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*C*ircular p*O*lyethylene drape in pre*VE*ntion of su*R*gical site infection (COVER Trial): Study protocol of a randomized controlled trial

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Abstract

Introduction: 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 and analysis: 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 tract, regardless of the type of wound classified by the Center for Disease Control. 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 within 30 days after surgery 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.

Ethics and dissemination: The trial protocol and informed consent document have been reviewed and approved by the institutional review board at each participating center. Written informed consent was obtained from each study participants. The clinical outcomes of this trial will be submitted in an international peer-reviewed journal and presented at international conferences.

Trial registration: The trial protocol was registered at ClinicalTrials.gov (NCT 03170843).

Strengths and limitations of this study:

1. This multicenter, randomized study aimed to investigate the protective effect of a dual-ring, plastic wound protector in open gastrointestinal surgery, compared with the conventional technique using surgical dressing gauze.
2. The primary endpoint, 30-day postoperative surgical site infection rate, will be assessed for open gastrointestinal surgery not only with clean/clean-contaminated wound but also with contaminated/dirty wound.
3. Limitations of this study are lack of blinding of surgeons and including only the Korean population who have relatively low body mass index.

INTRODUCTION

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 [1 4 5]. 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 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.

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 [9 10]. 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 [11]. 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 [12].

The effect of the wound protector in abdominal surgery is still controversial and remains to be elucidated. 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.

METHODS AND ANALYSIS

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. In particular, the COVER trial includes patients who are undergoing an emergency laparotomy for contaminated or dirty/infected wounds, as well as those undergoing a laparotomy for clean or clean-contaminated wounds, which allows a thorough investigation of the wound protector's effects, depending on the degree of contamination.

Trial sites

Initially, eight sites of secondary or tertiary hospitals in South Korea have begun this trial. All participating investigators have been educated on the basis of the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, which serves as the good clinical practice (GCP) guidelines for 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 hepatobiliopancreatic 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.

Trial type

This clinical trial is a prospective, multicentered, patient-blinded, randomized controlled trial with two parallel comparison arms. A total of 458 patients will be enrolled, and 229 patients will be assigned to each group (Fig. 1).

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. 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 participants 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 is the rate of SSI, defined by the diagnostic criteria suggested by the Center for Disease Control (CDC) within 30 days after surgery. According to the CDC definition, SSIs are classified as being either superficial incisional, deep incisional or organ/space [13]. The postoperative wound condition will be evaluated at postoperative weeks 1, 2, and 4-5. 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 [14].

Data management and monitoring

A newly developed, web-based, electronic case reporting form (eCRF) will be used to record data for the included patients. 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, wound closure material, length of skin incision, draining tube for the wound and body temperature during the operative procedure, will be collected. The surgical wounds are classified into clean, clean-contaminated, contaminated and dirty wounds, according to the magnitude of the bacterial

load [15]. Postoperatively, the surgical wound will be evaluated at postoperative weeks 1, 2, and 4-5. 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. 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 (Medical Excellence, Inc.) in Seoul, Korea. Monitoring will be performed in accordance with ICH-GCP guidelines [16].

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 was calculated based on the primary end point of this trial. 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 [17]. The incidence of SSI for clean/clean-contaminated wounds has been reported to be as high as 10% [18]. For contaminated wounds, the incidence was approximately 25% [7 17]. For dirty, infected wounds, the incidence may reach up to 40% [5-7]. In this trial, the ratio of operations with clean/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 drop-out (lost to follow-up, retracted consent or protocol violation) rate of up to 5%, a total of 458 patients, 229 patients in each group, will be enrolled in this study.

Statistical analysis

The statistical analysis will be performed by an independent statistician from the Catholic Medical Center (Seoul, South Korea). The interim and final results will be analyzed mainly for the intention-to-treat population and, additionally, for the per-protocol population. The rate of 30-day postoperative SSI will be evaluated in total patients and also analyzed according to the wound classification (superficial incisional, deep incisional and organ/space SSIs), as defined by the CDC. Pearson's chi-squared test or Fisher's exact test will be used to analyze nominal data; Student's *t*-test and the Wilcoxon rank-sum test will be used for continuous data. To estimate the independent risk factors for 30-day postoperative SSI, logistic regression analysis will be performed. The statistical analysis will be conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Withdrawals

Enrolled patients can withdraw their participation at any time, if desired. In this case, the patients will have no disadvantages. The investigator will record any patient's withdrawal in the eCRF.

Patient and public involvement

Patients and the public were not involved in the protocol of this study.

ETHICS AND DISSEMINATION

Research ethics

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.

Study registration

The trial protocol was registered at ClinicalTrials.gov (NCT 03170843) on May 31, 2017.

Dissemination

The final results will be discussed with participating surgeons and presented at domestic and international scientific conferences. The final results will be submitted in an international peer-reviewed scientific journal.

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 [2 19-22]. 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 [23]. Another method is the application of negative-pressure wound therapy (NPWT) without primary closure of the abdominal wound in highly contaminated abdominal surgery [24]. 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 [25]. 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* [17], 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 [26]. 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 [12 27 28]. 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 [29]. 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.

Trial status

Recruitment of participants began at July 11, 2017. A total of 211 patients had been recruited to this trial as of September 21, 2019. The trial is currently ongoing. (Current study protocol version 7.0., revised at October 23, 2018)

Contributors

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

JIL, WKK, BHK, CWK, SUB, SMN 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.

Funding

This trial is supported by the Korean Surgical Infection Society (Award number: KSIS 2019-021), 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.

Competing interests

The authors declare that they have no competing interests.

Patient consent for publication

Not required

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438 **FIGURE LEGENDS**

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440 Figure 1. Trial flow

441

442 Figure 2. SPIRIT figure

443 PO = postoperative; SSI = Surgical site infection

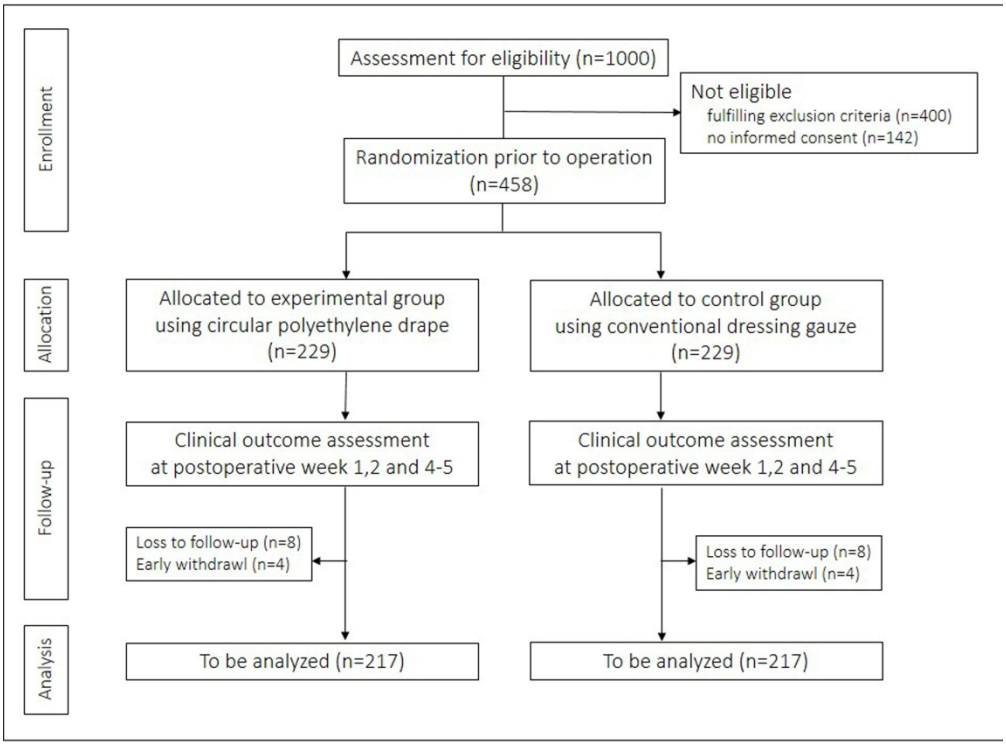

Figure 1. Trial flow

254x190mm (300 x 300 DPI)

	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 4-5 week	PO 4-5 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					
Documentation of SSI				X	X	X	
Documentation of other complication				X	X	X	
Length of hospital stay							X
Readmission							X

Figure 2. SPIRIT figure

215x279mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Lines 1–2
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Lines 68, 281-282
	2b	All items from the World Health Organization Trial Registration Data Set	Throughout
Protocol version	3	Date and version identifier	Lines 332-335
Funding	4	Sources and types of financial, material, and other support	Lines 345-349
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Lines 4-21, 337-343
	5b	Name and contact information for the trial sponsor	Lines 345-349
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Lines 345-349
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Lines 233-234, 256-257

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Lines 90-119
	6b	Explanation for choice of comparators	Lines 99-105
Objectives	7	Specific objectives or hypotheses	Lines 127-134
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Lines 157-160, Fig 1
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Lines 136-141, 163-164
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Lines 143-155
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Lines 185-196
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Lines 266-269
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Lines 214-215, 233-234
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Not applicable
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Lines 204-211
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Lines 162-171. Fig. 2.

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Lines 241-254
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Lines 140-141
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Lines 173-183
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Lines 176-178
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Lines 176-179
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Lines 179-183
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Lines 213-234
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Lines 227-231

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Lines 230-234
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Lines 255-264
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Lines 257-258
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Lines 257-264
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Lines 233-234
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Lines 169-171
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Lines 236-238
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	None. Trial conduct will be audited by the IRB at each participating center.
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Lines 275-279

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	None. Study protocol modification will be approved by the IRB at each participating center and recorded at the registry (ClinicalTrial.gov).
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Lines 154-155
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Lines 124-125, 230-234
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Lines 345-349
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Lines 256-257, 233-234
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	None. The authors plan to publish the results of this trial in scientific journal.
	31b	Authorship eligibility guidelines and any intended use of professional writers	None
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	None

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	None
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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*C*ircular p*O*lyethylene drape in pre*VE*ntion of su*R*gical site infection (COVER Trial): Study protocol of a randomized controlled trial

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Abstract

Introduction: Surgical site infection (SSI) after abdominal surgery is still a significant morbidity associated with an increased socioeconomic burden and reduced quality of life. Circular wound protector has been expected to reduce the risk of SSI, but previous studies reported conflicting results on its protective effects. The purpose of this study is to evaluate the efficacy of circular wound protector in reducing SSI in open abdominal surgery.

Methods and analysis: The COVER trial investigates whether the application of a dual-ring circular plastic wound protector reduces the rate of SSI in patients undergoing elective or emergent open abdominal surgery related to the gastrointestinal tract, regardless of the type of wound classified by the Center for Disease Control. The COVER trial is a multicenter, randomized controlled clinical trial with two parallel arms – one using a dual-ring wound protector with circular polyethylene drape and the other using conventional surgical dressing gauze. The primary outcome will measure the rate of SSI within 30 days after surgery 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.

Ethics and dissemination: The trial protocol and informed consent document have been reviewed and approved by the institutional review board at each participating center. Written informed consent was obtained from each study participants. The clinical outcomes of this trial will be submitted in an international peer-reviewed journal and presented at international conferences.

Trial registration: The trial protocol was registered at ClinicalTrials.gov (NCT 03170843).

Strengths and limitations of this study:

1. This multicenter, randomized study include elective and emergent surgery for stomach, small and large intestine to ensure generalizability.
2. The primary endpoint, 30-day postoperative surgical site infection rate, will be assessed for open abdominal surgery not only with clean/clean-contaminated wounds but also with contaminated/dirty wounds.
3. COVER Trial is a study with the largest number of patients among the studies for a dual-ring, plastic wound protector.
4. Wound condition will be assessed not only by the observer but also by other investigators using wound photography in the eCRF to provide the reliability of diagnosis for SSIs.
5. Limitations of this study are the lack of blinding of surgeons and including only the Korean population who have relatively low body mass index.

INTRODUCTION

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 [1 4 5]. 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 risk of developing SSI will absolutely increase when the surgical incision site is exposed to loads of virulent bacteria in the contaminated surgical field [9]. 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 [8 10-13].

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[10 11]. 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[12]. 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 [13].

The effect of the wound protector in abdominal surgery is still controversial and remains to be elucidated. A well-designed, multicentered, RCT evaluating the effect of the dual-ring type of wound protector used in open abdominal surgery, particularly for contaminated or dirty infected wounds, has not yet been conducted.

METHODS AND ANALYSIS

Objective

The COVER trial aims to investigate the effect of a dual-ring, plastic wound protector in open abdominal 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. In particular, the COVER trial includes patients who are undergoing an open abdominal surgery for contaminated or dirty/infected wounds, as well as those undergoing an open abdominal surgery for clean or clean-contaminated wounds, which allows a thorough investigation of the wound protector's effects, depending on the degree of contamination.

Trial sites

Initially, eight sites of secondary or tertiary hospitals in South Korea have begun this trial. All participating investigators have been educated on the basis of the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, which serves as the good clinical practice (GCP) guidelines for 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) elective or emergent open abdominal surgery; 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 hepatobiliopancreatic 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.

Trial type

This clinical trial is a prospective, multicentered, patient-blinded, randomized controlled trial with two parallel comparison arms. A total of 458 patients will be enrolled, and 229 patients will be assigned to each group (Fig. 1).

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. 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 participants 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 is the rate of SSI, defined by the diagnostic criteria suggested by the Center for Disease Control (CDC) within 30 days after surgery. According to the CDC definition, SSIs are classified as being either superficial incisional, deep incisional or organ/space [14]. The postoperative wound condition will be evaluated at postoperative weeks 1, 2, and 4-5. 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 [15].

Data management and monitoring

A newly developed, web-based, electronic case reporting form (eCRF) will be used to record data for the included patients. 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, wound closure material, length of skin incision, draining tube for the wound and body temperature during the operative procedure, will be collected. The surgical wounds are classified into clean, clean-contaminated, contaminated and dirty wounds, according to the magnitude of the

bacterial load [16]. Postoperatively, the surgical wound will be evaluated at postoperative weeks 1, 2, and 4-5. A photograph of the wound at each office visit will be taken and documented in the eCRF. 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. 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 (Medical Excellence, Inc.) in Seoul, Korea. Monitoring will be performed in accordance with ICH-GCP guidelines [17].

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 was calculated based on the primary end point of this trial. 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 [18]. The incidence of SSI for clean/clean-contaminated wounds has been reported to be as high as 10% [19]. For contaminated wounds, the incidence was approximately 25% [7 18]. For dirty, infected wounds, the

incidence may reach up to 40% [5-7]. In this trial, the ratio of operations with clean/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 drop-out (lost to follow-up, retracted consent or protocol violation) rate of up to 5%, a total of 458 patients, 229 patients in each group, will be enrolled in this study.

Statistical analysis

The statistical analysis will be performed by an independent statistician from the Catholic Medical Center (Seoul, South Korea). The interim and final results will be analyzed mainly for the intention-to-treat population and, additionally, for the per-protocol population. The rate of 30-day postoperative SSI will be evaluated in total patients and also analyzed according to the wound classification (superficial incisional, deep incisional and organ/space SSIs), as defined by the CDC. Pearson's chi-squared test or Fisher's exact test will be used to analyze nominal data; Student's *t*-test and the Wilcoxon rank-sum test will be used for continuous data. To estimate the independent risk factors for 30-day postoperative SSI, logistic regression analysis will be performed. The statistical analysis will be conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Withdrawals

Enrolled patients can withdraw their participation at any time, if desired. In this case, the patients will have no disadvantages. The investigator will record any patient's withdrawal in the eCRF.

Patient and public involvement

Patients and the public were not involved in the protocol of this study.

ETHICS AND DISSEMINATION

Research ethics

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. List of ethics committee: Central Institutional Review Board of The Catholic Medical Center (XC17DCDI0016), Institutional Review Board of Kyung Hee University Hospital at Gangdong (KHNMC 2017-06-042), Institutional Review Board of Keimyung University Donsan Medical Center (2017-06-051-001), Institutional Review Board of National Health Insurance Service Ilsan Hospital (NHIMC 2017-08-014) and Institutional Review Board of Hallym University Chuncheon Sacred Heart Hosptial (2017-70).

Study registration

The trial protocol was registered at ClinicalTrials.gov (NCT 03170843) on May 31, 2017.

Dissemination

The final results will be discussed with participating surgeons and presented at domestic and international scientific conferences. The final results will be submitted in an international peer-reviewed scientific journal.

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 [2 20-23]. 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]. 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* [18], 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. A meta-analysis by Mihaljevic et al. showed that wound edge protectors significantly reduced the rate of SSIs in open abdominal surgery, and available data for double-ring wound protector might be lower quality compared with that for the single-ring device [28]. 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 [13 29 30]. 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 [31]. 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 [32]. 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.

Trial status

Recruitment of participants began at July 11, 2017. A total of 211 patients had been recruited to this trial as of September 21, 2019. The trial is currently ongoing. (Current study protocol version 7.0., revised at October 23, 2018)

Contributors

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

JIL, WKK, BHK, CWK, SUB, SMN 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.

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Korea) given free of charge. There is no other financial support and conflict of interest. The industrial funder and trial management are independent.

Competing interests

The authors declare that they have no competing interests.

Patient consent for publication

Not required

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FIGURE LEGENDS

Figure 1. Trial flow

Figure 2. SPIRIT figure

PO = postoperative; SSI = Surgical site infection

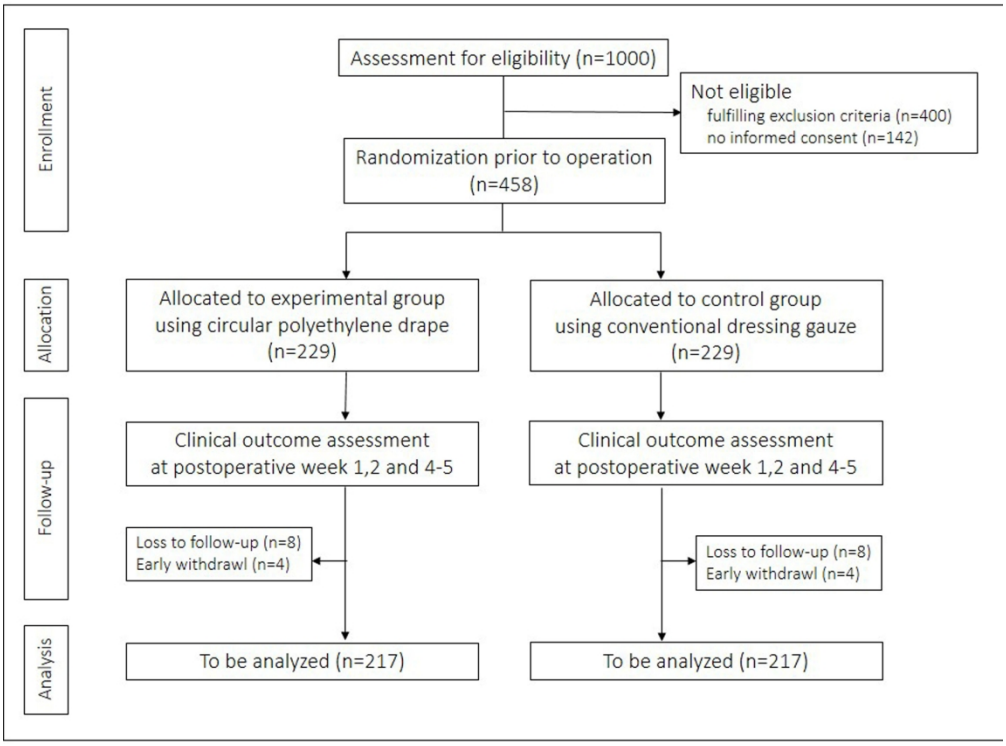

Figure 1. Trial flow

254x190mm (300 x 300 DPI)

	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 4-5 week	PO 4-5 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					
Documentation of SSI				X	X	X	
Documentation of other complication				X	X	X	
Length of hospital stay							X
Readmission							X

Figure 2. SPIRIT figure

215x279mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Lines 1–2
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Lines 68, 281-282
	2b	All items from the World Health Organization Trial Registration Data Set	Throughout
Protocol version	3	Date and version identifier	Lines 332-335
Funding	4	Sources and types of financial, material, and other support	Lines 345-349
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Lines 4-21, 337-343
	5b	Name and contact information for the trial sponsor	Lines 345-349
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Lines 345-349
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Lines 233-234, 256-257

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Lines 90-119
	6b	Explanation for choice of comparators	Lines 99-105
Objectives	7	Specific objectives or hypotheses	Lines 127-134
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Lines 157-160, Fig 1
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Lines 136-141, 163-164
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Lines 143-155
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Lines 185-196
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Lines 266-269
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Lines 214-215, 233-234
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Not applicable
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Lines 204-211
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Lines 162-171. Fig. 2.

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Lines 241-254
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Lines 140-141
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Lines 173-183
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Lines 176-178
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Lines 176-179
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Lines 179-183
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Lines 213-234
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Lines 227-231

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Lines 230-234
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Lines 255-264
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Lines 257-258
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Lines 257-264
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Lines 233-234
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Lines 169-171
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Lines 236-238
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	None. Trial conduct will be audited by the IRB at each participating center.
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Lines 275-279

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	None. Study protocol modification will be approved by the IRB at each participating center and recorded at the registry (ClinicalTrial.gov).
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Lines 154-155
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Lines 124-125, 230-234
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Lines 345-349
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Lines 256-257, 233-234
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	None. The authors plan to publish the results of this trial in scientific journal.
	31b	Authorship eligibility guidelines and any intended use of professional writers	None
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	None

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	None
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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*C*ircular p*O*lyethylene drape in pre*VE*ntion of su*R*gical site infection (COVER Trial): Study protocol for a randomized controlled trial

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Abstract

Introduction: Surgical site infection (SSI) after abdominal surgery remains a significant cause of morbidity and is associated with an increased socioeconomic burden and a reduced quality of life. Circular wound protectors have been expected to reduce the risk of SSI, but previous studies reported conflicting results on their protective effects. The purpose of this study was to evaluate the efficacy of circular wound protectors in reducing SSI in open abdominal surgery.

Methods and analysis: The COVER trial investigates whether the application of a dual-ring circular plastic wound protector reduces the rate of SSI in patients undergoing elective or emergent open abdominal surgery related to the gastrointestinal tract, regardless of the type of wound classified by the Centers for Disease Control. The COVER trial is a multicenter, randomized controlled clinical trial with two parallel arms – one using a dual-ring wound protector with circular polyethylene drape and the other using conventional surgical dressing gauze. The primary outcome will measure the rate of SSI within 30 days after surgery in two groups. Statistical analysis of the primary end point will be based on the intention-to-treat population. The sample size was determined to achieve a study power of 80% with 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.

Ethics and dissemination: The trial protocol and informed consent document have been reviewed and approved by the institutional review board at each participating center. Written informed consent will be obtained from each study participant. The clinical outcomes of this trial will be submitted to an international peer-reviewed journal and presented at international conferences.

Trial registration: The trial protocol was registered at ClinicalTrials.gov (NCT 03170843).

Strengths and limitations of this study:

1. This multicenter, randomized study includes elective and emergent surgery on the stomach, small and large intestine to ensure generalizability.
2. The primary endpoint, the 30-day postoperative surgical site infection (SSI) rate, will be assessed for open abdominal surgery not only with clean/clean-contaminated wounds but also with contaminated/dirty wounds.
3. The COVER trial will have the largest number of patients among all studies on a dual-ring, plastic wound protectors.
4. Wound condition will be assessed not only by the observer but also by other investigators using wound photographs in the eCRF to provide reliable diagnosis of SSIs.
5. The limitations of this study are the lack of blinding of surgeons and the inclusion of only Korean individuals with a relatively low body mass index.

INTRODUCTION

Surgical site infection (SSI) is a common postoperative complication that is associated not only with considerable morbidity and mortality but also with a significant socioeconomic burden [1-3]. The rate of SSI is estimated to range from approximately 10% to 30% after elective abdominal surgery, depending on the presence of risk factors, type of procedure, and degree of endogenous contaminants [1 4 5]. 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 costs, prolonged hospital stays, and unsatisfactory quality of life [8].

The risk of developing a SSI will increase when the surgical incision site is exposed to large amounts of virulent bacteria in a contaminated surgical field [9]. This risk has led 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 that are designed for wound edge protection and have a similar design involving a flexible plastic wound cover placed in the laparotomy site are currently on the market. Prospective studies and randomized clinical trials (RCTs) have been conducted to evaluate the effectiveness of plastic wound protectors for reducing the incidence of SSI [8 10-13].

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 type of wound protector was compared to standard intraoperative care. The results 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 [10 11]. 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[12]. A Japanese single-center RCT with 221 patients enrolled to investigate 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 [13].

The effect of wound protectors in abdominal surgery is still controversial and remains to be elucidated. A well-designed, multicenter, RCT evaluating the effect of the dual-ring type of wound protector in open abdominal surgery, particularly for contaminated or dirty infected wounds, has not yet been conducted.

METHODS AND ANALYSIS

Objective

The COVER trial aims to investigate the effect of a dual-ring, plastic wound protector in open abdominal 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 that of the control group. In particular, the COVER trial includes patients who are undergoing an open abdominal surgery for contaminated or dirty/infected wounds, as well as those undergoing an open abdominal surgery for clean or clean-contaminated wounds, which allows a thorough investigation of the wound protector's effects, depending on the degree of contamination.

Trial sites

Initially, eight sites at secondary or tertiary hospitals in South Korea began this trial. All participating investigators have been educated on the basis of the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, which serves as the good clinical practice (GCP) guidelines for 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) between the ages of 18 and 75 years; 2) undergoing elective or emergent open abdominal surgery; and 3) undergoing surgery on the 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) undergoing combined hepatobiliopancreatic surgery; 5) pregnancy or breast-feeding; and 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.

Trial type

This clinical trial is a prospective, multicenter, patient-blinded, randomized controlled trial with two parallel comparison arms. A total of 458 patients will be enrolled, and 229 patients will be assigned to each group (Fig. 1).

Recruitment and trial timeline

The eight centers at 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 made 30 days after the last recruited patient undergoes the trial intervention. The SPIRIT figure shows the study schedule for 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 group with clean or clean-contaminated wounds and the other group with contaminated or dirty, infected wounds. A web-based patient registry (http://cover.e-trial.co.kr) will be applied to generate the allocation sequence immediately 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 from

the Catholic Medical Center in Seoul, South Korea. A permuted block randomization with the size of 2 or 4 will be applied. Participating surgeons cannot be blinded to the allocated treatment. However, the patient will be blinded to 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 at 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 immediately before closing the abdominal wall. The method of wound closure and insertion of wound drainage will also follow the policy of an individual surgeon at 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 environment.

Risks

No additional risks to the participants are expected. The circular polyethylene wound protector has established clinical safety and has already been used 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 is the rate of SSI, defined by the diagnostic criteria suggested by the Centers for Disease Control (CDC), within 30 days after surgery. According to the CDC definition, SSIs are classified as either superficial incisional, deep incisional or organ/space [14]. The postoperative wound condition will be evaluated at postoperative weeks 1, 2, and 4-5. The secondary end points include the length of postoperative hospital stay, the readmission rate, and the rate of surgical complications other than SSI. The incidence of 30-day postoperative complications will be stratified according to the modified Clavien-Dindo classification [15].

Data management and monitoring

A newly developed, web-based, electronic case reporting form (eCRF) will be used to record data for the included patients. 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, or 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 counts 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 the 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, antibiotic use, operation time, bowel anastomosis and stoma

formation, wound closure material, length of skin incision, draining tube for the wound and body temperature during the surgical procedure, will be collected. The surgical wounds are classified as clean, clean-contaminated, contaminated and dirty wounds, according to the magnitude of the bacterial load [16]. Postoperatively, the surgical wound will be evaluated at postoperative weeks 1, 2, and 4-5. A photograph of the wound will be taken at each office visit and documented in the eCRF. 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 readmission will be noted. An investigator or research coordinator at each center will enter the data using the eCRF. 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 (Medical Excellence, Inc.) in Seoul, Korea. Monitoring will be performed in accordance with ICH-GCP guidelines [17].

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 was calculated based on the primary end point of this trial. 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 [18]. The incidence

of SSI for clean/clean-contaminated wounds has been reported to be as high as 10% [19]. For contaminated wounds, the incidence was approximately 25% [7 18]. For dirty, infected wounds, the incidence may reach up to 40% [5-7]. In this trial, the ratio of operations with clean/clean-contaminated, contaminated, and dirty, infected wounds was assumed to be 20:40:40; therefore, the expected incidence of SSI for the control group was 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 was 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 (lost to follow-up, retracted consent or protocol violation) rate of up to 5%, a total of 458 patients, 229 patients in each group, will be enrolled in this study.

Statistical analysis

The statistical analysis will be performed by an independent statistician from the Catholic Medical Center (Seoul, South Korea). The interim and final results will be analyzed mainly for the intention-to-treat population and, additionally, for the per-protocol population. The rate of 30-day postoperative SSI will be evaluated in all patients and analyzed according to the wound classification (superficial incisional, deep incisional and organ/space SSIs), as defined by the CDC. Pearson's chi-squared test or Fisher's exact test will be used to analyze nominal data; Student's *t*-test and the Wilcoxon rank-sum test will be used for continuous data. To estimate the independent risk factors for 30-day postoperative SSI, logistic regression analysis will be performed. The statistical analysis will be conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Withdrawals

Enrolled patients can withdraw their participation at any time, if desired. In this case, the patients will have no disadvantages. The investigator will record any patient withdrawal in the eCRF.

Patient and public involvement

Patients and the public were not involved in the protocol of this study.

ETHICS AND DISSEMINATION

Research ethics

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. The names of the ethics committees are as follows: Central Institutional Review Board of The Catholic Medical Center (XC17DCDI0016), Institutional Review Board of Kyung Hee University Hospital at Gangdong (KHNMC 2017-06-042), Institutional Review Board of Keimyung University Donsan Medical Center (2017-06-051-001), Institutional Review Board of National Health Insurance Service Ilsan Hospital (NHIMC 2017-08-014) and Institutional Review Board of Hallym University Chuncheon Sacred Heart Hospital (2017-70). Written informed consent was obtained from each study participant in accordance with ethical approval.

Study registration

The trial protocol was registered at ClinicalTrials.gov (NCT 03170843) on May 31, 2017.

Dissemination

The final results will be discussed with participating surgeons and presented at domestic and international scientific conferences. The final results will be submitted to an international peer-reviewed scientific journal.

DISCUSSION

SSI has been recognized worldwide as a costly, debilitating surgical complication for decades. Despite vigorous efforts to control SSI through campaigns and publications by international organizations, the rate of SSI has changed only slightly [2 20-23]. Even such recommendations are limited to the use of prophylactic antibiotics or antiseptic skin cleansing, which can be applied only during elective surgeries. In cases of abdominal surgery, diffuse purulent peritonitis with or without fecal contamination, which requires emergency surgery, is frequently encountered. Prophylactic antibiotics or antiseptic skin cleansing is not applicable in emergent surgical cases. Several preventive measures other than the use of prophylactic 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, there are potential adverse effects of tissue toxicity and increased bacterial resistance [24]. 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 on 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 bactericidal 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 costs. 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 findings for the pathogens most frequently isolated in SSI, including *Staphylococcus aureus*, coagulase-negative *staphylococci*, *Enterococcus* species, and *Escherichia coli* [18], 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 this hypothesis [27]. These trials have varied by using different designs of wound protectors: namely, single-ring or dual-ring types. A meta-analysis by Mihaljevic et al. showed that wound edge protectors significantly reduced the rate of SSIs in open abdominal surgery, but the available data for double-ring wound protectors might be lower quality than those available for the single-ring device [28]. 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 [13 29 30]. Therefore, the effectiveness of the dual-ring type of wound protector in controlling SSI in contaminated and dirty, infected wounds can be addressed. In the COVER trial, patients more than 75 years will be excluded. Prevalence of cognitive impairment increased with age in patients more than 75 years [31] and these patients often have difficulties in understanding the concepts of clinical trial. In addition, extreme age itself is associated with an increased risk of SSI [32].

The COVER trial is a 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 ensured by adherence to the SPIRIT statement [33]. Assessments of wound condition will be not only performed by the observer but also reviewed by other investigators via photographs documented in the eCRF. This will provide an objective and reliable method for the

evaluation of wound infections [34]. 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 the use of a circular polyethylene drape in open abdominal surgery with all types of wounds to reduce the incidence of SSI.

Trial status

Recruitment of participants began on July 11, 2017. A total of 211 patients were recruited for this trial as of September 21, 2019. The trial is currently ongoing. (current study protocol version 7.0., revised on October 23, 2018)

Contributors

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

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

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Competing interests

The authors declare that they have no competing interests.

Patient consent for publication

Not required

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FIGURE LEGENDS

Figure 1. Trial flow

Figure 2. SPIRIT figure

PO = postoperative; SSI = surgical site infection

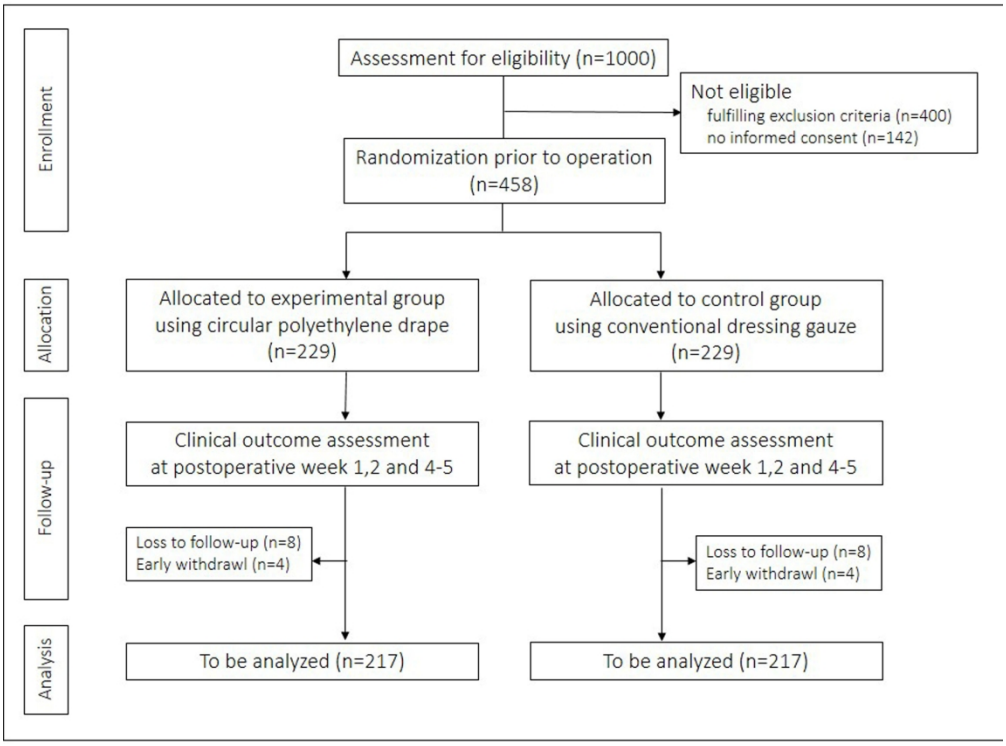

Figure 1. Trial flow

254x190mm (300 x 300 DPI)

	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 4-5 week	PO 4-5 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					
Documentation of SSI				X	X	X	
Documentation of other complication				X	X	X	
Length of hospital stay							X
Readmission							X

Figure 2. SPIRIT figure

215x279mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Lines 1–2
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Lines 68, 281-282
	2b	All items from the World Health Organization Trial Registration Data Set	Throughout
Protocol version	3	Date and version identifier	Lines 332-335
Funding	4	Sources and types of financial, material, and other support	Lines 345-349
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Lines 4-21, 337-343
	5b	Name and contact information for the trial sponsor	Lines 345-349
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Lines 345-349
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Lines 233-234, 256-257

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Lines 90-119
	6b	Explanation for choice of comparators	Lines 99-105
Objectives	7	Specific objectives or hypotheses	Lines 127-134
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Lines 157-160, Fig 1
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Lines 136-141, 163-164
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Lines 143-155
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Lines 185-196
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Lines 266-269
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Lines 214-215, 233-234
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Not applicable
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Lines 204-211
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Lines 162-171. Fig. 2.

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Lines 241-254
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Lines 140-141
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Lines 173-183
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Lines 176-178
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Lines 176-179
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Lines 179-183
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Lines 213-234
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Lines 227-231

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Lines 230-234
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Lines 255-264
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Lines 257-258
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Lines 257-264
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Lines 233-234
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Lines 169-171
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Lines 236-238
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	None. Trial conduct will be audited by the IRB at each participating center.
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Lines 275-279

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	None. Study protocol modification will be approved by the IRB at each participating center and recorded at the registry (ClinicalTrial.gov).
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Lines 154-155
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Lines 124-125, 230-234
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Lines 345-349
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Lines 256-257, 233-234
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	None. The authors plan to publish the results of this trial in scientific journal.
	31b	Authorship eligibility guidelines and any intended use of professional writers	None
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	None

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	None
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.