

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

Circular polyethylene drape in prevention of surgical site infection (COVER Trial): Study protocol of a randomized controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-034687
Article Type:	Protocol
Date Submitted by the Author:	01-Oct-2019
Complete List of Authors:	Yoo, Ri Na; Catholic University of Korea Saint Vincent's Hospital, Surgery Kim, Hyung Jin; Catholic University of Korea Saint Vincent's Hospital, Surgery Lee, Jae Im; Catholic University of Korea Uijeongbu St. Mary's Hospital, Surgery Kang, Won-Kyung; Catholic University of Korea Yeouido Saint Mary's Hospital, Surgery Kye, Bong-Hyeon; Catholic University of Korea Seoul St. Mary's Hospital, Surgery Kim, Chang Woo; Kyung Hee University Hospital at Gangdong, Surgery Bae, Sung Uk; Keimyung University Dongsan Medical Center, Surgery Nam, Soomin; National Health Insurance Corporation Ilsan Hospital, Surgery Kang, Byung Mo; Chuncheon Sacred Heart Hospital, Surgery
Keywords:	GASTROENTEROLOGY, Infection control < INFECTIOUS DISEASES, SURGERY, WOUND MANAGEMENT

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4 1 Circular pOlyethylene drape in preVEntion of suRgical site infection (COVER Trial): Study
5
6 2 protocol of a randomized controlled trial
7
8
9
10 3

11
12
13 4 Ri Na Yoo¹, Hyung Jin Kim¹, Jae Im Lee², Won-Kyung Kang³, Bong-Hyeon Kye^{1,4}, Chang Woo Kim⁵,
14
15 5 Sung Uk Bae⁶, Soomin Nam⁷ and Byung Mo Kang⁸
16
17
18 6

- 19
20
21 7 1. Department of Surgery, St. Vincent's Hospital, The Catholic University of Korea, Suwon,
22
23 8 Korea
24
25
26 9 2. Department of Surgery, Uijeongbu St. Mary's Hospital. The Catholic University of Korea,
27
28 10 Uijeongbu, Korea
29
30
31 11 3. Department of Surgery, Yeouido St. Mary's Hospital, The Catholic University of Korea, Seoul,
32
33 12 Korea
34
35
36 13 4. Department of Surgery, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul,
37
38 14 Korea
39
40
41 15 5. Department of Surgery, Kyung Hee University Hospital at Gangdong, Kyung Hee University
42
43 16 School of Medicine, Seoul, Korea
44
45
46 17 6. Department of Surgery, School of Medicine, Keimyung University and Dongsan Medical
47
48 18 Center, Daegu, Korea
49
50
51 19 7. Department of Surgery, National Health Insurance Service Ilsan Hospital, Goyang, Korea
52
53
54 20 8. Department of Surgery, Chuncheon Sacred Heart Hospital, Hallym University College of
55
56 21 Medicine, Chuncheon, Korea
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45

Correspondence to: Byung Mo Kang, Department of Surgery, Chuncheon Sacred Heart Hospital,
Hallym University College of Medicine, 77, Sakju-ro, Chuncheon 24253, Korea.

Telephone: +821085866963

E-mail address: kbm0728@yahoo.co.kr



Word Count: 3,112 words

1
2
3
4 **Abstract**
5
6

7 **Introduction:** Surgical site infection (SSI) after abdominal surgery is still a significant morbidity
8 associated with an increased socioeconomic burden and poor quality of life. SSI prevalence rates as
9 high as 40% in cases of fecal contamination have been reported; however, current methods to reduce
10 SSI are limited to elective abdominal surgery. Further evaluation of preventive measures for reducing
11 SSI is necessary.
12
13
14
15
16
17
18
19
20

21 **Methods and analysis:** The COVER trial investigates whether the application of a dual-ring circular
22 plastic wound protector reduces the rate of SSI in patients undergoing open abdominal surgery related
23 to the gastrointestinal tract, regardless of the type of wound classified by the Center for Disease Control.
24 The COVER trial is a multicenter, randomized controlled clinical trial with two parallel arms – one
25 using a wound protector and the other using conventional surgical dressing gauze. The primary outcome
26 will measure the rate of SSI within 30 days after surgery in two groups. Statistical analysis of the
27 primary end point will be based on the intention-to-treat population. The sample size is determined to
28 achieve a study power of 80% at 95% 2-sided confidence limits. Considering a dropout rate of up to
29 5%, a total of 458 patients, 229 patients in each group, will be enrolled in this study.
30
31
32
33
34
35
36
37
38
39
40
41
42
43

44 **Ethics and dissemination:** The trial protocol and informed consent document have been reviewed and
45 approved by the institutional review board at each participating center. Written informed consent was
46 obtained from each study participants. The clinical outcomes of this trial will be submitted in an
47 international peer-reviewed journal and presented at international conferences.
48
49
50
51
52
53
54
55

56 **Trial registration:** The trial protocol was registered at ClinicalTrials.gov (NCT 03170843).
57
58
59
60

69

Strengths and limitations of this study:

71

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.

80

81

82

83

84

85

86

87

88

89 INTRODUCTION

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

98
99 The risk of developing SSI will absolutely increase when the surgical incision site is exposed
100 to loads of virulent bacteria in the contaminated surgical field. This risk leads to the idea of developing
101 a physical barrier for the wound edge that can hinder direct exposure of the surgical incision edges to
102 the contaminated field. Several devices purposed for wound edge protection and with the similar design
103 of a flexible plastic wound cover placed into the laparotomy site are currently on the market. Prospective
104 studies and randomized clinical trials (RCTs) have been conducted to evaluate the effectiveness of the
105 plastic wound protector to reduce the incidence of SSI.

106 107 **Previous trials**

108 The largest RCT evaluating the effectiveness of wound protectors in reducing SSI is the
109 ROSSINI trial, with 760 patients undergoing laparotomy at 21 different hospitals in the UK ⁸. In this
110 study, the drape design of the wound protector was compared to standard intraoperative care. The result
111 showed that the use of a wound edge protector during open abdominal surgery did not reduce the rate

1
2
3
4 112 of SSI. Similarly, RCTs using a drape type of wound protector applied in colorectal surgery reported
5
6 113 no benefit of the wound protector in reducing SSI ^{9 10}. However, several other studies have claimed
7
8 114 contrasting results. The BaFO trial, with 608 patients undergoing laparotomy at 16 different medical
9
10 115 centers in Germany, demonstrated that the patients who used wound protection drape devices
11
12 116 experienced SSI at a lower rate than those who did not ¹¹. A Japanese single-centered RCT with 221
13
14 117 patients enrolled for investigating the effect of a double-ring, circular wound protector applied in
15
16 118 nontraumatic gastrointestinal surgery also showed that the rate of SSI was significantly lower in the
17
18 119 experimental group than in the control group ¹².

20
21
22 120

23
24
25 121 The effect of the wound protector in abdominal surgery is still controversial and remains to be
26
27 122 elucidated. A well-designed, multicentered, RCT evaluating the effect of the dual-ring type of wound
28
29 123 protector used in open laparotomy, particularly for contaminated or dirty infected wounds, has not yet
30
31 124 been conducted.

32
33
34 125

35 36 37 126 **METHODS AND ANALYSIS**

38 39 40 127 **Objective**

41
42
43 128 The COVER trial aims to investigate the effect of a dual-ring, plastic wound protector in open
44
45 129 gastrointestinal surgery. It is designed to test whether the device helps to reduce the overall rate of SSI
46
47 130 development within 30 days postoperatively by 40% compared with the control group. In particular,
48
49 131 the COVER trial includes patients who are undergoing an emergency laparotomy for contaminated or
50
51 132 dirty/infected wounds, as well as those undergoing a laparotomy for clean or clean-contaminated
52
53 133 wounds, which allows a thorough investigation of the wound protector's effects, depending on the
54
55 134 degree of contamination.

1
2
3
4 1355
6
7 136 **Trial sites**

8
9
10 137 Initially, eight sites of secondary or tertiary hospitals in South Korea have begun this trial. All
11
12 138 participating investigators have been educated on the basis of the International Conference on
13
14 139 Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use,
15
16 140 which serves as the good clinical practice (GCP) guidelines for this trial. This trial is still open for
17
18 141 recruitment at participating centers.
19

20
21 14222
23
24 143 **Trial population and eligibility**

25
26
27 144 All gastrointestinal surgical patients undergoing open abdominal surgery, either elective or
28
29 145 emergent, will be screened for eligibility. Patients who satisfy the following criteria will be included:
30
31 146 1) patients must be in between the ages of 18 to 75; 2) open laparotomy; and 3) surgery for stomach,
32
33 147 small intestine, or colon and rectum. Patients with any of the following will be excluded: 1) presence
34
35 148 of concurrent infection in the abdominal wall; 2) open conversion from laparoscopic surgery; 3)
36
37 149 presence of poor nutritional status indicated by a nutrition risk screening (NRS) 2002 score greater than
38
39 150 3; 4) patients undergoing combined hepatobiliopancreatic surgery; 5) pregnant or breast-feeding women;
40
41 151 6) moderate to severe immunosuppression state, defined as previous organ or bone marrow
42
43 152 transplantation, concurrent steroid administration (more than 10 mg prednisolone daily or an equivalent
44
45 153 dose of any other steroid), or concurrent administration of other immunosuppressive or
46
47 154 chemotherapeutic agents within the last 2 weeks prior to trial intervention. Once an investigator explains
48
49 155 the extent and nature of the COVER trial to an eligible patient, informed consent will be obtained.
50
51

52
53 15654
55
56 157 **Trial type**

1
2
3
4 158 This clinical trial is a prospective, multicentered, patient-blinded, randomized controlled trial
5
6 159 with two parallel comparison arms. A total of 458 patients will be enrolled, and 229 patients will be
7
8 160 assigned to each group (Fig. 1).
9

10
11 161

12 13 14 162 **Recruitment and trial timeline**

15
16
17 163 The eight centers of secondary or tertiary hospitals in South Korea have been actively
18
19 164 conducting the trial since June 2017. Since then, 4 other centers have joined the trial recruitment, and
20
21 165 this trial is still open for recruiting participating centers. All investigators, physicians or nurses are
22
23 166 required to complete the ICH-GCP training course. Patients will be recruited for approximately 48
24
25 167 months. The last follow-up will be taken at 30 days after the last recruited patient undergoes the trial
26
27 168 intervention. The SPIRIT figure shows the study schedule of enrollment, interventions and assessments
28
29 169 (Fig. 2). A SPIRIT checklist is available in Additional file 1. An interim analysis is planned when 50%
30
31 170 of the enrollment is reached. Depending on the results of the interim analysis, the subsequent research
32
33 171 process and timeline can be modified.
34
35
36

37 172

38 39 40 173 **Randomization and blinding**

41
42
43 174 Stratification will be performed according to the participating center and the type of wound
44
45 175 classification. The wound types will be divided into two groups: one with clean or clean-contaminated
46
47 176 and the other with contaminated or dirty, infected. A web-based patient registry ([http://cover.e-](http://cover.e-trial.co.kr)
48
49 177 [trial.co.kr](http://cover.e-trial.co.kr)) will be applied to generate the allocation sequence just before the beginning of the operation,
50
51 178 providing adequate concealment for the allocation sequence. The group allocation and randomization
52
53 179 number will be predefined by a biostatistician of the Catholic Medical Center in Seoul, South Korea. A
54
55 180 permuted block randomization with the size of 2 or 4 is applied. Participating surgeons cannot be
56
57
58
59
60

1
2
3
4 181 blinded to allocated treatment. However, the patient will be blinded for the trial intervention since they
5
6 182 are under general anesthesia once the operation starts. The data manager will also be blinded because
7
8 183 there is no direct access to either the trial intervention or the randomization.
9
10

11 184

14 185 **Interventions**

16
17 186 Preoperative bowel preparation, type of skin preparation and drape, the use of perioperative
18
19 187 antibiotics, and the details of the surgical procedure will follow the policy of an individual surgeon in
20
21 188 each center. The experimental arm will be provided with a circular polyethylene drape (O Trac[®], Asung
22
23 189 Medical Inc. South Korea) to cover the incision site in the abdomen. It is a double-ring type of sterile,
24
25 190 cylindrical wound protector consisting of inner and outer rings with a polyethylene sheath. The wound
26
27 191 protector is left in situ throughout the operation and is removed just before closing the abdominal wall.
28
29 192 The method of wound closure and insertion of wound drainage will also follow the policy of an
30
31 193 individual surgeon in each center.
32
33

34
35 194 For the control arm, conventional surgical dressing gauze will be used to protect the incision
36
37 195 site during the surgical procedure. There are no differences in surgical technique, other devices, or the
38
39 196 environment.
40
41

42 197

45 198 **Risks**

46
47
48 199 No additional risks to the participants are expected. The circular polyethylene wound protector
49
50 200 has established clinical safety and has been already in clinical applications with the approval of the
51
52 201 Korean Medical Device Information and Technology Assistance Center, MDITAC. None of the
53
54 202 technical details other than wound protection are affected by the trial.
55
56
57
58
59
60

203

204 Outcomes

205 The primary end point is the rate of SSI, defined by the diagnostic criteria suggested by the
206 Center for Disease Control (CDC) within 30 days after surgery. According to the CDC definition, SSIs
207 are classified as being either superficial incisional, deep incisional or organ/space¹³. The postoperative
208 wound condition will be evaluated at postoperative weeks 1, 2, and 4-5. The secondary end points
209 include the length of postoperative hospital stay, the re-admission rate, and the rate of surgical
210 complication other than SSI. The incidence of 30-day postoperative complications will be stratified
211 according to the modified Clavien-Dindo Classification¹⁴.

212

213 Data management and monitoring

214 A newly developed, web-based, electronic case reporting form (eCRF) will be used to record
215 data for the included patients. Baseline characteristics, including age, sex, body mass index, American
216 Society of Anesthesiologists score, history of smoking and alcohol consumption, history of previous
217 chemotherapy, radiotherapy, abdominal surgery, steroid or immunosuppressive drug use, history of
218 diabetes or malignancies in the gastrointestinal tract and nutritional status based on the NRS 2002 score
219 will be collected. Laboratory parameters (white blood cell count and c-reactive protein and albumin
220 levels) will be collected preoperatively, on the operation day and on postoperative day 2, if available.
221 The parameters for surgical procedure, including operation type (emergent or elective), site of operation
222 (stomach, small intestine or large intestine), level of wound contamination according to CDC
223 classification, method of skin preparation, antibiotics use, operation time, bowel anastomosis and stoma
224 formation, wound closure material, length of skin incision, draining tube for the wound and body
225 temperature during the operative procedure, will be collected. The surgical wounds are classified into
226 clean, clean-contaminated, contaminated and dirty wounds, according to the magnitude of the bacterial

1
2
3
4 227 load ¹⁵. Postoperatively, the surgical wound will be evaluated at postoperative weeks 1, 2, and 4-5. If
5
6 228 SSI is detected, the classification and the postoperative date of diagnosis will be recorded. Bacterial
7
8 229 culture of the infected wound will be performed. Postoperative complications according to the modified
9
10 230 Clavien-Dindo classification, postoperative length of hospital stay and re-admission will be noted. An
11
12 231 investigator or research coordinator at each center will enter the data using the eCRF. At the end of the
13
14
15 232 trial, the study data and personal information of the enrolled patients will be archived for 3 years.

16
17
18 233 The trial data will be monitored by an independent institution (Medical Excellence, Inc.) in
19
20 234 Seoul, Korea. Monitoring will be performed in accordance with ICH-GCP guidelines ¹⁶.

21
22
23 235

24 25 26 236 **Safety evaluation and reporting of adverse events**

27
28
29 237 All adverse events or serious adverse events, occurring from the moment of randomization
30
31 238 until the end of the 30-day follow-up, will be recorded and reported by the investigators.

32
33
34 239

35 36 37 240 **Statistical methods**

38 39 40 241 Sample size calculation

41
42 242 The sample size was calculated based on the primary end point of this trial. Previous reports
43
44 243 on the incidence of SSI have indicated that the rate of SSI may vary depending on the wound
45
46 244 classification, the procedure, the surveillance criteria, and the quality of data collection ¹⁷. The incidence
47
48 245 of SSI for clean/clean-contaminated wounds has been reported to be as high as 10% ¹⁸. For contaminated
49
50 246 wounds, the incidence was approximately 25% ^{7 17}. For dirty, infected wounds, the incidence may reach
51
52 247 up to 40% ⁵⁻⁷. In this trial, the ratio of operations with clean/clean-contaminated, contaminated, and
53
54
55 248 dirty, infected wound is assumed to be 20:40:40; therefore, the expected incidence of SSI for the control

1
2
3
4 249 group is 28%. For the experimental group, the incidence of SSI will be decreased by 40%. Thus, the
5
6 250 rate of SSI in the experimental group will be approximately 17%. The sample size is determined to
7
8 251 achieve a study power of 80%, with 95% 2-sided confidence limits. The actual sample size amounts to
9
10 252 434 participants. However, considering a drop-out (lost to follow-up, retracted consent or protocol
11
12 253 violation) rate of up to 5%, a total of 458 patients, 229 patients in each group, will be enrolled in this
13
14
15 254 study.

17 255 Statistical analysis

20 256 The statistical analysis will be performed by an independent statistician from the Catholic
21
22
23 257 Medical Center (Seoul, South Korea). The interim and final results will be analyzed mainly for the
24
25 258 intention-to-treat population and, additionally, for the per-protocol population. The rate of 30-day
26
27 259 postoperative SSI will be evaluated in total patients and also analyzed according to the wound
28
29 260 classification (superficial incisional, deep incisional and organ/space SSIs), as defined by the CDC.
30
31 261 Pearson's chi-squared test or Fisher's exact test will be used to analyze nominal data; Student's *t*-test
32
33 262 and the Wilcoxon rank-sum test will be used for continuous data. To estimate the independent risk
34
35 263 factors for 30-day postoperative SSI, logistic regression analysis will be performed. The statistical
36
37 264 analysis will be conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

39
40 265

43 266 **Withdrawals**

45
46 267 Enrolled patients can withdraw their participation at any time, if desired. In this case, the
47
48
49 268 patients will have no disadvantages. The investigator will record any patient's withdrawal in
50
51 269 the eCRF.

52
53
54 270

57 271 **Patient and public involvement**

1
2
3
4 272 Patients and the public were not involved in the protocol of this study.
5
6
7 273
8
9

10 274 **ETHICS AND DISSEMINATION**

13 275 **Research ethics**

16 276 The trial protocol, informed consent document and any other documents necessary to
17
18 277 legitimately start a clinical trial were reviewed and approved by the institutional review board at each
19
20 278 participating center. Written informed consent was obtained from each study participants in accordance
21
22 279 with ethics approval.
23
24

25 280

28 281 **Study registration**

31 282 The trial protocol was registered at ClinicalTrials.gov (NCT 03170843) on May 31, 2017.
32
33

34 283
35
36

37 284 **Dissemination**

40 285 The final results will be discussed with participating surgeons and presented at domestic and
41
42 286 international scientific conferences. The final results will be submitted in an international peer-reviewed
43
44 287 scientific journal.
45
46

47 288
48
49

50 289 **DISCUSSION**

53 290 SSI has been recognized as a costly, debilitating surgical complication over decades worldwide.
54
55 291 Despite vigorous efforts to control SSI through campaigns and publications by international
56
57

1
2
3
4 292 organizations, the rate of SSI has changed only slightly ^{2 19-22}. Even such recommendations are limited
5
6 293 to the use of prophylactic antibiotics or antiseptic skin cleansing, which can only be applied during
7
8 294 elective surgeries. In cases of abdominal surgery, diffuse purulent peritonitis with or without fecal
9
10 295 contamination, which requires emergency surgery, is frequently encountered. Prophylactic antibiotics or
11
12 296 antiseptic skin cleansing is not applicable in emergent surgical cases. Several preventive measures other
13
14
15 297 than the use of prophylactic antibiotics or antiseptic skin cleansing have been proposed to prevent SSI.
16
17 298 Intraoperative wound irrigation with antibiotic solution is one method that can be implemented.
18
19 299 Intraoperative wound irrigation with antibiotic solution seems to reduce the incidence of SSI; however,
20
21 300 the problem lies with potential adverse effects of tissue toxicity and increased bacterial resistance ²³.
22
23 301 Another method is the application of negative-pressure wound therapy (NPWT) without primary
24
25 302 closure of the abdominal wound in highly contaminated abdominal surgery ²⁴. A recent meta-analysis
26
27 303 on the use of NPWT in open and infected wounds after vascular surgery demonstrated that it could be
28
29 304 effective in controlling SSI ²⁵. However, there are only a few case reports of its use in contaminated
30
31 305 abdominal surgery, and no trial or analysis of its efficacy is available. The first two methods require the
32
33 306 application of a bactericidal substance directly to the tissue that may or may not present a bacterial
34
35 307 infection. Thus, the adverse effects of tissue toxicity and bacterial resistance cannot be ignored. The use
36
37 308 of NPWT also requires additional resources and time to heal, which potentially involves a longer
38
39 309 hospital stay and additional medical cost. Therefore, adopting these methods is not easy in daily practice.

40
41
42
43 310 The application of a plastic wound protector in abdominal surgery has been tested for its
44
45 311 efficacy for more than a decade. Based on the findings for pathogens most frequently isolated for SSI,
46
47 312 including *Staphylococcus aureus*, coagulase-negative *staphylococci*, *Enterococcus* species, and
48
49 313 *Escherichia coli* ¹⁷, plastic wound protectors that hinder direct exposure of the surgical wound to
50
51 314 virulent endogenous bacteria during surgical procedures have been created. Several previous studies
52
53 315 and trials have been conducted to investigate such a hypothesis ²⁶. These trials have varied by using
54
55 316 different designs of wound protectors: namely, single-ring or dual-ring types. The COVER trial will

1
2
3
4 317 test a dual-ring type of wound protector that can tightly conceal the surgical incision edge during the
5
6 318 entire operation time. Previously, the trials on the dual-ring design were conducted in a single center
7
8 319 with a small sample size. In addition, these trials excluded emergent surgeries with contaminated and
9
10 320 dirty, infected wounds resulting from perforated viscera^{12 27 28}. Therefore, the effectiveness of the dual-
11
12 321 ring type of wound protector in controlling SSI contaminated and dirty, infected wounds can be
13
14
15 322 addressed.

16
17
18 323 The COVER trial is pragmatic, two-armed RCT that will be conducted by at least 11 surgeons
19
20 324 at 11 different centers and possibly more, which will increase external validity. Internal validation and
21
22 325 data quality will be assured by adherence to the SPIRIT statement²⁹. Assessments of the wound
23
24 326 condition will not only be done by the observer but will also be reviewed by other investigators via
25
26 327 photographs documented in the eCRF. This will provide an objective and reliable method for the
27
28 328 evaluation of wound infections. Finally, the risk that patients may experience from participating in this
29
30 329 trial is minimal and will remain within the boundaries of routine clinical practice.

31
32
33 330 The results of the COVER trial will provide high-quality evidence for using a circular
34
35 331 polyethylene drape in open abdominal surgery with all types of wound to reduce the incidence of SSI.

36
37
38 332

39 40 41 333 **Trial status**

42
43
44 334 Recruitment of participants began at July 11, 2017. A total of 211 patients had been recruited to
45
46 335 this trial as of September 21, 2019. The trial is currently ongoing. (Current study protocol version 7.0.,
47
48 336 revised at October 23, 2018)

49
50
51 337

52 53 54 338 **Contributors**

1
2
3
4 339 HJK and RNY designed the COVER trial and were responsible for the protocol development.

5
6
7 340 JIL, WKK, BHK, CWK, SUB, SMN and BMK revised the draft of the protocol and approved
8
9 341 the final version of protocol.

10
11
12 342 RNY and BMK wrote the manuscript.

13
14
15 343 BMK and HJK critically revised the manuscript.

16
17
18 344 All of the authors conducted the COVER trial and approved the final version of manuscript.

19
20
21 345

22
23
24 346 **Funding**

25
26
27 347 This trial is supported by the Korean Surgical Infection Society (Award number: KSIS 2019-
28
29 348 021), with the use of the circular polyethylene wound protector (O Trac®, Asung Medical Inc. South
30
31 349 Korea) given free of charge. There is no other financial support and conflict of interest. The industrial
32
33 350 funder and trial management are independent.

34
35
36 351

37
38
39 352 **Competing interests**

40
41
42 353 The authors declare that they have no competing interests.

43
44
45 354

46
47
48 355 **Patient consent for publication**

49
50
51 356 Not required

52
53
54 357

55
56
57 358 **REFERENCES**

- 1
2
3
4 359 1. De Pastena M, Paiella S, Marchegiani G, *et al*. Postoperative infections represent a major
5
6 360 determinant of outcome after pancreaticoduodenectomy: Results from a high-volume center.
7
8 361 *Surgery* 2017;162:792-801.
- 10 362 2. Badia JM, Casey AL, Petrosillo N, *et al*. Impact of surgical site infection on healthcare costs
11
12 363 and patient outcomes: a systematic review in six European countries. *J Hosp Infect* 2017;96:1-
13
14 364 15.
- 16 365 3. Mujagic E, Marti WR, Coslovsky M, *et al*. Associations of Hospital Length of Stay with
17
18 366 Surgical Site Infections. *World J Surg* 2018; doi:10.1007/s00268-018-4733-4.
- 20 367 4. Culver DH, Horan TC, Gaynes RP, *et al*. Surgical wound infection rates by wound class,
21
22 368 operative procedure, and patient risk index. National Nosocomial Infections Surveillance
23
24 369 System. *Am J Med* 1991;91:152s-7s.
- 26 370 5. Smith RL, Bohl JK, McElearney ST, *et al*. Wound infection after elective colorectal resection.
27
28 371 *Ann Surg* 2004;239:599-605; discussion -7.
- 30 372 6. Hernandez K, Ramos E, Seas C, *et al*. Incidence of and risk factors for surgical-site infections
31
32 373 in a Peruvian hospital. *Infect Control Hosp Epidemiol* 2005;26:473-7.
- 34 374 7. Ruiz-Tovar J, Alonso N, Morales V, *et al*. Association between Triclosan-Coated Sutures for
35
36 375 Abdominal Wall Closure and Incisional Surgical Site Infection after Open Surgery in Patients
37
38 376 Presenting with Fecal Peritonitis: A Randomized Clinical Trial. *Surg Infect (Larchmt)*
39
40 377 2015;16:588-94.
- 42 378 8. Pinkney TD, Calvert M, Bartlett DC, *et al*. Impact of wound edge protection devices on surgical
43
44 379 site infection after laparotomy: multicentre randomised controlled trial (ROSSINI Trial). *Bmj*
45
46 380 2013;347:f4305.
- 48 381 9. Psaila JV, Wheeler MH, Crosby DL. The role of plastic wound drapes in the prevention of
49
50 382 wound infection following abdominal surgery. *Br J Surg* 1977;64:729-32.
- 52 383 10. Nystrom PO, Broome A, Hojer H, *et al*. A controlled trial of a plastic wound ring drape to
53
54 384 prevent contamination and infection in colorectal surgery. *Dis Colon Rectum* 1984;27:451-3.

- 1
2
3
4 385 11. Mihaljevic AL, Schirren R, Ozer M, *et al.* Multicenter double-blinded randomized controlled
5
6 386 trial of standard abdominal wound edge protection with surgical dressings versus coverage with
7
8 387 a sterile circular polyethylene drape for prevention of surgical site infections: a CHIR-Net trial
9
10 388 (BaFO; NCT01181206). *Ann Surg* 2014;260:730-7; discussion 7-9.
- 11
12 389 12. Horiuchi T, Tanishima H, Tamagawa K, *et al.* Randomized, controlled investigation of the anti-
13
14 390 infective properties of the Alexis retractor/protector of incision sites. *J Trauma* 2007;62:212-5.
- 15 391 13. Horan TC, Gaynes RP, Martone WJ, *et al.* CDC definitions of nosocomial surgical site
16
17 392 infections, 1992: a modification of CDC definitions of surgical wound infections. *Am J Infect*
18
19 393 *Control.* 1992;20:271-4.
- 20
21 394 14. Clavien PA, Barkun J, de Oliveira ML, *et al.* The Clavien-Dindo classification of surgical
22
23 395 complications: five-year experience. *Ann Surg* 2009;250:187-96.
- 24
25 396 15. Barie PS. Surgical site infections: epidemiology and prevention. *Surg Infect (Larchmt)* 2002;3
26
27 397 Suppl 1:S9-21.
- 28
29 398 16. International Conference on Harmonisation of Technical Requirements for Registration of
30
31 399 Pharmaceuticals for Human Use (ICH) adopts Consolidated Guideline on Good Clinical
32
33 400 Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use. *Int Dig Health*
34
35 401 *Legis* 1997;48:231-4.
- 36
37 402 17. Owens CD, Stoessel K. Surgical site infections: epidemiology, microbiology and prevention. *J*
38
39 403 *Hosp Infect* 2008;70 Suppl 2:3-10.
- 40
41 404 18. Leaper DJ, van Goor H, Reilly J, *et al.* Surgical site infection - a European perspective of
42
43 405 incidence and economic burden. *Int Wound J* 2004;1:247-73.
- 44
45 406 19. Mangram AJ. A brief overview of the 1999 CDC Guideline for the Prevention of Surgical Site
46
47 407 Infection. Centers for Disease Control and Prevention. *J Chemother* 2001;13 Spec No 1:35-9.
- 48
49 408 20. Alexander JW, Solomkin JS, Edwards MJ. Updated recommendations for control of surgical
50
51 409 site infections. *Ann Surg* 2011;253:1082-93.
- 52
53 410 21. Berrios-Torres SI. Evidence-Based Update to the U.S. Centers for Disease Control and
54
55
56
57
58
59
60

- 1
2
3
4 411 Prevention and Healthcare Infection Control Practices Advisory Committee Guideline for the
5
6 412 Prevention of Surgical Site Infection: Developmental Process. *Surg Infect (Larchmt)*
7
8 413 2016;17:256-61.
9
10 414 22. Gulland A. WHO launches global guidelines to stop surgical site infections. *Bmj*
11
12 415 2016;355:i5942.
13
14 416 23. Mueller TC, Loos M, Haller B, *et al.* Intra-operative wound irrigation to reduce surgical site
15
16 417 infections after abdominal surgery: a systematic review and meta-analysis. *Langenbecks Arch*
17
18 418 *Surg* 2015;400:167-81.
19
20 419 24. Yoshioka T, Kondo Y, Fujiwara T. Successful wound treatment using negative pressure wound
21
22 420 therapy without primary closure in a patient undergoing highly contaminated abdominal
23
24 421 surgery. *Surg Case Rep* 2018;4:85.
25
26 422 25. Acosta S, Bjorck M, Wanhainen A. Negative-pressure wound therapy for prevention and
27
28 423 treatment of surgical-site infections after vascular surgery. *Br J Surg* 2017;104:e75-e84.
29
30 424 26. Kang SI, Oh HK, Kim MH, *et al.* Systematic review and meta-analysis of randomized
31
32 425 controlled trials of the clinical effectiveness of impervious plastic wound protectors in reducing
33
34 426 surgical site infections in patients undergoing abdominal surgery. *Surgery* 2018;
35
36 427 doi:10.1016/j.surg.2018.05.024.
37
38 428 27. Reid K, Pockney P, Draganic B, *et al.* Barrier wound protection decreases surgical site infection
39
40 429 in open elective colorectal surgery: a randomized clinical trial. *Dis Colon Rectum*
41
42 430 2010;53:1374-80.
43
44 431 28. Cheng KP, Roslani AC, Sehha N, *et al.* ALEXIS O-Ring wound retractor vs conventional
45
46 432 wound protection for the prevention of surgical site infections in colorectal resections(1).
47
48 433 *Colorectal Dis* 2012;14:e346-51.
49
50 434 29. Chan AW, Tetzlaff JM, Gotzsche PC, *et al.* SPIRIT 2013 explanation and elaboration: guidance
51
52 435 for protocols of clinical trials. *Bmj* 2013;346:e7586.
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

436

437

438 **FIGURE LEGENDS**

439

440 Figure 1. Trial flow

441

442 Figure 2. SPIRIT figure

443 PO = postoperative; SSI = Surgical site infection

For peer review only

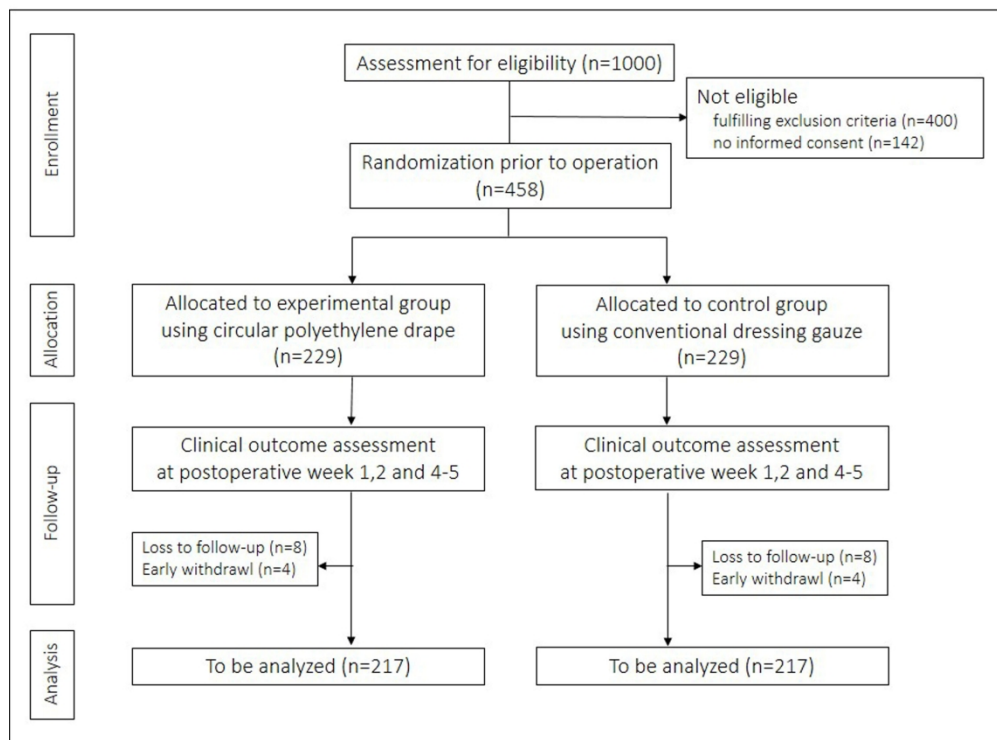


Figure 1. Trial flow

254x190mm (300 x 300 DPI)

TIMEPOINT	STUDY PERIOD						
	Enrolment	Allocation	Post-allocation				Close-out
	-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)



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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	<u>Lines 1–2</u>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	<u>Lines 68, 281-282</u>
	2b	All items from the World Health Organization Trial Registration Data Set	<u>Throughout</u>
Protocol version	3	Date and version identifier	<u>Lines 332-335</u>
Funding	4	Sources and types of financial, material, and other support	<u>Lines 345-349</u>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	<u>Lines 4-21, 337-343</u>
	5b	Name and contact information for the trial sponsor	<u>Lines 345-349</u>
	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	<u>Lines 345-349</u>
	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)	<u>Lines 233-234, 256-257</u>

1	Introduction			
2				
3	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	<u>Lines 90-119</u>
4				
5				
6		6b	Explanation for choice of comparators	<u>Lines 99-105</u>
7				
8	Objectives	7	Specific objectives or hypotheses	<u>Lines 127-134</u>
9				
10	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)	<u>Lines 157-160, Fig 1</u>
11				
12				
13				
14	Methods: Participants, interventions, and outcomes			
15				
16	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	<u>Lines 136-141, 163-164</u>
17				
18				
19	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)	<u>Lines 143-155</u>
20				
21				
22				
23	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	<u>Lines 185-196</u>
24				
25				
26		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)	<u>Lines 266-269</u>
27				
28				
29		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	<u>Lines 214-215, 233-234</u>
30				
31				
32		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	<u>Not applicable</u>
33				
34	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	<u>Lines 204-211</u>
35				
36				
37				
38				
39				
40	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)	<u>Lines 162-171, Fig. 2.</u>
41				
42				
43				
44				
45				
46				

1	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	<u>Lines 241-254</u>
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	<u>Lines 140-141</u>
5				
6	Methods: Assignment of interventions (for controlled trials)			
7	Allocation:			
8				
9				
10	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	<u>Lines 173-183</u>
11				
12				
13				
14				
15				
16	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	<u>Lines 176-178</u>
17				
18				
19				
20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	<u>Lines 176-179</u>
21				
22				
23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	<u>Lines 179-183</u>
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	<u>Not applicable</u>
28				
29				
30				
31	Methods: Data collection, management, and analysis			
32				
33	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	<u>Lines 213-234</u>
34				
35				
36				
37				
38				
39		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	<u>Lines 227-231</u>
40				
41				
42				
43				
44				
45				
46				

1	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	<u>Lines 230-234</u>
2				
3				
4				
5	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	<u>Lines 255-264</u>
6				
7				
8				
9				
10		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	<u>Lines 257-258</u>
11				
12		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)	<u>Lines 257-264</u>
13				
14				
15				
16	Methods: Monitoring			
17				
18	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	<u>Lines 233-234</u>
19				
20				
21				
22				
23				
24		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	<u>Lines 169-171</u>
25				
26				
27	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	<u>Lines 236-238</u>
28				
29				
30	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.
31				
32				
33				
34				
35				
36	Ethics and dissemination			
37				
38	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	<u>Lines 275-279</u>
39				
40				
41				
42				
43				
44				
45				
46				

1	Protocol	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).
2	amendments			
3				
4				
5				
6				
7				
8				
9				
10	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	<u>Lines 154-155</u>
11				
12				
13		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	<u>Not applicable</u>
14				
15				
16	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	<u>Lines 124-125, 230-234</u>
17				
18				
19	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	<u>Lines 345-349</u>
20				
21				
22				
23	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	<u>Lines 256-257, 233-234</u>
24				
25				
26	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	<u>Not applicable</u>
27				
28				
29	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	<u>None. The authors plan to publish the results of this trial in scientific journal.</u>
30				
31				
32				
33				
34				
35		31b	Authorship eligibility guidelines and any intended use of professional writers	<u>None</u>
36				
37		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	<u>None</u>
38				
39				

Appendices

1	Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogates	<u>None</u>
4	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	<u>Not applicable</u>

*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

For peer review only

BMJ Open

Circular polyethylene drape in prevention of surgical site infection (COVER Trial): Study protocol of a randomized controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-034687.R1
Article Type:	Protocol
Date Submitted by the Author:	18-Nov-2019
Complete List of Authors:	Yoo, Ri Na; Catholic University of Korea Saint Vincent's Hospital, Surgery Kim, Hyung Jin; Catholic University of Korea Saint Vincent's Hospital, Surgery Lee, Jae Im; Catholic University of Korea Uijeongbu St. Mary's Hospital, Surgery Kang, Won-Kyung; Catholic University of Korea Yeouido Saint Mary's Hospital, Surgery Kye, Bong-Hyeon; Catholic University of Korea Seoul St. Mary's Hospital, Surgery Kim, Chang Woo; Kyung Hee University Hospital at Gangdong, Surgery Bae, Sung Uk; Keimyung University Dongsan Medical Center, Surgery Nam, Soomin; National Health Insurance Corporation Ilsan Hospital, Surgery Kang, Byung Mo; Chuncheon Sacred Heart Hospital, Surgery
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Gastroenterology and hepatology
Keywords:	GASTROENTEROLOGY, Infection control < INFECTIOUS DISEASES, SURGERY, WOUND MANAGEMENT

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4 1 Circular pOlyethylene drape in preVEntion of suRgical site infection (COVER Trial): Study
5
6 2 protocol of a randomized controlled trial
7
8
9
10 3

11
12
13 4 Ri Na Yoo¹, Hyung Jin Kim¹, Jae Im Lee², Won-Kyung Kang³, Bong-Hyeon Kye^{1,4}, Chang Woo
14
15 5 Kim⁵, Sung Uk Bae⁶, Soomin Nam⁷ and Byung Mo Kang⁸
16
17
18 6

- 19
20
21 7 1. Department of Surgery, St. Vincent's Hospital, The Catholic University of Korea, Suwon,
22
23 8 Korea
24
25
26 9 2. Department of Surgery, Uijeongbu St. Mary's Hospital. The Catholic University of Korea,
27
28 10 Uijeongbu, Korea
29
30
31 11 3. Department of Surgery, Yeouido St. Mary's Hospital, The Catholic University of Korea,
32
33 12 Seoul, Korea
34
35
36 13 4. Department of Surgery, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul,
37
38 14 Korea
39
40
41 15 5. Department of Surgery, Kyung Hee University Hospital at Gangdong, Kyung Hee University
42
43 16 School of Medicine, Seoul, Korea
44
45
46 17 6. Department of Surgery, School of Medicine, Keimyung University and Dongsan Medical
47
48 18 Center, Daegu, Korea
49
50
51 19 7. Department of Surgery, National Health Insurance Service Ilsan Hospital, Goyang, Korea
52
53
54 20 8. Department of Surgery, Chuncheon Sacred Heart Hospital, Hallym University College of
55
56 21 Medicine, Chuncheon, Korea
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45

Correspondence to: Byung Mo Kang, Department of Surgery, Chuncheon Sacred Heart Hospital,
Hallym University College of Medicine, 77, Sakju-ro, Chuncheon 24253, Korea.

Telephone: +821085866963

E-mail address: kbm0728@yahoo.co.kr



Word Count: 3,150 words

1
2
3
4 **Abstract**
5
6

7 **Introduction:** Surgical site infection (SSI) after abdominal surgery is still a significant morbidity
8 associated with an increased socioeconomic burden and reduced quality of life. Circular wound
9 protector has been expected to reduce the risk of SSI, but previous studies reported conflicting results
10 on its protective effects. The purpose of this study is to evaluate the efficacy of circular wound
11 protector in reducing SSI in open abdominal surgery.
12
13
14
15
16
17
18
19
20

21 **Methods and analysis:** The COVER trial investigates whether the application of a dual-ring circular
22 plastic wound protector reduces the rate of SSI in patients undergoing elective or emergent open
23 abdominal surgery related to the gastrointestinal tract, regardless of the type of wound classified by
24 the Center for Disease Control. The COVER trial is a multicenter, randomized controlled clinical trial
25 with two parallel arms – one using a dual-ring wound protector with circular polyethylene drape and
26 the other using conventional surgical dressing gauze. The primary outcome will measure the rate of
27 SSI within 30 days after surgery in two groups. Statistical analysis of the primary end point will be
28 based on the intention-to-treat population. The sample size is determined to achieve a study power of
29 80% at 95% 2-sided confidence limits. Considering a dropout rate of up to 5%, a total of 458 patients,
30 229 patients in each group, will be enrolled in this study.
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45

46 **Ethics and dissemination:** The trial protocol and informed consent document have been reviewed
47 and approved by the institutional review board at each participating center. Written informed consent
48 was obtained from each study participants. The clinical outcomes of this trial will be submitted in an
49 international peer-reviewed journal and presented at international conferences.
50
51
52
53
54
55
56
57
58
59
60

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

70

71 **Strengths and limitations of this study:**

72

73 1. This multicenter, randomized study include elective and emergent surgery for stomach, small
74 and large intestine to ensure generalizability.

75 2. The primary endpoint, 30-day postoperative surgical site infection rate, will be assessed for
76 open abdominal surgery not only with clean/clean-contaminated wounds but also with
77 contaminated/dirty wounds.

78 3. COVER Trial is a study with the largest number of patients among the studies for a dual-ring,
79 plastic wound protector.

80 4. Wound condition will be assessed not only by the observer but also by other investigators
81 using wound photography in the eCRF to provide the reliability of diagnosis for SSIs.

82 5. Limitations of this study are the lack of blinding of surgeons and including only the Korean
83 population who have relatively low body mass index.

84

85

86

87

88

89 INTRODUCTION

90 Surgical site infection (SSI) is a common postoperative complication that is associated not
91 only with considerable morbidity and mortality but also significant socioeconomic burden ¹⁻³. The rate
92 of SSI is estimated to range from approximately 10% to 30% in elective abdominal surgery,
93 depending on the presence of risk factors, type of procedure, and degree of endogenous contaminant ¹
94 ^{4 5}. In cases of fecal peritonitis, the SSI rate may reach up to 35~40% ^{6 7}. Despite organizational,
95 systematic approaches for preventing SSI based on evidence, such as preoperative antibiotic
96 prophylaxis and antiseptic skin cleansing, SSI is still a major problem associated with increased
97 hospital cost, prolonged hospital stay, and unsatisfactory quality of life ⁸.

98
99 The risk of developing SSI will absolutely increase when the surgical incision site is exposed
100 to loads of virulent bacteria in the contaminated surgical field ⁹. This risk leads to the idea of
101 developing a physical barrier for the wound edge that can hinder direct exposure of the surgical
102 incision edges to the contaminated field. Several devices purposed for wound edge protection and
103 with the similar design of a flexible plastic wound cover placed into the laparotomy site are currently
104 on the market. Prospective studies and randomized clinical trials (RCTs) have been conducted to
105 evaluate the effectiveness of the plastic wound protector to reduce the incidence of SSI ^{8 10-13}.

106 107 Previous trials

108 The largest RCT evaluating the effectiveness of wound protectors in reducing SSI is the
109 ROSSINI trial, with 760 patients undergoing laparotomy at 21 different hospitals in the UK ⁸. In this
110 study, the drape design of the wound protector was compared to standard intraoperative care. The
111 result showed that the use of a wound edge protector during open abdominal surgery did not reduce

1
2
3
4 112 the rate of SSI. Similarly, RCTs using a drape type of wound protector applied in colorectal surgery
5
6 113 reported no benefit of the wound protector in reducing SSI^{10 11}. However, several other studies have
7
8 114 claimed contrasting results. The BaFO trial, with 608 patients undergoing laparotomy at 16 different
9
10 115 medical centers in Germany, demonstrated that the patients who used wound protection drape devices
11
12 116 experienced SSI at a lower rate than those who did not¹². A Japanese single-centered RCT with 221
13
14 117 patients enrolled for investigating the effect of a double-ring, circular wound protector applied in
15
16 118 nontraumatic gastrointestinal surgery also showed that the rate of SSI was significantly lower in the
17
18 119 experimental group than in the control group ¹³.
19
20
21
22
23
24

25 121 The effect of the wound protector in abdominal surgery is still controversial and remains to
26
27 122 be elucidated. A well-designed, multicentered, RCT evaluating the effect of the dual-ring type of
28
29 123 wound protector used in open abdominal surgery, particularly for contaminated or dirty infected
30
31 124 wounds, has not yet been conducted.
32
33
34
35
36

37 126 **METHODS AND ANALYSIS**

38 39 40 127 **Objective**

41
42
43 128 The COVER trial aims to investigate the effect of a dual-ring, plastic wound protector in
44
45 129 open abdominal surgery. It is designed to test whether the device helps to reduce the overall rate of
46
47 130 SSI development within 30 days postoperatively by 40% compared with the control group. In
48
49 131 particular, the COVER trial includes patients who are undergoing an open abdominal surgery for
50
51 132 contaminated or dirty/infected wounds, as well as those undergoing an open abdominal surgery for
52
53 133 clean or clean-contaminated wounds, which allows a thorough investigation of the wound protector's
54
55 134 effects, depending on the degree of contamination.
56
57
58
59
60

1
2
3
4 1357 136 **Trial sites**

10 137 Initially, eight sites of secondary or tertiary hospitals in South Korea have begun this trial.
11
12 138 All participating investigators have been educated on the basis of the International Conference on
13
14 139 Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use,
15
16 140 which serves as the good clinical practice (GCP) guidelines for this trial. This trial is still open for
17
18 141 recruitment at participating centers.
19

20
21 14223
24 143 **Trial population and eligibility**

26
27 144 All gastrointestinal surgical patients undergoing open abdominal surgery, either elective or
28
29 145 emergent, will be screened for eligibility. Patients who satisfy the following criteria will be included:
30
31 146 1) patients must be in between the ages of 18 to 75; 2) elective or emergent open abdominal surgery;
32
33 147 and 3) surgery for stomach, small intestine, or colon and rectum. Patients with any of the following
34
35 148 will be excluded: 1) presence of concurrent infection in the abdominal wall; 2) open conversion from
36
37 149 laparoscopic surgery; 3) presence of poor nutritional status indicated by a nutrition risk screening
38
39 150 (NRS) 2002 score greater than 3; 4) patients undergoing combined hepatobiliarypancreatic surgery; 5)
40
41 151 pregnant or breast-feeding women; 6) moderate to severe immunosuppression state, defined as
42
43 152 previous organ or bone marrow transplantation, concurrent steroid administration (more than 10 mg
44
45 153 prednisolone daily or an equivalent dose of any other steroid), or concurrent administration of other
46
47 154 immunosuppressive or chemotherapeutic agents within the last 2 weeks prior to trial intervention.
48
49 155 Once an investigator explains the extent and nature of the COVER trial to an eligible patient,
50
51 156 informed consent will be obtained.
52

53
54
55 157
56
57
58
59
60

158 **Trial type**

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

163 **Recruitment and trial timeline**

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

174 **Randomization and blinding**

175 Stratification will be performed according to the participating center and the type of wound
176 classification. The wound types will be divided into two groups: one with clean or clean-contaminated
177 and the other with contaminated or dirty, infected. A web-based patient registry (<http://cover.e-trial.co.kr>)
178 will be applied to generate the allocation sequence just before the beginning of the
179 operation, providing adequate concealment for the allocation sequence. The group allocation and
180 randomization number will be predefined by a biostatistician of the Catholic Medical Center in Seoul,

1
2
3
4 181 South Korea. A permuted block randomization with the size of 2 or 4 is applied. Participating
5
6 182 surgeons cannot be blinded to allocated treatment. However, the patient will be blinded for the trial
7
8 183 intervention since they are under general anesthesia once the operation starts. The data manager will
9
10 184 also be blinded because there is no direct access to either the trial intervention or the randomization.
11
12

13
14 185

16 186 **Interventions**

17
18
19 187 Preoperative bowel preparation, type of skin preparation and drape, the use of perioperative
20
21 188 antibiotics, and the details of the surgical procedure will follow the policy of an individual surgeon in
22
23 189 each center. The experimental arm will be provided with a circular polyethylene drape (O Trac[®],
24
25 190 Asung Medical Inc. South Korea) to cover the incision site in the abdomen. It is a double-ring type of
26
27 191 sterile, cylindrical wound protector consisting of inner and outer rings with a polyethylene sheath. The
28
29 192 wound protector is left in situ throughout the operation and is removed just before closing the
30
31 193 abdominal wall. The method of wound closure and insertion of wound drainage will also follow the
32
33 194 policy of an individual surgeon in each center.
34
35

36
37 195 For the control arm, conventional surgical dressing gauze will be used to protect the incision
38
39 196 site during the surgical procedure. There are no differences in surgical technique, other devices, or the
40
41 197 environment.
42
43

44 198

47 199 **Risks**

48
49
50 200 No additional risks to the participants are expected. The circular polyethylene wound
51
52 201 protector has established clinical safety and has been already in clinical applications with the approval
53
54 202 of the Korean Medical Device Information and Technology Assistance Center, MDITAC. None of the
55
56 203 technical details other than wound protection are affected by the trial.
57

204

205 Outcomes

206 The primary end point is the rate of SSI, defined by the diagnostic criteria suggested by the
207 Center for Disease Control (CDC) within 30 days after surgery. According to the CDC definition,
208 SSIs are classified as being either superficial incisional, deep incisional or organ/space ¹⁴. The
209 postoperative wound condition will be evaluated at postoperative weeks 1, 2, and 4-5. The secondary
210 end points include the length of postoperative hospital stay, the re-admission rate, and the rate of
211 surgical complication other than SSI. The incidence of 30-day postoperative complications will be
212 stratified according to the modified Clavien-Dindo Classification ¹⁵.

213

214 Data management and monitoring

215 A newly developed, web-based, electronic case reporting form (eCRF) will be used to record
216 data for the included patients. Baseline characteristics, including age, sex, body mass index, American
217 Society of Anesthesiologists score, history of smoking and alcohol consumption, history of previous
218 chemotherapy, radiotherapy, abdominal surgery, steroid or immunosuppressive drug use, history of
219 diabetes or malignancies in the gastrointestinal tract and nutritional status based on the NRS 2002
220 score will be collected. Laboratory parameters (white blood cell count and c-reactive protein and
221 albumin levels) will be collected preoperatively, on the operation day and on postoperative day 2, if
222 available. The parameters for surgical procedure, including operation type (emergent or elective), site
223 of operation (stomach, small intestine or large intestine), level of wound contamination according to
224 CDC classification, method of skin preparation, antibiotics use, operation time, bowel anastomosis
225 and stoma formation, wound closure material, length of skin incision, draining tube for the wound and
226 body temperature during the operative procedure, will be collected. The surgical wounds are classified
227 into clean, clean-contaminated, contaminated and dirty wounds, according to the magnitude of the

1
2
3
4 228 bacterial load ¹⁶. Postoperatively, the surgical wound will be evaluated at postoperative weeks 1, 2,
5
6 229 and 4-5. A photograph of the wound at each office visit will be taken and documented in the eCRF. If
7
8 230 SSI is detected, the classification and the postoperative date of diagnosis will be recorded. Bacterial
9
10 231 culture of the infected wound will be performed. Postoperative complications according to the
11
12 232 modified Clavien-Dindo classification, postoperative length of hospital stay and re-admission will be
13
14 233 noted. An investigator or research coordinator at each center will enter the data using the eCRF. At
15
16 234 the end of the trial, the study data and personal information of the enrolled patients will be archived
17
18
19 235 for 3 years.

20
21
22 236 The trial data will be monitored by an independent institution (Medical Excellence, Inc.) in
23
24 237 Seoul, Korea. Monitoring will be performed in accordance with ICH-GCP guidelines ¹⁷.

25
26
27 238

28 29 30 239 **Safety evaluation and reporting of adverse events**

31
32
33 240 All adverse events or serious adverse events, occurring from the moment of randomization
34
35 241 until the end of the 30-day follow-up, will be recorded and reported by the investigators.

36
37
38 242

39 40 41 243 **Statistical methods**

42 43 44 244 Sample size calculation

45
46
47 245 The sample size was calculated based on the primary end point of this trial. Previous reports
48
49 246 on the incidence of SSI have indicated that the rate of SSI may vary depending on the wound
50
51 247 classification, the procedure, the surveillance criteria, and the quality of data collection ¹⁸. The
52
53 248 incidence of SSI for clean/clean-contaminated wounds has been reported to be as high as 10% ¹⁹. For
54
55 249 contaminated wounds, the incidence was approximately 25% ^{7 18}. For dirty, infected wounds, the

1
2
3
4 250 incidence may reach up to 40%⁵⁻⁷. In this trial, the ratio of operations with clean/clean-contaminated,
5
6 251 contaminated, and dirty, infected wound is assumed to be 20:40:40; therefore, the expected incidence
7
8 252 of SSI for the control group is 28%. For the experimental group, the incidence of SSI will be
9
10 253 decreased by 40%. Thus, the rate of SSI in the experimental group will be approximately 17%. The
11
12 254 sample size is determined to achieve a study power of 80%, with 95% 2-sided confidence limits. The
13
14 255 actual sample size amounts to 434 participants. However, considering a drop-out (lost to follow-up,
15
16 256 retracted consent or protocol violation) rate of up to 5%, a total of 458 patients, 229 patients in each
17
18
19 257 group, will be enrolled in this study.

22 258 Statistical analysis

25 259 The statistical analysis will be performed by an independent statistician from the Catholic
26
27 260 Medical Center (Seoul, South Korea). The interim and final results will be analyzed mainly for the
28
29 261 intention-to-treat population and, additionally, for the per-protocol population. The rate of 30-day
30
31 262 postoperative SSI will be evaluated in total patients and also analyzed according to the wound
32
33 263 classification (superficial incisional, deep incisional and organ/space SSIs), as defined by the CDC.
34
35 264 Pearson's chi-squared test or Fisher's exact test will be used to analyze nominal data; Student's *t*-test
36
37 265 and the Wilcoxon rank-sum test will be used for continuous data. To estimate the independent risk
38
39 266 factors for 30-day postoperative SSI, logistic regression analysis will be performed. The statistical
40
41 267 analysis will be conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

44
45 268

47 269 **Withdrawals**

50 270 Enrolled patients can withdraw their participation at any time, if desired. In this case, the
51
52 271 patients will have no disadvantages. The investigator will record any patient's withdrawal in
53
54
55 272 the eCRF.

1
2
3
4 2735
6
7 274 **Patient and public involvement**
8
910 275 Patients and the public were not involved in the protocol of this study.
11
1213 276
14
1516 277 **ETHICS AND DISSEMINATION**
17
1819 278 **Research ethics**
20
2122 279 The trial protocol, informed consent document and any other documents necessary to
23
24 280 legitimately start a clinical trial were reviewed and approved by the institutional review board at each
25
26 281 participating center. Written informed consent was obtained from each study participants in
27
28 282 accordance with ethics approval. List of ethics committee: Central Institutional Review Board of The
29
30 283 Catholic Medical Center (XC17DCDI0016), Institutional Review Board of Kyung Hee University
31
32 284 Hospital at Gangdong (KHNMC 2017-06-042), Institutional Review Board of Keimyung University
33
34 285 Donsan Medical Center (2017-06-051-001), Institutional Review Board of National Health Insurance
35
36 286 Service Ilsan Hospital (NHIMC 2017-08-014) and Institutional Review Board of Hallym University
37
38 287 Chuncheon Sacred Heart Hosptial (2017-70).
39
40
41
42 288
43
4445 289 **Study registration**
46
4748 290 The trial protocol was registered at ClinicalTrials.gov (NCT 03170843) on May 31, 2017.
49
5051 291
52
5354 292 **Dissemination**
55
56
57
58
59
60

1
2
3
4 293 The final results will be discussed with participating surgeons and presented at domestic and
5
6 294 international scientific conferences. The final results will be submitted in an international peer-
7
8 295 reviewed scientific journal.
9

10
11 296

12 13 14 297 **DISCUSSION**

15
16
17 298 SSI has been recognized as a costly, debilitating surgical complication over decades
18
19 299 worldwide. Despite vigorous efforts to control SSI through campaigns and publications by
20
21 300 international organizations, the rate of SSI has changed only slightly ² 20-23. Even such
22
23 301 recommendations are limited to the use of prophylactic antibiotics or antiseptic skin cleansing, which
24
25 302 can only be applied during elective surgeries. In cases of abdominal surgery, diffuse purulent
26
27 303 peritonitis with or without fecal contamination, which requires emergency surgery, is frequently
28
29 304 encountered. Prophylactic antibiotics or antiseptic skin cleansing is not applicable in emergent surgical
30
31 305 cases. Several preventive measures other than the use of prophylactic antibiotics or antiseptic skin
32
33 306 cleansing have been proposed to prevent SSI. Intraoperative wound irrigation with antibiotic solution
34
35 307 is one method that can be implemented. Intraoperative wound irrigation with antibiotic solution seems
36
37 308 to reduce the incidence of SSI; however, the problem lies with potential adverse effects of tissue
38
39 309 toxicity and increased bacterial resistance ²⁴. Another method is the application of negative-pressure
40
41 310 wound therapy (NPWT) without primary closure of the abdominal wound in highly contaminated
42
43 311 abdominal surgery ²⁵. A recent meta-analysis on the use of NPWT in open and infected wounds after
44
45 312 vascular surgery demonstrated that it could be effective in controlling SSI ²⁶. However, there are only
46
47 313 a few case reports of its use in contaminated abdominal surgery, and no trial or analysis of its efficacy
48
49 314 is available. The first two methods require the application of a bactericidal substance directly to the
50
51 315 tissue that may or may not present a bacterial infection. Thus, the adverse effects of tissue toxicity and
52
53
54
55 316 bacterial resistance cannot be ignored. The use of NPWT also requires additional resources and time

1
2
3
4 317 to heal, which potentially involves a longer hospital stay and additional medical cost. Therefore,
5
6 318 adopting these methods is not easy in daily practice.
7
8

9 319 The application of a plastic wound protector in abdominal surgery has been tested for its
10
11 320 efficacy for more than a decade. Based on the findings for pathogens most frequently isolated for SSI,
12
13 321 including *Staphylococcus aureus*, coagulase-negative *staphylococci*, *Enterococcus* species, and
14
15 322 *Escherichia coli*¹⁸, plastic wound protectors that hinder direct exposure of the surgical wound to
16
17 323 virulent endogenous bacteria during surgical procedures have been created. Several previous studies
18
19 324 and trials have been conducted to investigate such a hypothesis²⁷. These trials have varied by using
20
21 325 different designs of wound protectors: namely, single-ring or dual-ring types. A meta-analysis by
22
23 326 Mihaljevic et al. showed that wound edge protectors significantly reduced the rate of SSIs in open
24
25 327 abdominal surgery, and available data for double-ring wound protector might be lower quality
26
27 328 compared with that for the single-ring device²⁸. The COVER trial will test a dual-ring type of wound
28
29 329 protector that can tightly conceal the surgical incision edge during the entire operation time.
30
31 330 Previously, the trials on the dual-ring design were conducted in a single center with a small sample
32
33 331 size. In addition, these trials excluded emergent surgeries with contaminated and dirty, infected
34
35 332 wounds resulting from perforated viscera^{13 29 30}. Therefore, the effectiveness of the dual-ring type of
36
37 333 wound protector in controlling SSI contaminated and dirty, infected wounds can be addressed.
38
39
40

41 334 The COVER trial is pragmatic, two-armed RCT that will be conducted by at least 11
42
43 335 surgeons at 11 different centers and possibly more, which will increase external validity. Internal
44
45 336 validation and data quality will be assured by adherence to the SPIRIT statement³¹. Assessments of
46
47 337 the wound condition will not only be done by the observer but will also be reviewed by other
48
49 338 investigators via photographs documented in the eCRF. This will provide an objective and reliable
50
51 339 method for the evaluation of wound infections³². Finally, the risk that patients may experience from
52
53 340 participating in this trial is minimal and will remain within the boundaries of routine clinical practice.
54
55
56
57
58
59
60

1
2
3
4 341 The results of the COVER trial will provide high-quality evidence for using a circular
5
6 342 polyethylene drape in open abdominal surgery with all types of wound to reduce the incidence of SSI.
7
8

9 343

10
11
12 344 **Trial status**

13
14
15 345 Recruitment of participants began at July 11, 2017. A total of 211 patients had been recruited
16
17 346 to this trial as of September 21, 2019. The trial is currently ongoing. (Current study protocol version
18
19 347 7.0., revised at October 23, 2018)
20
21

22 348

23
24
25 349 **Contributors**

26
27
28 350 HJK and RNY designed the COVER trial and were responsible for the protocol
29
30 351 development.

31
32
33 352 JIL, WKK, BHK, CWK, SUB, SMN and BMK revised the draft of the protocol and
34
35 353 approved the final version of protocol.

36
37
38 354 RNY and BMK wrote the manuscript.

39
40
41 355 BMK and HJK critically revised the manuscript.

42
43
44 356 All of the authors conducted the COVER trial and approved the final version of manuscript.
45
46

47 357

48
49
50 358 **Funding**

51
52
53 359 This trial is supported by the Korean Surgical Infection Society (Award number: KSIS 2019-
54
55 360 021), with the use of the circular polyethylene wound protector (O Trac®, Asung Medical Inc. South
56
57

1
2
3
4 361 Korea) given free of charge. There is no other financial support and conflict of interest. The industrial
5
6 362 funder and trial management are independent.
7
8

9 363

10
11
12 364 **Competing interests**

13
14
15 365 The authors declare that they have no competing interests.
16
17

18 366

19
20
21 367 **Patient consent for publication**

22
23
24 368 Not required
25
26

27 369

28
29
30 370 **REFERENCES**

- 31
32
33 371 1. De Pastena M, Paiella S, Marchegiani G, *et al.* Postoperative infections represent a major
34 372 determinant of outcome after pancreaticoduodenectomy: Results from a high-volume center.
35 373 *Surgery* 2017;162:792-801.
36 374 2. Badia JM, Casey AL, Petrosillo N, *et al.* Impact of surgical site infection on healthcare costs
37 375 and patient outcomes: a systematic review in six European countries. *J Hosp Infect*
38 376 2017;96:1-15.
39 377 3. Mujagic E, Marti WR, Coslovsky M, *et al.* Associations of Hospital Length of Stay with
40 378 Surgical Site Infections. *World J Surg* 2018; doi:10.1007/s00268-018-4733-4.
41 379 4. Culver DH, Horan TC, Gaynes RP, *et al.* Surgical wound infection rates by wound class,
42 380 operative procedure, and patient risk index. National Nosocomial Infections Surveillance
43 381 System. *Am J Med* 1991;91:152s-7s.
44 382 5. Smith RL, Bohl JK, McElearney ST, *et al.* Wound infection after elective colorectal
45 383 resection. *Ann Surg* 2004;239:599-605; discussion -7.
46 384 6. Hernandez K, Ramos E, Seas C, *et al.* Incidence of and risk factors for surgical-site infections
47 385 in a Peruvian hospital. *Infect Control Hosp Epidemiol* 2005;26:473-7.
48 386 7. Ruiz-Tovar J, Alonso N, Morales V, *et al.* Association between Triclosan-Coated Sutures for

- 1
2
3
4 387 Abdominal Wall Closure and Incisional Surgical Site Infection after Open Surgery in Patients
5 Presenting with Fecal Peritonitis: A Randomized Clinical Trial. *Surg Infect (Larchmt)*
6 388 2015;16:588-94.
7 389
8
9 390 8. Pinkney TD, Calvert M, Bartlett DC, *et al.* Impact of wound edge protection devices on
10 391 surgical site infection after laparotomy: multicentre randomised controlled trial (ROSSINI
11 392 Trial). *Bmj* 2013;347:f4305.
12
13 393 9. Bruce J, Russell EM, Mollison J, *et al.* The measurement and monitoring of surgical adverse
14 394 events. *Health Technol Assess* 2001;5:1-194.
15
16 395 10. Psaila JV, Wheeler MH, Crosby DL. The role of plastic wound drapes in the prevention of
17 396 wound infection following abdominal surgery. *Br J Surg.* 1977;64:729-32.
18
19 397 11. Nystrom PO, Broome A, Hojer H, *et al.* A controlled trial of a plastic wound ring drape to
20 398 prevent contamination and infection in colorectal surgery. *Dis Colon Rectum.* 1984;27:451-3.
21
22 399 12. Mihaljevic AL, Schirren R, Ozer M, *et al.* Multicenter double-blinded randomized controlled
23 400 trial of standard abdominal wound edge protection with surgical dressings versus coverage
24 401 with a sterile circular polyethylene drape for prevention of surgical site infections: a CHIR-
25 402 Net trial (BaFO; NCT01181206). *Ann Surg* 2014;260:730-7; discussion 7-9.
26
27 403 13. Horiuchi T, Tanishima H, Tamagawa K, *et al.* Randomized, controlled investigation of the
28 404 anti-infective properties of the Alexis retractor/protector of incision sites. *J Trauma.*
29 405 2007;62:212-5. doi: 10.1097/01.ta.0000196704.78785.ae.
30
31 406 14. National Healthcare Safety Network, Centers for Disease Control and Prevention. Surgical
32 407 site infection (SSI) event. <http://www.cdc.gov/nhsn/pdfs/pscmanual/9pscscscurrent.pdf>.
33 408 Published January 2017. Accessed January 25, 2017.
34
35 409 15. Clavien PA, Barkun J, de Oliveira ML, *et al.* The Clavien-Dindo classification of surgical
36 410 complications: five-year experience. *Ann Surg* 2009;250:187-96.
37
38 411 16. Barie PS. Surgical site infections: epidemiology and prevention. *Surg Infect (Larchmt)* 2002;3
39 412 Suppl 1:S9-21.
40
41 413 17. International Conference on Harmonisation of Technical Requirements for Registration of
42 414 Pharmaceuticals for Human Use (ICH) adopts Consolidated Guideline on Good Clinical
43 415 Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use. *Int Dig*
44 416 *Health Legis* 1997;48:231-4.
45
46 417 18. Owens CD, Stoessel K. Surgical site infections: epidemiology, microbiology and prevention.
47 418 *J Hosp Infect* 2008;70 Suppl 2:3-10.
48
49 419 19. Leaper DJ, van Goor H, Reilly J, *et al.* Surgical site infection - a European perspective of
50 420 incidence and economic burden. *Int Wound J* 2004;1:247-73.
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4 421 20. Mangram AJ. A brief overview of the 1999 CDC Guideline for the Prevention of Surgical
5 422 Site Infection. Centers for Disease Control and Prevention. *J Chemother* 2001;13 Spec No
6 423 1:35-9.
7
8
9 424 21. Alexander JW, Solomkin JS, Edwards MJ. Updated recommendations for control of surgical
10 425 site infections. *Ann Surg* 2011;253:1082-93.
11
12 426 22. Berrios-Torres SI. Evidence-Based Update to the U.S. Centers for Disease Control and
13 427 Prevention and Healthcare Infection Control Practices Advisory Committee Guideline for the
14 428 Prevention of Surgical Site Infection: Developmental Process. *Surg Infect (Larchmt)*
15 429 2016;17:256-61.
16
17 430 23. Gulland A. WHO launches global guidelines to stop surgical site infections. *Bmj*
18 431 2016;355:i5942.
19
20 432 24. Mueller TC, Loos M, Haller B, *et al.* Intra-operative wound irrigation to reduce surgical site
21 433 infections after abdominal surgery: a systematic review and meta-analysis. *Langenbecks Arch*
22 434 *Surg* 2015;400:167-81.
23
24 435 25. Yoshioka T, Kondo Y, Fujiwara T. Successful wound treatment using negative pressure
25 436 wound therapy without primary closure in a patient undergoing highly contaminated
26 437 abdominal surgery. *Surg Case Rep* 2018;4:85.
27
28 438 26. Acosta S, Bjorck M, Wanhainen A. Negative-pressure wound therapy for prevention and
29 439 treatment of surgical-site infections after vascular surgery. *Br J Surg* 2017;104:e75-e84.
30
31 440 27. Kang SI, Oh HK, Kim MH, *et al.* Systematic review and meta-analysis of randomized
32 441 controlled trials of the clinical effectiveness of impervious plastic wound protectors in
33 442 reducing surgical site infections in patients undergoing abdominal surgery. *Surgery* 2018;
34 443 doi:10.1016/j.surg.2018.05.024.
35
36 444 28. Mihaljevic AL, Muller TC, Kehl V, *et al.* Wound edge protectors in open abdominal surgery
37 445 to reduce surgical site infections: a systematic review and meta-analysis. *PLoS One*.
38 446 2015;10:e0121187. doi: 10.1371/journal.pone.. eCollection 2015.
39
40 447 29. Reid K, Pockney P, Draganic B, *et al.* Barrier wound protection decreases surgical site
41 448 infection in open elective colorectal surgery: a randomized clinical trial. *Dis Colon Rectum*.
42 449 2010;53:1374-80. doi: 10.007/DCR.0b013e3181ed3f7e.
43
44 450 30. Cheng KP, Roslani AC, Sehha N, *et al.* ALEXIS O-Ring wound retractor vs conventional
45 451 wound protection for the prevention of surgical site infections in colorectal resections(1).
46 452 *Colorectal Dis* 2012;14:e346-51.
47
48 453 31. Chan AW, Tetzlaff JM, Gotsche PC, *et al.* SPIRIT 2013 explanation and elaboration:
49 454 guidance for protocols of clinical trials. *Bmj* 2013;346:e7586.

1
2
3
4 455 32. Sanger PC, Simianu VV, Gaskill CE, *et al.* Diagnosing Surgical Site Infection Using Wound
5 456 Photography: A Scenario-Based Study. *J Am Coll Surg* 2017;224:8-15.e1.
6
7

8 457
9

10
11 458
12

13
14 459 **FIGURE LEGENDS**
15

16
17 460
18

19
20 461 Figure 1. Trial flow
21
22

23 462
24

25
26 463 Figure 2. SPIRIT figure
27

28
29 464 PO = postoperative; SSI = Surgical site infection
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

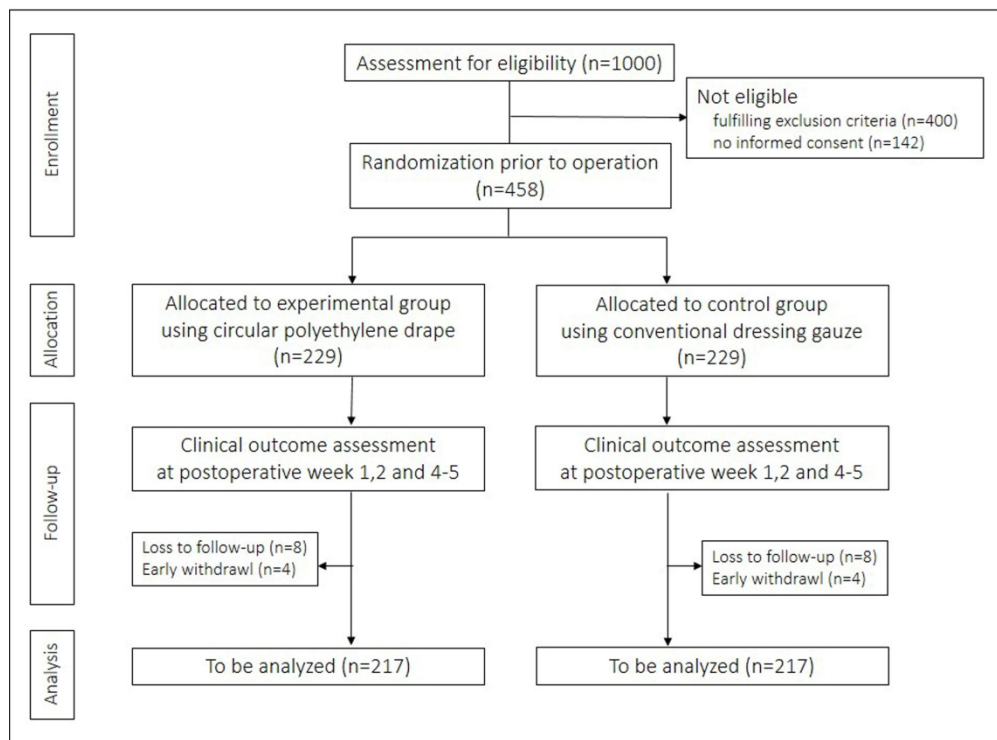


Figure 1. Trial flow

254x190mm (300 x 300 DPI)

TIMEPOINT	STUDY PERIOD						
	Enrolment	Allocation	Post-allocation				Close-out
	-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)



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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	<u>Lines 1–2</u>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	<u>Lines 68, 281-282</u>
	2b	All items from the World Health Organization Trial Registration Data Set	<u>Throughout</u>
Protocol version	3	Date and version identifier	<u>Lines 332-335</u>
Funding	4	Sources and types of financial, material, and other support	<u>Lines 345-349</u>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	<u>Lines 4-21, 337-343</u>
	5b	Name and contact information for the trial sponsor	<u>Lines 345-349</u>
	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	<u>Lines 345-349</u>
	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)	<u>Lines 233-234, 256-257</u>

1	Introduction			
2				
3	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	<u>Lines 90-119</u>
4				
5				
6		6b	Explanation for choice of comparators	<u>Lines 99-105</u>
7				
8	Objectives	7	Specific objectives or hypotheses	<u>Lines 127-134</u>
9				
10	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)	<u>Lines 157-160, Fig 1</u>
11				
12				
13				
14	Methods: Participants, interventions, and outcomes			
15				
16	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	<u>Lines 136-141, 163-164</u>
17				
18				
19	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)	<u>Lines 143-155</u>
20				
21				
22				
23	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	<u>Lines 185-196</u>
24				
25				
26		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)	<u>Lines 266-269</u>
27				
28				
29		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	<u>Lines 214-215, 233-234</u>
30				
31				
32		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	<u>Not applicable</u>
33				
34	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	<u>Lines 204-211</u>
35				
36				
37				
38				
39				
40	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)	<u>Lines 162-171, Fig. 2.</u>
41				
42				
43				
44				
45				
46				

1	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	<u>Lines 241-254</u>
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	<u>Lines 140-141</u>
5				
6	Methods: Assignment of interventions (for controlled trials)			
7	Allocation:			
8				
9				
10	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	<u>Lines 173-183</u>
11				
12				
13				
14				
15				
16	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	<u>Lines 176-178</u>
17				
18				
19				
20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	<u>Lines 176-179</u>
21				
22				
23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	<u>Lines 179-183</u>
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	<u>Not applicable</u>
28				
29				
30				
31	Methods: Data collection, management, and analysis			
32				
33	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	<u>Lines 213-234</u>
34				
35				
36				
37				
38				
39		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	<u>Lines 227-231</u>
40				
41				
42				
43				
44				
45				
46				

1	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	<u>Lines 230-234</u>
2				
3				
4				
5	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	<u>Lines 255-264</u>
6				
7				
8				
9				
10		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	<u>Lines 257-258</u>
11				
12		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)	<u>Lines 257-264</u>
13				
14				
15				
16	Methods: Monitoring			
17				
18	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	<u>Lines 233-234</u>
19				
20				
21				
22				
23				
24		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	<u>Lines 169-171</u>
25				
26				
27	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	<u>Lines 236-238</u>
28				
29				
30	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.
31				
32				
33				
34				
35				
36	Ethics and dissemination			
37				
38	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	<u>Lines 275-279</u>
39				
40				
41				
42				
43				
44				
45				
46				

1	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).
10	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	<u>Lines 154-155</u>
13		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	<u>Not applicable</u>
17	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	<u>Lines 124-125, 230-234</u>
20	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	<u>Lines 345-349</u>
23	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	<u>Lines 256-257, 233-234</u>
26	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	<u>Not applicable</u>
29	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	<u>None. The authors plan to publish the results of this trial in scientific journal.</u>
35		31b	Authorship eligibility guidelines and any intended use of professional writers	<u>None</u>
37		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	<u>None</u>

Appendices

1	Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogates	<u>None</u>
4	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	<u>Not applicable</u>

*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.

For peer review only

BMJ Open

Circular polyethylene drape in prevention of surgical site infection (COVER Trial): Study protocol for a randomized controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-034687.R2
Article Type:	Protocol
Date Submitted by the Author:	31-Dec-2019
Complete List of Authors:	Yoo, Ri Na; Catholic University of Korea Saint Vincent's Hospital, Surgery Kim, Hyung Jin; Catholic University of Korea Saint Vincent's Hospital, Surgery Lee, Jae Im; Catholic University of Korea Uijeongbu St. Mary's Hospital, Surgery Kang, Won-Kyung; Catholic University of Korea Yeouido Saint Mary's Hospital, Surgery Kye, Bong-Hyeon; Catholic University of Korea Seoul St. Mary's Hospital, Surgery Kim, Chang Woo; Kyung Hee University Hospital at Gangdong, Surgery Bae, Sung Uk; Keimyung University Dongsan Medical Center, Surgery Nam, Soomin; National Health Insurance Corporation Ilsan Hospital, Surgery Kang, Byung Mo; Chuncheon Sacred Heart Hospital, Surgery
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Gastroenterology and hepatology
Keywords:	GASTROENTEROLOGY, Infection control < INFECTIOUS DISEASES, SURGERY, WOUND MANAGEMENT

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4 1 Circular pOlyethylene drape in preVEntion of suRgical site infection (COVER Trial): Study
5
6 2 protocol for a randomized controlled trial
7
8
9
10 3

11
12
13 4 Ri Na Yoo¹, Hyung Jin Kim¹, Jae Im Lee², Won-Kyung Kang³, Bong-Hyeon Kye^{1,4}, Chang Woo Kim⁵,
14
15 5 Sung Uk Bae⁶, Soomin Nam⁷ and Byung Mo Kang⁸
16
17
18 6

- 19
20
21 7 1. Department of Surgery, St. Vincent's Hospital, The Catholic University of Korea, Suwon,
22
23 8 Korea
24
25
26 9 2. Department of Surgery, Uijeongbu St. Mary's Hospital. The Catholic University of Korea,
27
28 10 Uijeongbu, Korea
29
30
31 11 3. Department of Surgery, Yeouido St. Mary's Hospital, The Catholic University of Korea, Seoul,
32
33 12 Korea
34
35
36 13 4. Department of Surgery, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul,
37
38 14 Korea
39
40
41 15 5. Department of Surgery, Kyung Hee University Hospital at Gangdong, Kyung Hee University
42
43 16 School of Medicine, Seoul, Korea
44
45
46 17 6. Department of Surgery, School of Medicine, Keimyung University and Dongsan Medical
47
48 18 Center, Daegu, Korea
49
50
51 19 7. Department of Surgery, National Health Insurance Service Ilsan Hospital, Goyang, Korea
52
53
54 20 8. Department of Surgery, Chuncheon Sacred Heart Hospital, Hallym University College of
55
56 21 Medicine, Chuncheon, Korea
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45

Correspondence to: Byung Mo Kang, Department of Surgery, Chuncheon Sacred Heart Hospital,
Hallym University College of Medicine, 77, Sakju-ro, Chuncheon 24253, Korea.

Telephone: +821085866963

E-mail address: kbm0728@yahoo.co.kr



Word count: 3,217 words

1
2
3
4 **Abstract**
5

6
7 **Introduction:** Surgical site infection (SSI) after abdominal surgery remains a significant cause of
8 morbidity and is associated with an increased socioeconomic burden and a reduced quality of life.
9
10 Circular wound protectors have been expected to reduce the risk of SSI, but previous studies reported
11
12 conflicting results on their protective effects. The purpose of this study was to evaluate the efficacy of
13
14
15 circular wound protectors in reducing SSI in open abdominal surgery.
16
17

18
19
20
21 **Methods and analysis:** The COVER trial investigates whether the application of a dual-ring circular
22
23 plastic wound protector reduces the rate of SSI in patients undergoing elective or emergent open
24
25 abdominal surgery related to the gastrointestinal tract, regardless of the type of wound classified by the
26
27 Centers for Disease Control. The COVER trial is a multicenter, randomized controlled clinical trial with
28
29 two parallel arms – one using a dual-ring wound protector with circular polyethylene drape and the
30
31 other using conventional surgical dressing gauze. The primary outcome will measure the rate of SSI
32
33 within 30 days after surgery in two groups. Statistical analysis of the primary end point will be based
34
35 on the intention-to-treat population. The sample size was determined to achieve a study power of 80%
36
37 with 95% 2-sided confidence limits. Considering a dropout rate of up to 5%, a total of 458 patients, 229
38
39 patients in each group, will be enrolled in this study.
40
41
42

43
44
45
46 **Ethics and dissemination:** The trial protocol and informed consent document have been reviewed and
47
48 approved by the institutional review board at each participating center. Written informed consent will
49
50 be obtained from each study participant. The clinical outcomes of this trial will be submitted to an
51
52 international peer-reviewed journal and presented at international conferences.
53
54

55
56
57
58
59
60

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

70

71 **Strengths and limitations of this study:**

72

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

84

85

86

87

88

89 INTRODUCTION

90 Surgical site infection (SSI) is a common postoperative complication that is associated not
91 only with considerable morbidity and mortality but also with a significant socioeconomic burden ¹⁻³.
92 The rate of SSI is estimated to range from approximately 10% to 30% after elective abdominal surgery,
93 depending on the presence of risk factors, type of procedure, and degree of endogenous contaminants ¹
94 ^{4 5}. In cases of fecal peritonitis, the SSI rate may reach up to 35~40% ^{6 7}. Despite organizational,
95 systematic approaches for preventing SSI based on evidence, such as preoperative antibiotic
96 prophylaxis and antiseptic skin cleansing, SSI is still a major problem associated with increased hospital
97 costs, prolonged hospital stays, and unsatisfactory quality of life ⁸.

99 The risk of developing a SSI will increase when the surgical incision site is exposed to large
100 amounts of virulent bacteria in a contaminated surgical field ⁹. This risk has led to the idea of developing
101 a physical barrier for the wound edge that can hinder direct exposure of the surgical incision edges to
102 the contaminated field. Several devices that are designed for wound edge protection and have a similar
103 design involving a flexible plastic wound cover placed in the laparotomy site are currently on the market.
104 Prospective studies and randomized clinical trials (RCTs) have been conducted to evaluate the
105 effectiveness of plastic wound protectors for reducing the incidence of SSI ^{8 10-13}.

107 Previous trials

108 The largest RCT evaluating the effectiveness of wound protectors in reducing SSI is the
109 ROSSINI trial, with 760 patients undergoing laparotomy at 21 different hospitals in the UK ⁸. In this
110 study, the drape type of wound protector was compared to standard intraoperative care. The results
111 showed that the use of a wound edge protector during open abdominal surgery did not reduce the rate

1
2
3
4 112 of SSI. Similarly, RCTs using a drape type of wound protector applied in colorectal surgery reported
5
6 113 no benefit of the wound protector in reducing SSI^{10 11}. However, several other studies have claimed
7
8 114 contrasting results. The BaFO trial, with 608 patients undergoing laparotomy at 16 different medical
9
10 115 centers in Germany, demonstrated that the patients who used wound protection drape devices
11
12 116 experienced SSI at a lower rate than those who did not¹². A Japanese single-center RCT with 221
13
14 117 patients enrolled to investigate the effect of a double-ring, circular wound protector applied in
15
16 118 nontraumatic gastrointestinal surgery also showed that the rate of SSI was significantly lower in the
17
18 119 experimental group than in the control group¹³.
19
20
21
22 120
23
24

25 121 The effect of wound protectors in abdominal surgery is still controversial and remains to be
26
27 122 elucidated. A well-designed, multicenter, RCT evaluating the effect of the dual-ring type of wound
28
29 123 protector in open abdominal surgery, particularly for contaminated or dirty infected wounds, has not
30
31 124 yet been conducted.
32
33

34 125
35
36

37 126 **METHODS AND ANALYSIS**

38
39

40 127 **Objective**

41
42

43 128 The COVER trial aims to investigate the effect of a dual-ring, plastic wound protector in open
44
45 129 abdominal surgery. It is designed to test whether the device helps to reduce the overall rate of SSI
46
47 130 development within 30 days postoperatively by 40% compared with that of the control group. In
48
49 131 particular, the COVER trial includes patients who are undergoing an open abdominal surgery for
50
51 132 contaminated or dirty/infected wounds, as well as those undergoing an open abdominal surgery for
52
53 133 clean or clean-contaminated wounds, which allows a thorough investigation of the wound protector's
54
55 134 effects, depending on the degree of contamination.
56
57
58
59
60

1
2
3
4 1355
6
7 136 **Trial sites**

8
9
10 137 Initially, eight sites at secondary or tertiary hospitals in South Korea began this trial. All
11
12 138 participating investigators have been educated on the basis of the International Conference on
13
14 139 Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use,
15
16 140 which serves as the good clinical practice (GCP) guidelines for this trial. This trial is still open for
17
18 141 recruitment at participating centers.
19

20
21 14222
23
24 143 **Trial population and eligibility**

25
26
27 144 All gastrointestinal surgical patients undergoing open abdominal surgery, either elective or
28
29 145 emergent, will be screened for eligibility. Patients who satisfy the following criteria will be included:
30
31 146 1) between the ages of 18 and 75 years; 2) undergoing elective or emergent open abdominal surgery;
32
33 147 and 3) undergoing surgery on the stomach, small intestine, or colon and rectum. Patients with any of
34
35 148 the following will be excluded: 1) presence of concurrent infection in the abdominal wall; 2) open
36
37 149 conversion from laparoscopic surgery; 3) presence of poor nutritional status indicated by a nutrition
38
39 150 risk screening (NRS) 2002 score greater than 3; 4) undergoing combined hepatobiliarypancreatic surgery;
40
41 151 5) pregnancy or breast-feeding; and 6) moderate to severe immunosuppression state, defined as previous
42
43 152 organ or bone marrow transplantation, concurrent steroid administration (more than 10 mg prednisolone
44
45 153 daily or an equivalent dose of any other steroid), or concurrent administration of other
46
47 154 immunosuppressive or chemotherapeutic agents within the last 2 weeks prior to trial intervention. Once
48
49 155 an investigator explains the extent and nature of the COVER trial to an eligible patient, informed
50
51 156 consent will be obtained.
52
53
54
55

56 157
57
58
59
60

158 **Trial type**

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

163 **Recruitment and trial timeline**

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

174 **Randomization and blinding**

175 Stratification will be performed according to the participating center and the type of wound
176 classification. The wound types will be divided into two groups: one group with clean or clean-
177 contaminated wounds and the other group with contaminated or dirty, infected wounds. A web-based
178 patient registry (<http://cover.e-trial.co.kr>) will be applied to generate the allocation sequence
179 immediately before the beginning of the operation, providing adequate concealment for the allocation
180 sequence. The group allocation and randomization number will be predefined by a biostatistician from

1
2
3
4 181 the Catholic Medical Center in Seoul, South Korea. A permuted block randomization with the size of 2
5
6 182 or 4 will be applied. Participating surgeons cannot be blinded to the allocated treatment. However, the
7
8 183 patient will be blinded to the trial intervention since they are under general anesthesia once the operation
9
10 184 starts. The data manager will also be blinded because there is no direct access to either the trial
11
12 185 intervention or the randomization.
13
14
15
16 186

17 18 187 **Interventions**

19
20
21 188 Preoperative bowel preparation, type of skin preparation and drape, the use of perioperative
22
23 189 antibiotics, and the details of the surgical procedure will follow the policy of an individual surgeon at
24
25 190 each center. The experimental arm will be provided with a circular polyethylene drape (O Trac®, Asung
26
27 191 Medical Inc. South Korea) to cover the incision site in the abdomen. It is a double-ring type of sterile,
28
29 192 cylindrical wound protector consisting of inner and outer rings with a polyethylene sheath. The wound
30
31 193 protector is left in situ throughout the operation and is removed immediately before closing the
32
33 194 abdominal wall. The method of wound closure and insertion of wound drainage will also follow the
34
35 195 policy of an individual surgeon at each center.
36
37
38

39 196 For the control arm, conventional surgical dressing gauze will be used to protect the incision
40
41 197 site during the surgical procedure. There are no differences in surgical technique, other devices, or
42
43 198 environment.
44
45

46 199

47 48 49 200 **Risks**

50
51
52 201 No additional risks to the participants are expected. The circular polyethylene wound protector
53
54 202 has established clinical safety and has already been used in clinical applications with the approval of
55
56
57
58
59
60

1
2
3
4 203 the Korean Medical Device Information and Technology Assistance Center (MDITAC). None of the
5
6 204 technical details other than wound protection are affected by the trial.
7
8

9 205
10
11

12 206 **Outcomes**

13
14
15 207 The primary end point is the rate of SSI, defined by the diagnostic criteria suggested by the
16
17 208 Centers for Disease Control (CDC), within 30 days after surgery. According to the CDC definition,
18
19 209 SSIs are classified as either superficial incisional, deep incisional or organ/space¹⁴. The postoperative
20
21 210 wound condition will be evaluated at postoperative weeks 1, 2, and 4-5. The secondary end points
22
23 211 include the length of postoperative hospital stay, the readmission rate, and the rate of surgical
24
25 212 complications other than SSI. The incidence of 30-day postoperative complications will be stratified
26
27 213 according to the modified Clavien-Dindo classification¹⁵.
28
29

30 214
31
32

33 215 **Data management and monitoring**

34
35
36 216 A newly developed, web-based, electronic case reporting form (eCRF) will be used to record
37
38 217 data for the included patients. Baseline characteristics, including age, sex, body mass index, American
39
40 218 Society of Anesthesiologists score, history of smoking and alcohol consumption, history of previous
41
42 219 chemotherapy, radiotherapy, abdominal surgery, or steroid or immunosuppressive drug use, history of
43
44 220 diabetes or malignancies in the gastrointestinal tract and nutritional status based on the NRS 2002 score,
45
46 221 will be collected. Laboratory parameters (white blood cell counts and c-reactive protein and albumin
47
48 222 levels) will be collected preoperatively, on the operation day and on postoperative day 2, if available.
49
50 223 The parameters for the surgical procedure, including operation type (emergent or elective), site of
51
52 224 operation (stomach, small intestine or large intestine), level of wound contamination according to CDC
53
54 225 classification, method of skin preparation, antibiotic use, operation time, bowel anastomosis and stoma
55
56
57
58
59
60

1
2
3
4 226 formation, wound closure material, length of skin incision, draining tube for the wound and body
5
6 227 temperature during the surgical procedure, will be collected. The surgical wounds are classified as clean,
7
8 228 clean-contaminated, contaminated and dirty wounds, according to the magnitude of the bacterial load
9
10 229 ¹⁶. Postoperatively, the surgical wound will be evaluated at postoperative weeks 1, 2, and 4-5. A
11
12 230 photograph of the wound will be taken at each office visit and documented in the eCRF. If SSI is
13
14 231 detected, the classification and the postoperative date of diagnosis will be recorded. Bacterial culture of
15
16 232 the infected wound will be performed. Postoperative complications according to the modified Clavien-
17
18 233 Dindo classification, postoperative length of hospital stay and readmission will be noted. An
19
20 234 investigator or research coordinator at each center will enter the data using the eCRF. At the end of the
21
22 235 trial, the study data and personal information of the enrolled patients will be archived for 3 years.

23
24
25
26 236 The trial data will be monitored by an independent institution (Medical Excellence, Inc.) in
27
28 237 Seoul, Korea. Monitoring will be performed in accordance with ICH-GCP guidelines ¹⁷.

29
30
31 238

32 33 34 239 **Safety evaluation and reporting of adverse events**

35
36
37 240 All adverse events or serious adverse events, occurring from the moment of randomization
38
39 241 until the end of the 30-day follow-up, will be recorded and reported by the investigators.

40
41
42 242

43 44 45 243 **Statistical methods**

46
47
48 244 Sample size calculation

49
50
51 245 The sample size was calculated based on the primary end point of this trial. Previous reports
52
53 246 on the incidence of SSI have indicated that the rate of SSI may vary depending on the wound
54
55 247 classification, the procedure, the surveillance criteria, and the quality of data collection ¹⁸. The incidence

1
2
3
4 248 of SSI for clean/clean-contaminated wounds has been reported to be as high as 10%¹⁹. For contaminated
5
6 249 wounds, the incidence was approximately 25%^{7,18}. For dirty, infected wounds, the incidence may reach
7
8 250 up to 40%⁵⁻⁷. In this trial, the ratio of operations with clean/clean-contaminated, contaminated, and
9
10 251 dirty, infected wounds was assumed to be 20:40:40; therefore, the expected incidence of SSI for the
11
12 252 control group was 28%. For the experimental group, the incidence of SSI will be decreased by 40%.
13
14 253 Thus, the rate of SSI in the experimental group will be approximately 17%. The sample size was
15
16 254 determined to achieve a study power of 80%, with 95% 2-sided confidence limits. The actual sample
17
18 255 size amounts to 434 participants. However, considering a dropout (lost to follow-up, retracted consent
19
20 256 or protocol violation) rate of up to 5%, a total of 458 patients, 229 patients in each group, will be enrolled
21
22 257 in this study.

26 258 Statistical analysis

29 259 The statistical analysis will be performed by an independent statistician from the Catholic
30
31 260 Medical Center (Seoul, South Korea). The interim and final results will be analyzed mainly for the
32
33 261 intention-to-treat population and, additionally, for the per-protocol population. The rate of 30-day
34
35 262 postoperative SSI will be evaluated in all patients and analyzed according to the wound classification
36
37 263 (superficial incisional, deep incisional and organ/space SSIs), as defined by the CDC. Pearson's chi-
38
39 264 squared test or Fisher's exact test will be used to analyze nominal data; Student's *t*-test and the Wilcoxon
40
41 265 rank-sum test will be used for continuous data. To estimate the independent risk factors for 30-day
42
43 266 postoperative SSI, logistic regression analysis will be performed. The statistical analysis will be
44
45 267 conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

48
49 268

51 269 **Withdrawals**

54 270 Enrolled patients can withdraw their participation at any time, if desired. In this case, the
55
56 271 patients will have no disadvantages. The investigator will record any patient withdrawal in the eCRF.

1
2
3
4 2725
6
7 **273 Patient and public involvement**8
9
10 274 Patients and the public were not involved in the protocol of this study.
11
1213 275
14
1516 **276 ETHICS AND DISSEMINATION**
1718
19 **277 Research ethics**
2021
22 278 The trial protocol, informed consent document and any other documents necessary to
23
24 279 legitimately start a clinical trial were reviewed and approved by the institutional review board at each
25
26 280 participating center. The names of the ethics committees are as follows: Central Institutional Review
27
28 281 Board of The Catholic Medical Center (XC17DCDI0016), Institutional Review Board of Kyung Hee
29
30 282 University Hospital at Gangdong (KHNMC 2017-06-042), Institutional Review Board of Keimyung
31
32 283 University Donsan Medical Center (2017-06-051-001), Institutional Review Board of National Health
33
34 284 Insurance Service Ilsan Hospital (NHIMC 2017-08-014) and Institutional Review Board of Hallym
35
36 285 University Chuncheon Sacred Heart Hospital (2017-70). Written informed consent was obtained from
37
38 286 each study participant in accordance with ethical approval.
39
4041 287
42
4344 **288 Study registration**
4546
47 289 The trial protocol was registered at ClinicalTrials.gov (NCT 03170843) on May 31, 2017.
48
4950 290
51
5253 **291 Dissemination**
54
55
56
57
58
59
60

1
2
3
4 292 The final results will be discussed with participating surgeons and presented at domestic and
5
6 293 international scientific conferences. The final results will be submitted to an international peer-reviewed
7
8 294 scientific journal.
9

10
11 295

14 296 **DISCUSSION**

17 297 SSI has been recognized worldwide as a costly, debilitating surgical complication for decades.
18
19 298 Despite vigorous efforts to control SSI through campaigns and publications by international
20
21 299 organizations, the rate of SSI has changed only slightly^{2 20-23}. Even such recommendations are limited
22
23 300 to the use of prophylactic antibiotics or antiseptic skin cleansing, which can be applied only during
24
25 301 elective surgeries. In cases of abdominal surgery, diffuse purulent peritonitis with or without fecal
26
27 302 contamination, which requires emergency surgery, is frequently encountered. Prophylactic antibiotics
28
29 303 or antiseptic skin cleansing is not applicable in emergent surgical cases. Several preventive measures
30
31 304 other than the use of prophylactic antibiotics or antiseptic skin cleansing have been proposed to prevent
32
33 305 SSI. Intraoperative wound irrigation with antibiotic solution is one method that can be implemented.
34
35 306 Intraoperative wound irrigation with antibiotic solution seems to reduce the incidence of SSI; however,
36
37 307 there are potential adverse effects of tissue toxicity and increased bacterial resistance²⁴. Another method
38
39 308 is the application of negative-pressure wound therapy (NPWT) without primary closure of the
40
41 309 abdominal wound in highly contaminated abdominal surgery²⁵. A recent meta-analysis on the use of
42
43 310 NPWT in open and infected wounds after vascular surgery demonstrated that it could be effective in
44
45 311 controlling SSI²⁶. However, there are only a few case reports on its use in contaminated abdominal
46
47 312 surgery, and no trial or analysis of its efficacy is available. The first two methods require the application
48
49 313 of a bactericidal substance directly to the tissue that may or may not present a bacterial infection. Thus,
50
51 314 the adverse effects of tissue toxicity and bacterial resistance cannot be ignored. The use of NPWT also
52
53
54
55
56
57
58
59
60

1
2
3
4 315 requires additional resources and time to heal, which potentially involves a longer hospital stay and
5
6 316 additional medical costs. Therefore, adopting these methods is not easy in daily practice.
7
8

9 317 The application of a plastic wound protector in abdominal surgery has been tested for its
10
11 318 efficacy for more than a decade. Based on findings for the pathogens most frequently isolated in SSI,
12
13 319 including *Staphylococcus aureus*, coagulase-negative *staphylococci*, *Enterococcus* species, and
14
15 320 *Escherichia coli*¹⁸, plastic wound protectors that hinder direct exposure of the surgical wound to
16
17 321 virulent endogenous bacteria during surgical procedures have been created. Several previous studies
18
19 322 and trials have been conducted to investigate this hypothesis²⁷. These trials have varied by using
20
21 323 different designs of wound protectors: namely, single-ring or dual-ring types. A meta-analysis by
22
23 324 Mihaljevic et al. showed that wound edge protectors significantly reduced the rate of SSIs in open
24
25 325 abdominal surgery, but the available data for double-ring wound protectors might be lower quality than
26
27 326 those available for the single-ring device²⁸. The COVER trial will test a dual-ring type of wound
28
29 327 protector that can tightly conceal the surgical incision edge during the entire operation time. Previously,
30
31 328 the trials on the dual-ring design were conducted in a single center with a small sample size. In addition,
32
33 329 these trials excluded emergent surgeries with contaminated and dirty, infected wounds resulting from
34
35 330 perforated viscera^{13 29 30}. Therefore, the effectiveness of the dual-ring type of wound protector in
36
37 331 controlling SSI in contaminated and dirty, infected wounds can be addressed. In the COVER trial,
38
39 332 patients more than 75 years will be excluded. Prevalence of cognitive impairment increased with age in
40
41 333 patients more than 75 years³¹ and these patients often have difficulties in understanding the concepts
42
43 334 of clinical trial. In addition, extreme age itself is associated with an increased risk of SSI³².
44
45
46
47

48 335 The COVER trial is a pragmatic, two-armed RCT that will be conducted by at least 11
49
50 336 surgeons at 11 different centers and possibly more, which will increase external validity. Internal
51
52 337 validation and data quality will be ensured by adherence to the SPIRIT statement³³. Assessments of
53
54 338 wound condition will be not only performed by the observer but also reviewed by other investigators
55
56 339 via photographs documented in the eCRF. This will provide an objective and reliable method for the
57
58
59
60

1
2
3
4 340 evaluation of wound infections³⁴. Finally, the risk that patients may experience from participating in
5
6 341 this trial is minimal and will remain within the boundaries of routine clinical practice.
7
8

9 342 The results of the COVER trial will provide high-quality evidence for the use of a circular
10
11 343 polyethylene drape in open abdominal surgery with all types of wounds to reduce the incidence of SSI.
12
13

14 344

15
16
17 345 **Trial status**
18

19
20 346 Recruitment of participants began on July 11, 2017. A total of 211 patients were recruited for
21
22 347 this trial as of September 21, 2019. The trial is currently ongoing. (current study protocol version 7.0.,
23
24 348 revised on October 23, 2018)
25
26

27 349

28
29
30 350 **Contributors**
31

32
33 351 HJK and RNY designed the COVER trial and were responsible for protocol development.
34

35
36 352 JIL, WKK, BHK, CWK, SUB, SMN and BMK revised the draft of the protocol and approved
37
38 353 the final version of the protocol.
39

40
41 354 RNY and BMK wrote the manuscript.
42

43
44 355 BMK and HJK critically revised the manuscript.
45

46
47 356 All of the authors conducted the COVER trial and approved the final version of the
48
49 357 manuscript.
50

51
52 358

53
54
55 359 **Funding**
56

1
2
3
4 360 This trial is supported by the Korean Surgical Infection Society (Award number: KSIS 2019-
5
6 361 021), with the use of the circular polyethylene wound protector (O Trac[®], Asung Medical Inc. South
7
8 362 Korea) given free of charge. There is no other financial support or conflict of interest. The industrial
9
10 363 funder and trial management are independent.
11
12

13 364

16 365 **Competing interests**

18
19 366 The authors declare that they have no competing interests.
20
21

22 367

25 368 **Patient consent for publication**

27
28 369 Not required
29
30

31 370

34 371 **REFERENCES**

- 37 372 1. De Pastena M, Paiella S, Marchegiani G, *et al.* Postoperative infections represent a major
38
39 373 determinant of outcome after pancreaticoduodenectomy: Results from a high-volume center.
40
41 374 *Surgery* 2017;162:792-801.
42
43 375 2. Badia JM, Casey AL, Petrosillo N, *et al.* Impact of surgical site infection on healthcare costs
44
45 376 and patient outcomes: a systematic review in six European countries. *J Hosp Infect* 2017;96:1-
46
47 377 15.
48
49 378 3. Mujagic E, Marti WR, Coslovsky M, *et al.* Associations of Hospital Length of Stay with
50
51 379 Surgical Site Infections. *World J Surg* 2018; doi:10.1007/s00268-018-4733-4.
52
53 380 4. Culver DH, Horan TC, Gaynes RP, *et al.* Surgical wound infection rates by wound class,
54
55 381 operative procedure, and patient risk index. National Nosocomial Infections Surveillance
56
57
58
59
60

- 1
2
3
4 382 System. *Am J Med* 1991;91:152s-7s.
- 5
6 383 5. Smith RL, Bohl JK, McElearney ST, *et al.* Wound infection after elective colorectal resection.
7
8 384 *Ann Surg* 2004;239:599-605; discussion -7.
- 9
10 385 6. Hernandez K, Ramos E, Seas C, *et al.* Incidence of and risk factors for surgical-site infections
11
12 386 in a Peruvian hospital. *Infect Control Hosp Epidemiol* 2005;26:473-7.
- 13
14 387 7. Ruiz-Tovar J, Alonso N, Morales V, *et al.* Association between Triclosan-Coated Sutures for
15
16 388 Abdominal Wall Closure and Incisional Surgical Site Infection after Open Surgery in Patients
17
18 389 Presenting with Fecal Peritonitis: A Randomized Clinical Trial. *Surg Infect (Larchmt)*
19
20 390 2015;16:588-94.
- 21
22 391 8. Pinkney TD, Calvert M, Bartlett DC, *et al.* Impact of wound edge protection devices on surgical
23
24 392 site infection after laparotomy: multicentre randomised controlled trial (ROSSINI Trial). *Bmj*
25
26 393 2013;347:f4305.
- 27
28 394 9. Bruce J, Russell EM, Mollison J, *et al.* The measurement and monitoring of surgical adverse
29
30 395 events. *Health Technol Assess* 2001;5:1-194.
- 31
32 396 10. Psaila JV, Wheeler MH, Crosby DL. The role of plastic wound drapes in the prevention of
33
34 397 wound infection following abdominal surgery. *Br J Surg.* 1977;64:729-32.
- 35
36 398 11. Nystrom PO, Broome A, Hojer H, *et al.* A controlled trial of a plastic wound ring drape to
37
38 399 prevent contamination and infection in colorectal surgery. *Dis Colon Rectum.* 1984;27:451-3.
- 39
40 400 12. Mihaljevic AL, Schirren R, Ozer M, *et al.* Multicenter double-blinded randomized controlled
41
42 401 trial of standard abdominal wound edge protection with surgical dressings versus coverage with
43
44 402 a sterile circular polyethylene drape for prevention of surgical site infections: a CHIR-Net trial
45
46 403 (BaFO; NCT01181206). *Ann Surg* 2014;260:730-7; discussion 7-9.
- 47
48 404 13. Horiuchi T, Tanishima H, Tamagawa K, *et al.* Randomized, controlled investigation of the anti-
49
50 405 infective properties of the Alexis retractor/protector of incision sites. *J Trauma.* 2007;62:212-
51
52 406 5. doi: 10.1097/01.ta.0000196704.78785.ae.
- 53
54 407 14. National Healthcare Safety Network, Centers for Disease Control and Prevention. Surgical site
55
56
57
58
59
60

- 1
2
3
4 408 infection (SSI) event. <http://www.cdc.gov/nhsn/pdfs/pscmanual/9pscscscurrent.pdf>. Published
5
6 409 January 2017. Accessed January 25, 2017. .
7
8 410 15. Clavien PA, Barkun J, de Oliveira ML, *et al*. The Clavien-Dindo classification of surgical
9 411 complications: five-year experience. *Ann Surg* 2009;250:187-96.
10
11 412 16. Barie PS. Surgical site infections: epidemiology and prevention. *Surg Infect (Larchmt)* 2002;3
12
13 413 Suppl 1:S9-21.
14
15 414 17. International Conference on Harmonisation of Technical Requirements for Registration of
16
17 415 Pharmaceuticals for Human Use (ICH) adopts Consolidated Guideline on Good Clinical
18
19 416 Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use. *Int Dig Health*
20
21 417 *Legis* 1997;48:231-4.
22
23 418 18. Owens CD, Stoessel K. Surgical site infections: epidemiology, microbiology and prevention. *J*
24
25 419 *Hosp Infect* 2008;70 Suppl 2:3-10.
26
27 420 19. Leaper DJ, van Goor H, Reilly J, *et al*. Surgical site infection - a European perspective of
28
29 421 incidence and economic burden. *Int Wound J* 2004;1:247-73.
30
31 422 20. Mangram AJ. A brief overview of the 1999 CDC Guideline for the Prevention of Surgical Site
32
33 423 Infection. Centers for Disease Control and Prevention. *J Chemother* 2001;13 Spec No 1:35-9.
34
35 424 21. Alexander JW, Solomkin JS, Edwards MJ. Updated recommendations for control of surgical
36
37 425 site infections. *Ann Surg* 2011;253:1082-93.
38
39 426 22. Berrios-Torres SI. Evidence-Based Update to the U.S. Centers for Disease Control and
40
41 427 Prevention and Healthcare Infection Control Practices Advisory Committee Guideline for the
42
43 428 Prevention of Surgical Site Infection: Developmental Process. *Surg Infect (Larchmt)*
44
45 429 2016;17:256-61.
46
47 430 23. Gulland A. WHO launches global guidelines to stop surgical site infections. *Bmj*
48
49 431 2016;355:i5942.
50
51 432 24. Mueller TC, Loos M, Haller B, *et al*. Intra-operative wound irrigation to reduce surgical site
52
53 433 infections after abdominal surgery: a systematic review and meta-analysis. *Langenbecks Arch*
54
55
56
57
58
59
60

- 1
2
3
4 434 *Surg* 2015;400:167-81.
- 5
6 435 25. Yoshioka T, Kondo Y, Fujiwara T. Successful wound treatment using negative pressure wound
7
8 436 therapy without primary closure in a patient undergoing highly contaminated abdominal
9
10 437 surgery. *Surg Case Rep* 2018;4:85.
- 11
12 438 26. Acosta S, Bjorck M, Wanhainen A. Negative-pressure wound therapy for prevention and
13
14 439 treatment of surgical-site infections after vascular surgery. *Br J Surg* 2017;104:e75-e84.
- 15
16 440 27. Kang SI, Oh HK, Kim MH, *et al.* Systematic review and meta-analysis of randomized
17
18 441 controlled trials of the clinical effectiveness of impervious plastic wound protectors in reducing
19
20 442 surgical site infections in patients undergoing abdominal surgery. *Surgery* 2018;
21
22 443 doi:10.1016/j.surg.2018.05.024.
- 23
24 444 28. Mihaljevic AL, Muller TC, Kehl V, *et al.* Wound edge protectors in open abdominal surgery
25
26 445 to reduce surgical site infections: a systematic review and meta-analysis. *PLoS One*.
27
28 446 2015;10:e0121187. doi: 10.1371/journal.pone.. eCollection 2015.
- 29
30 447 29. Reid K, Pockney P, Draganic B, *et al.* Barrier wound protection decreases surgical site infection
31
32 448 in open elective colorectal surgery: a randomized clinical trial. *Dis Colon Rectum*.
33
34 449 2010;53:1374-80. doi: 10.007/DCR.0b013e3181ed3f7e.
- 35
36 450 30. Cheng KP, Roslani AC, Sehha N, *et al.* ALEXIS O-Ring wound retractor vs conventional
37
38 451 wound protection for the prevention of surgical site infections in colorectal resections(1).
39
40 452 *Colorectal Dis* 2012;14:e346-51.
- 41
42 453 31. Alexander M, Perera G, Ford L, *et al.* Age-Stratified Prevalence of Mild Cognitive Impairment
43
44 454 and Dementia in European Populations: A Systematic Review. *J Alzheimers Dis* 2015;48:355-9.
- 45
46 455 32. Mangram AJ, Horan TC, Pearson ML, *et al.* Guideline for Prevention of Surgical Site Infection,
47
48 456 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices
49
50 457 Advisory Committee. *Am J Infect Control*. 1999;27:97-132; quiz 3-4; discussion 96.
- 51
52 458 33. Chan AW, Tetzlaff JM, Gotzsche PC, *et al.* SPIRIT 2013 explanation and elaboration: guidance
53
54 459 for protocols of clinical trials. *Bmj* 2013;346:e7586.

- 1
2
3
4 460 34. Sanger PC, Simianu VV, Gaskill CE, *et al.* Diagnosing Surgical Site Infection Using Wound
5
6 461 Photography: A Scenario-Based Study. *J Am Coll Surg* 2017;224:8-15.e1.
7
8
9 462
10
11
12 463
13
14

15 464 **FIGURE LEGENDS**
16
17

18 465
19
20
21 466 Figure 1. Trial flow
22
23

24 467
25
26
27 468 Figure 2. SPIRIT figure
28
29

30 469 PO = postoperative; SSI = surgical site infection
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

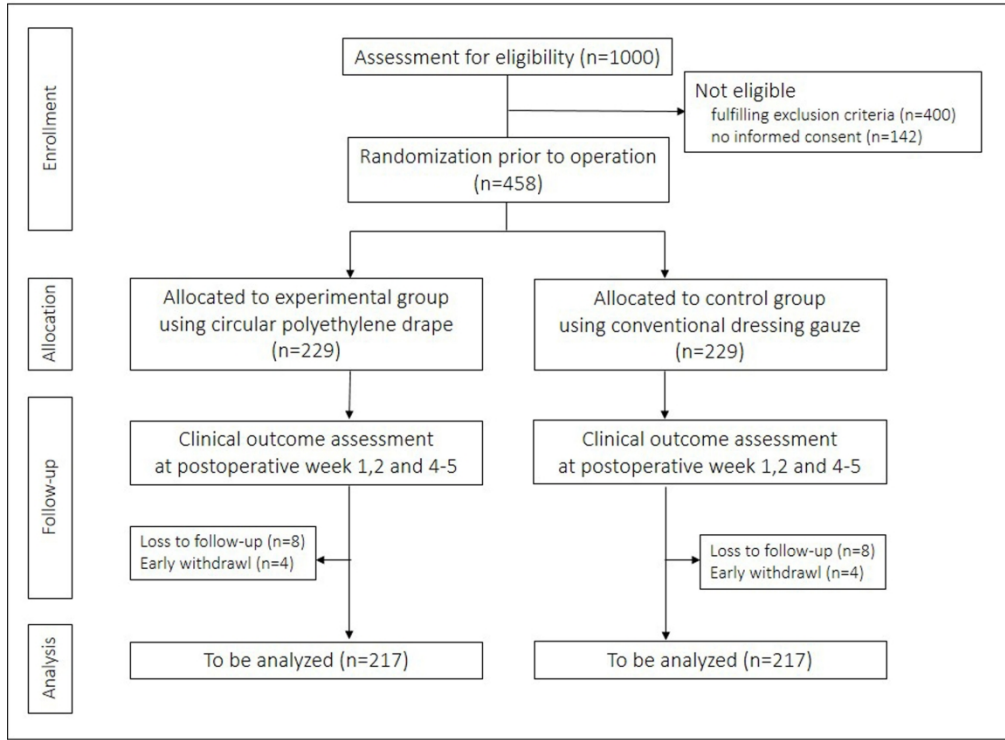


Figure 1. Trial flow

254x190mm (300 x 300 DPI)

TIMEPOINT	STUDY PERIOD						
	Enrolment	Allocation	Post-allocation				Close-out
	-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)



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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	<u>Lines 1–2</u>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	<u>Lines 68, 281-282</u>
	2b	All items from the World Health Organization Trial Registration Data Set	<u>Throughout</u>
Protocol version	3	Date and version identifier	<u>Lines 332-335</u>
Funding	4	Sources and types of financial, material, and other support	<u>Lines 345-349</u>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	<u>Lines 4-21, 337-343</u>
	5b	Name and contact information for the trial sponsor	<u>Lines 345-349</u>
	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	<u>Lines 345-349</u>
	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)	<u>Lines 233-234, 256-257</u>

1 Introduction

2			
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention
5			
6		6b	Explanation for choice of comparators
7			
8	Objectives	7	Specific objectives or hypotheses
9			
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
12			
13			
14	Methods: Participants, interventions, and outcomes		
15			
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will
17			be collected. Reference to where list of study sites can be obtained
18			
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)
21			
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be
23			administered
24		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose
25			change in response to harms, participant request, or improving/worsening disease)
26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence
27			(eg, drug tablet return, laboratory tests)
28		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
29			
30	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood
31			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,
32			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen
33			efficacy and harm outcomes is strongly recommended
34	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for
35			participants. A schematic diagram is highly recommended (see Figure)
36			
37			
38			
39			
40			
41			
42			
43			
44			
45			
46			

1	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	<u>Lines 241-254</u>
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	<u>Lines 140-141</u>
5				
6	Methods: Assignment of interventions (for controlled trials)			
7	Allocation:			
8				
9				
10	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	<u>Lines 173-183</u>
11				
12				
13				
14				
15				
16	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	<u>Lines 176-178</u>
17				
18				
19				
20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	<u>Lines 176-179</u>
21				
22				
23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	<u>Lines 179-183</u>
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	<u>Not applicable</u>
28				
29				
30				
31	Methods: Data collection, management, and analysis			
32				
33	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	<u>Lines 213-234</u>
34				
35				
36				
37				
38				
39		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	<u>Lines 227-231</u>
40				
41				
42				
43				
44				
45				
46				

1	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	<u>Lines 230-234</u>
2				
3				
4				
5	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	<u>Lines 255-264</u>
6				
7				
8				
9				
10		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	<u>Lines 257-258</u>
11				
12		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)	<u>Lines 257-264</u>
13				
14				
15				
16	Methods: Monitoring			
17				
18	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	<u>Lines 233-234</u>
19				
20				
21				
22				
23				
24		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	<u>Lines 169-171</u>
25				
26				
27	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	<u>Lines 236-238</u>
28				
29				
30	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.
31				
32				
33				
34				
35				
36	Ethics and dissemination			
37				
38	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	<u>Lines 275-279</u>
39				
40				
41				
42				
43				
44				
45				
46				

1	Protocol	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).
2	amendments			
3				
4				
5				
6				
7				
8				
9				
10	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	<u>Lines 154-155</u>
11				
12				
13		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	<u>Not applicable</u>
14				
15				
16	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	<u>Lines 124-125, 230-234</u>
17				
18				
19	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	<u>Lines 345-349</u>
20				
21				
22				
23	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	<u>Lines 256-257, 233-234</u>
24				
25				
26	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	<u>Not applicable</u>
27				
28				
29	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	<u>None. The authors plan to publish the results of this trial in scientific journal.</u>
30				
31				
32				
33				
34				
35		31b	Authorship eligibility guidelines and any intended use of professional writers	<u>None</u>
36				
37		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	<u>None</u>
38				
39				

Appendices

1 Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogates	<u>None</u>
4 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	<u>Not applicable</u>

*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

For peer review only

bmjopen-2019-034683 on 22 June 2020. Downloaded from <http://bmjopen.bmj.com/> on April 27, 2024 by guest. Protected by copyright.