joined the trial recruitment, and this trial is still open for recruiting participating centers. All investigators, physicians or nurses are required to complete the ICH-GCP training course. Patients will be recruited for approximately 48 months. The last follow-up will be taken at 30 days after the last recruited patient undergoes the trial intervention. The SPIRIT figure shows the study schedule of enrollment, interventions and assessments (Fig. 2). A SPIRIT checklist is available in Additional file 1. An interim analysis is planned when 50% of the enrollment is reached. Depending on the results of the interim analysis, the subsequent research process and timeline can be modified.

Randomization and blinding

Stratification will be performed according to the participating center and the type of wound classification. The wound types will be divided into two groups: one with clean or clean-contaminated and the other with contaminated or dirty, infected. A web-based patient registry (http://cover.e-trial.co.kr) will be applied to generate the allocation sequence just before the beginning of the operation, providing adequate concealment for the allocation sequence. The group allocation and randomization number will be predefined by a biostatistician of the Catholic Medical Center in Seoul, South Korea. To assure balanced group size in the course of the accrual, a permuted block randomization with the size of 2 or 4 is applied. Participating surgeons cannot be blinded to allocated treatment. However, the patient will be blinded for the trial intervention since they are under general anesthesia once the operation starts. The data manager will also be blinded because there is no direct access to either the trial intervention or the randomization.

Interventions

Preoperative bowel preparation, type of skin preparation and drape, the use of perioperative antibiotics, and the details of the surgical procedure will follow the policy of an individual surgeon in each center. The experimental arm will be provided with a circular polyethylene drape (O Trac®, Asung Medical Inc. South Korea) to cover the incision site in the abdomen. It is a double-ring type of sterile, cylindrical wound protector consisting of inner and outer rings with a polyethylene sheath. The wound protector is left in situ throughout the operation and is removed just before closing the abdominal wall. The method of wound closure and insertion of wound drainage will also follow the policy of an individual surgeon in each center.

For the control arm, conventional surgical dressing gauze will be used to protect the incision site during the surgical procedure. There are no differences in surgical technique, other devices, or the environment.

Risks

No additional risks to the study patients are expected. The circular polyethylene wound protector has established clinical safety and has been already in clinical applications with the approval of the Korean Medical Device Information and Technology Assistance Center, MDITAC. None of the technical details other than wound protection are affected by the trial.

Outcomes

The primary end point of the COVER trial is the rate of SSI, defined by the diagnostic criteria suggested by the Center for Disease Control (CDC) within 30 days after surgery [4]. The postoperative wound condition will be evaluated at postoperative weeks 1, 2, and 4. The secondary end points include the length of postoperative hospital stay, the re-admission rate, and the rate of surgical complication other than SSI. The incidence of 30-day postoperative complications will be stratified according to the modified Clavien-Dindo Classification [18].

Data management and monitoring

All required information will be recorded through an electronic case reporting form (eCRF) on the web-based patient registry by the investigator or a designated representative. Baseline characteristics, including age, sex, body mass index, American Society of Anesthesiologists score, history of smoking and alcohol consumption, history of previous chemotherapy, radiotherapy, abdominal surgery, steroid or immunosuppressive drug use, history of diabetes or malignancies in the gastrointestinal tract and nutritional status based on the NRS 2002 score will be collected. Laboratory parameters (white blood cell count and c-reactive protein and albumin levels) will be collected preoperatively, on the operation day and on postoperative day 2, if available. The parameters for surgical procedure, including operation type (emergent or elective), site of operation (stomach, small intestine or large intestine), level of wound contamination according to CDC classification, method of skin preparation, antibiotics use, operation time, bowel anastomosis and stoma formation, skin closure material, length of skin incision, draining tube for the wound and body temperature during the operative procedure, will be collected. Postoperatively, the surgical wound will be evaluated at postoperative weeks 1, 2, and 4. A photograph of the wound at each office visit will be taken and documented, if agreed. If SSI is detected, the classification and the postoperative date of diagnosis will be recorded. Bacterial culture of the infected wound will be performed. Postoperative complications according to the modified Clavien-Dindo classification, postoperative length of hospital stay and re-admission will be noted. An investigator or research coordinator at each center will enter the data using the eCRF. The principle investigator is responsible for data completeness and the accuracy of the documentation. At the end of the trial, the study data and personal information of the enrolled patients will be archived for 3 years.

The trial data will be monitored by an independent institution experienced in the monitoring of clinical trials (Medical Excellence, Inc.) in Seoul, Korea. Monitoring will be performed in accordance with ICH-GCP guidelines [19].

Safety evaluation and reporting of adverse events

All adverse events or serious adverse events, occurring from the moment of randomization until the end of the 30-day follow-up, will be recorded and reported by the investigators.

Statistical methods

Sample size calculation

The sample size calculation is based on the primary end point of surgical site infections within 30 days after the index operation. Previous reports on the incidence of SSI have indicated that the rate of SSI may vary depending on the wound classification, the procedure, the surveillance criteria, and the quality of data collection [11]. The incidence of SSI for clean-contaminated wounds has been reported to be as high as 10% [20]. For contaminated wounds, the incidence was approximately 25% [11,7]. For dirty, infected wounds, the incidence may reach up to 40% [5-7]. In this trial, the ratio of operations with clean-contaminated, contaminated, and dirty, infected wound is assumed to be 20:40:40; therefore, the expected incidence of SSI for the control group is 28%. For the experimental group, the incidence of SSI will be decreased by 40%. Thus, the rate of SSI in the experimental group will be approximately 17%. The sample size is determined to achieve a study power of 80%, with 95% 2-sided confidence limits. The actual sample size amounts to 434 participants. However, considering a dropout rate of up to 5%, a total of 458 patients, 229 patients in each group, will be enrolled in this study.

Discussion

SSI has been recognized as a costly, debilitating surgical complication over decades worldwide. Despite vigorous efforts to control SSI through campaigns and publications by international organizations, the rate of SSI has changed only slightly [10,21-23,2]. Even such recommendations are limited to the use of prophylatic antibiotics or antiseptic skin cleansing, which can only be applied during elective surgeries. In cases of abdominal surgery, diffuse purulent peritonitis with or without fecal contamination, which requires emergency surgery, is frequently encountered. Prophylatic antibiotics or antiseptic skin cleansing is not applicable in emergent surgical cases. Several preventive measures other than the use of prophylatic antibiotics or antiseptic skin cleansing have been proposed to prevent SSI. Intraoperative wound irrigation with antibiotic solution is one method that can be implemented. Intraoperative wound irrigation with antibiotic solution seems to reduce the incidence of SSI; however, the problem lies with potential adverse effects of tissue toxicity and increased bacterial resistance [24]. The use of triclosan-coated sutures for abdominal wall closure in open surgery with fecal peritonitis has shown good results in reducing the incidence of SSI [7]. Although only a small number of samples have been tested, bactericidal suture material has been demonstrated to be effective. Another method is the application of negative-pressure wound therapy (NPWT) without primary closure of the abdominal wound in highly contaminated abdominal surgery [25]. A recent meta-analysis on the use of NPWT in open and infected wounds after vascular surgery demonstrated that it could be effective in controlling SSI [26]. However, there are only a few case reports of its use in contaminated abdominal surgery, and no trial or analysis of

its efficacy is available. The first two methods require the application of a bactericial substance directly to the tissue that may or may not present a bacterial infection. Thus, the adverse effects of tissue toxicity and bacterial resistance cannot be ignored. The use of NPWT also requires additional resources and time to heal, which potentially involves a longer hospital stay and additional medical cost. Therefore, adopting these methods is not easy in daily practice.

The application of a plastic wound protector in abdominal surgery has been tested for its efficacy for more than a decade. Based on the findings for pathogens most frequently isolated for SSI, including *Staphylococcus aureus*, coagulase-negative *staphylococci*, *Enterococcus* species, and *Escherichia coli* [11], plastic wound protectors that hinder direct exposure of the surgical wound to virulent endogenous bacteria during surgical procedures have been created. Several previous studies and trials have been conducted to investigate such a hypothesis [27]. These trials have varied by using different designs of wound protectors: namely, single-ring or dual-ring types. The COVER trial will test a dual-ring type of wound protector that can tightly conceal the surgical incision edge during the entire operation time. Previously, the trials on the dual-ring design were conducted in a single center with a small sample size. In addition, these trials excluded emergent surgeries with contaminated and dirty, infected wounds resulting from perforated viscera [15-17]. Therefore, the effectiveness of the dual-ring type of wound protector in controlling SSI contaminated and dirty, infected wounds can be addressed.

The COVER trial is pragmatic, two-armed RCT that will be conducted by at least 11 surgeons at 11 different centers and possibly more, which will increase external validity. Internal validation and data quality will be assured by adherence to the SPIRIT statement [28]. Assessments of the wound condition will not only be done by the observer but will also be reviewed by other investigators via photographs documented in the eCRF. This will provide an objective and reliable method for the evaluation of wound infections. Finally, the risk that patients may experience from participating in this trial is minimal and will remain within the boundaries of routine clinical practice.

The results of the COVER trial will provide high-quality evidence for using a circular polyethylene drape in open abdominal surgery with all types of wound to reduce the incidence of SSI.

Abbreviations

SSI, surgical site infection; RCT, randomized clinical trial; ICH, International Conference on Harmonisation; GCP, Good Clinical Practice; NRS, nutrition risk screening; CDC, the Centers for Disease Control; eCRF, electronic case reporting form; NPWT, negative-pressure wound therapy.

Declarations

Trial status

Recruitment of participants began at July 11, 2017. A total of 135 patients had been recruited to this trial as of September 16, 2018. Recruitment will be completed at July, 2021. (Current study protocol version

7.0., revised at October 23, 2018)

Ethics approval and consent of participate

The trial protocol, informed consent document and any other documents necessary to legitimately start a clinical trial were reviewed and approved by the institutional review board at each participating center. Written informed consent was obtained from each study participants in accordance with ethics approval.

Consent for publication

Not applicable

Availability of data and material

Not applicable

Competing interests

The authors declare that they have no competing interests.

Funding

This trial is supported by the Korean Surgical Infection Society, with the use of the circular polyethylene wound protector (O Trac®, Asung Medical Inc. South Korea) given free of charge. There is no other financial support and conflict of interest. The industrial funder and trial management are independent.

Authors' contribution

HJK and RNY designed the COVER trial and were responsible for the protocol development.

JIL, WKK, BHK, CWK, SUB, JHL and BMK revised the draft of the protocol and approved the final version of protocol.

RNY and BMK wrote the manuscript.

BMK and HJK critically revised the manuscript.

All of the authors conducted the COVER trial and approved the final version of manuscript.

Acknowledgement

Not applicable

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Figures

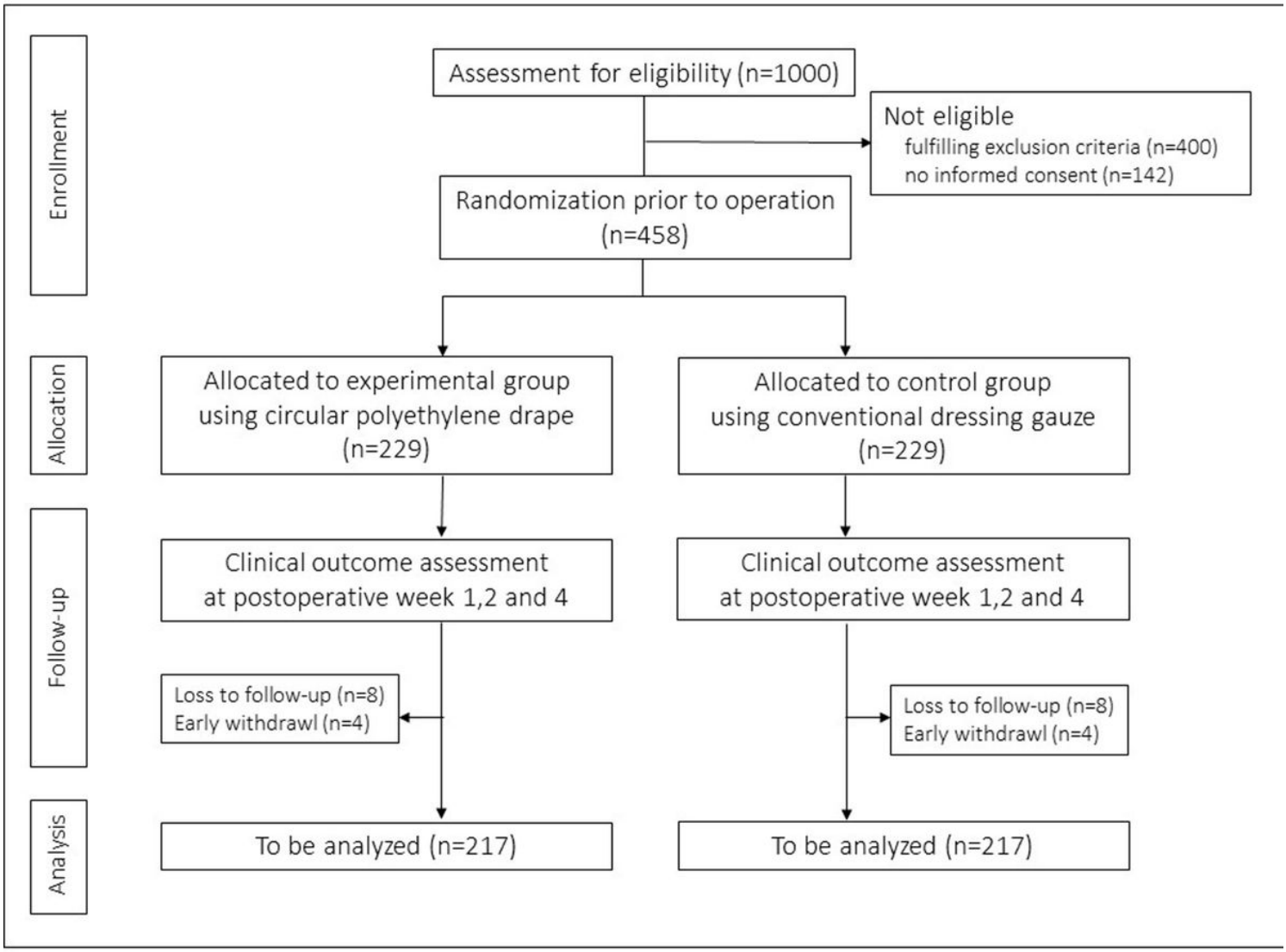

Figure 1

Trial flow.

	STUDY PERIOD						
	Enrolment	Allocation	Post-allocation				Close-out
TIMEPOINT	-2 to 0 day	Operation day (day 0)	PO 2 day	PO 1 week	PO 2 week	PO 4 week	PO 4 week
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Randomization		X					
Allocation		X					
INTERVENTIONS:							
Experimental intervention		X					
Control intervention		X					
ASSESSMENTS:							
Demographical data	X						
Medical history	X						
Nutritional status	X						
Laboratory examination	X	X	X				
Parameters of surgical procedure		X					
Body temperature		X					
Photograph of the wound				X	X	X	
Documentation of SSI				X	X	X	
Documentation of other complication				X	X	X	
Length of hospital stay							X
Readmission							X

Figure 2

SPIRIT figure - PO = postoperative; SSI = Surgical site infection.

Supplementary Files

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- supplement1.pdf