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Comparison of olanexidine versus povidone-iodine for preventing surgical site infection in gastrointestinal surgery: study protocol for a multicenter, single-blind, randomized controlled clinical trial

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ABSTRACT

Introduction: Although several guidelines have indicated the efficacy of chlorhexidine and povidone-iodine for reducing the surgical site infection (SSI) rate, the optimal recommendation has still not been established, and the prevalence of SSI remains high in gastrointestinal surgery. Therefore, it is necessary to determine the more effective antiseptic for surgical site preparation. Olanexidine (1.5% Olanedine®, Otsuka Pharmaceutical Factory, Inc., Tokushima, Japan), which is a new antiseptic in Japan, has antimicrobial activity against a wide range of bacteria, including gram-positive bacteria and gram-negative bacteria.

Methods and analysis: We propose a multicenter, single-blind, randomized controlled clinical trial for comparing two treatments, that is, 1.5% olanexidine or 10% povidone-iodine, for surgical skin preparation to prevent SSI in gastrointestinal surgeries with class II surgical wounds. Patients aged ≥20 years at the time of consent will be included. The primary outcome measure is the 30-day postoperative SSI rate. Pearson's chi-square test or Fisher's exact test and Student's t-test will be used in the statistical analyses.

Ethics and dissemination: Participant recruitment began in June 2018. The final results will be published in international peer-reviewed medical journals.

Trial registration number: UMIN 000031560 (https://upload.umin.ac.jp/cgi-open-

bin/ctr_e/ctr_view.cgi?recptno=R000036031)

Article Summary

Strengths and limitations of this study

- This is the first study to evaluate the effect of olanexidine, which has been commercially available since 2015 in Japan.
- To evaluate whether olanexidine or povidone-iodine, the conventional skin antiseptic used in Japan, is useful for preventing surgical site infection (SSI) in gastrointestinal surgery.
- The study design is a multicenter, single-blind, randomized controlled clinical trial.
- The primary outcome measure is the 30-day postoperative SSI rate.

INTRODUCTION

Surgical site infection (SSI) is one of the most common nosocomial infections in surgical patients.[1] Especially, the rate of SSI is higher in gastrointestinal surgery than in other surgeries, such as cardiothoracic surgery, gynecologic surgery, and neurosurgery,[2-4] and it has been reported that 10% to 30% of patients suffer from SSI after gastrointestinal surgery.[5] SSI not only causes prolonged hospitalization and delay of postoperative therapy, but it also causes increased medical costs—$1300-5000 per person for inpatient treatment including antibiotic therapy.[6,7] Therefore, prevention of SSI is extremely important to both the patient and all medical practitioners involved in the surgery.

Many perioperative measures for decreasing SSI have been reported, including enhanced nutritional support, perioperative oxygenation, surgical technique, wound dressing, and use of an antimicrobial agent.[1,8] Surgical site preparation is one of the useful procedures for preventing SSI because microorganisms are removed from the skin. Thus far, two types of preparations, povidone-iodine and chlorhexidine,[9-12] have been commonly used as preoperative antiseptic procedures worldwide. The Centers for Disease Control and Prevention (CDC) guideline just recommends skin preparation with an alcohol-containing agent if there are no contraindications to its use, and other guidelines do not favor one antiseptic agent over another

for skin preparation.[1,13,14] Both preparations have broad-spectrum antibacterial effectiveness; however, chlorhexidine is not effective against some pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA)[15] and vancomycin-resistant enterococci (VRE),[16] of which infection should be avoided. On the other hand, povidone-iodine is known to decrease its activity under the presence of organic materials included blood or pus.[17] Therefore, it is necessary to determine the more effective antiseptic for surgical site preparation.

Olanexidine (1.5% Olanedine®; Otsuka Pharmaceutical Factory, Inc., Tokushima, Japan), which is a new antiseptic, is one of the biguanide bactericidal disinfectants that contains olanexidine gluconate as its active ingredient.[18,19] It has been commercially available since 2015 in Japan. It can disrupt membrane integrity by binding to the cell membrane; this results in irreversible leakage of intracellular components, and its bacteriostatic and fungicidal activities are exerted.[18] Olanexidine has antimicrobial activity against a wide range of bacteria, including gram-positive bacteria and gram-negative bacteria. Moreover, Inoue et al. reported that compared to chlorhexidine and povidone-iodine, olanexidine showed more potent bactericidal activity against MRSA and VRE both in vitro and in vivo.[18] Therefore, the use of olanexidine is highly expected to lead to decreases in the SSI rate. However, to date, no study

has evaluated the effectiveness and safety of olanexidine compared to conventional antiseptics in large-scale clinical trials.

In this multicenter, single-blinded, randomized controlled clinical trial, we aim to evaluate whether olanexidine or povidone-iodine, which is the conventional skin antiseptic used in Japan, is useful for preventing SSI in gastrointestinal surgery. We hypothesize that olanexidine will be more useful for preventing SSI than povidone-iodine without increasing toxicity.

METHODS

Trial design

This trial is a multi-center, prospective, randomized, open-label, blinded-endpoint trial (PROBE) designed to assess the efficacy of 1.5% olanexidine for surgical skin preparation for preventing SSIs in gastrointestinal surgery. The trial was designed and will independently be conducted by Keio University with approval from the ethics committee of Keio University School of Medicine in accordance with the principals of the Declaration of Helsinki. All analyses will be conducted by Keio University, independent of the sponsor, according to the prespecified statistical analysis plan (SAP). As a prospective randomized controlled trial, the study strategy will be constructed and presented in accordance with the recommendations of the CONSORT statement.

Eligibility criteria

Eligible patients are those who meet all of the following inclusion criteria and who do not have any listed exclusion criteria.

- Inclusion criteria

1) Scheduled to undergo elective gastrointestinal surgery involving the esophagus, stomach,

duodenum, small intestine, colorectal, liver, biliary tract, and pancreas that has a class II surgical wound (Figure 1).

2) Age ≥20 years at the time of consent by nonblinded investigators

3) Provision of written informed consent by the patient.

- Exclusion criteria

1) Allergy to olanexidine gluconate or povidone-iodine.

2) Unable to undergo follow-up 30 days postoperatively.

3) Active bacterial infection at the time of informed consent (except for viral hepatitis).

4) Receipt of antimicrobial therapy on the day before surgery.

5) Undergoing non-elective surgery or surgery requiring antisepsis of the mucosal surfaces or surgical wound sites.

6) Unsuitable conditions for safe conduct of this trial according to the nonblinded investigators.

Intervention

Study arm A (experimental group): Surgical skin antisepsis with 1.5% olanexidine is administered just before gastrointestinal surgery.

Study arm B (control group): Surgical skin antisepsis with 10% povidone-iodine is

administered just before gastrointestinal surgery.

Recruitment of study participants

The trial protocol (October/ 24/2018, ver1.3) was approved by each participating institution's institutional review board and registered in the University Hospital Medical Information Network Clinical Trials Registry (number UMIN 000031560). Recruitment into the trial started in May 2018 and will continue until 600 participants are registered. All participants who meet inclusion criteria will be provided with a participant information sheet by investigators before giving written informed consent. This study is being conducted in 4 general centers: Keio University Hospital (Tokyo, Japan), National Tokyo Medical Center (Tokyo, Japan), Tokyo Saiseikai Central Hospital (Tokyo, Japan), and Kawasaki Municipal Hospital (Kanagawa, Japan).

Randomization

Registration and allocation of participants is generated by nonblinded investigators using the CapTool® Lite (Mebix, Inc., Tokyo, Japan). Eligible patients will be randomized to either surgical skin antisepsis with olanexidine (study arm A) or surgical skin antisepsis with

povidone-iodine (study arm B) in a 1:1 replacement ratio. The random sequence will be generated from computer-generated block randomization. We designated the factor of surgical approach (laparoscopy versus laparotomy) as the allocation adjustment factor because of evidence that there is a significantly higher SSI rate in laparotomy than in laparoscopy.[20]

Blinding

Both patients and blinded investigators will be masked to the assigned group. Although there is a difference in color between povidone-iodine and olanexidine, it is feasible for patients to be masked because we wipe the stain of the antiseptic off their skin postoperatively. Nonblinded investigators cannot be masked because he/she will be in the operating room when the antiseptic is used.

A diagnosis of SSI, which is reported by nonblinded investigators, will be verified by chart review, and blinded investigators will verify the diagnosis without knowledge of the group to which the patients were assigned.

Outcome measures

The duration of observation will be 30 days postoperatively. The nonblinded investigators

will observe the surgical wound site daily during admission. After discharge, participants will undergo outpatient observation at least once if it is within 30 days postoperatively. Nonblinded investigators will observe the surgical wound in the same manner as during the hospital stay. We also recommend that patients visit outpatient clinic or an emergency department if there are any symptoms suggestive of SSI such as pain or redness. If SSI is suspected based on the clinical findings, a microbiological culture would be collected using a cotton swab. The diagnosis of SSI will be determined by blinded investigators who will be unaware of the patients' group assignment. The investigator will verify the SSI via chart review by using the questionnaire for SSI provided by the nonblinded investigators in accordance with the CDC guideline. Moreover, blinded investigators will assess the seriousness of all adverse events and determine whether they are related to the study.

(1) Primary outcome measure

Postoperative 30-day SSI rate.

(2) Secondary outcome measures

Postoperative 30-day superficial incisional SSI rate, deep incisional SSI rate, organ/space SSI rate, rate of positive bacterial wound culture, bacterial strains, and rates of toxicity and allergy events (e.g., erythema and symptoms of allergy).

Definitions

SSIs are classified as superficial incisional SSIs, deep incisional SSIs, and organ/space SSIs based on criteria in the CDC guidelines.[1]

(i) Superficial incisional SSI

Superficial incisional SSI must meet the following three criteria (A, B, and C).

A) Infection occurred within 30 days postoperatively.

B) The infection affects only the incision in the skin and the subcutaneous tissue.

C) At least one of the following is applicable:

a. purulent drainage is observed from the superficial incision,

b. organisms are identified from the superficial incision or subcutaneous tissue by a culture or non-culture based microbiologic testing method, and/or

c. the superficial incision is deliberately opened by a nonblinded investigators, and culture or non-culture based testing is not performed.

In addition, at least one of the following symptoms for infection must be applicable: pain, pressure pain, localized swelling, erythema, or fever.

(ii) Deep incisional SSI

Deep incisional SSI must meet the following three criteria (A, B, and C).

A) Infection occurred within 30 days postoperatively.

B) The infection reaches the deep soft tissues of the incision (fascia or muscle layer).

C) At least one of the following is applicable:

a. purulent drainage is observed from the deep incision,

b. the deep incision spontaneously dehisces, or is deliberately opened or aspirated by a nonblinded investigators, and/or

c. an abscess or other evidence of infection is present and involves the deep incision.

In addition, the organism is identified by a culture or non-culture based microbiologic testing method that is performed for purposes of clinical diagnosis or treatment, and symptoms for infection must be applicable: fever, localized pain, or tenderness. Negative finding of a culture does not meet this criterion.

(iii) Organ/space SSI

Organ/space SSI involves any part of the body other than the skin incision, fascia, or muscle layer that has been opened or manipulated during surgery. The specific site is classified as organ/space for the purpose of further identification of the infection site. Organ/space SSI must meet the following three criteria (A, B, and C).

A) Infection occurred within 30 days postoperatively.

B) The infection involves any part of the body that is opened or manipulated during the operative procedure (except for the facial/muscle layers).

C) At least one of the following is applicable:

a. purulent drainage is observed from a drain that is placed into the organ/space,

b. organisms are identified from fluid or tissue in the organ/space by a culture or non-culture based microbiologic testing method, and/or

c. an abscess or other evidence of infection is present and involves the organ/space.

Data collection

All data will be collected and recorded into the web-based electric CRF (CapTool® Lite) by the trial or nonblinded investigators. From the electric CRF, the trial database will be established. Patients' characteristics, such as sex, age, smoking status, comorbidities, such as diabetes mellitus, and steroid use, will be collected.

Data will also be collected regarding the surgical procedures such as the type of surgery, use of laparoscopy, method of wound closure, type of prophylactic antiseptic agent, repeat application of an antiseptic agent, use of sterilized sutures for wound closure, amount of

intraperitoneal irrigation, amounts of wound irrigation and blood loss, and status of excision site into the electric CRF. We will confirm that personal identifying information such as name, medical record ID are deleted from data. Thereafter, a linkable anonymization number is set and stored by a personal information manager for at least 5 years after study completion.

Sample size calculation

In our institution, the estimated proportions of SSI in gastrointestinal surgery with wound class II are 12% after povidone-iodine use and 6% after olanexidine use. Assuming a group difference of 6% during the study period, 281 patients per group would provide a power over 80%, which is sufficient for detecting a difference in the proportion of SSI between olanexidine and povidone-iodine using a one-sided, chi-square test at a 5% level of significance. A dropout rate of about 5% is allowed; thus, with 300 patients required per group, a total sample size of 600 patients is required for the trial.

Statistical analysis

Analyses of the primary and secondary efficacy outcomes will be performed using the full analysis set, which includes all patients who took at least one dose of treatment during the study, did not have any serious violation of the study protocol, and had data collected after treatment commencement. Safety analysis will be conducted in the safety analysis population. For the

baseline variables, summary statistics will be performed using frequencies and proportions for categorical data, and means and standard deviations for continuous variables. Patient characteristics will be compared using Pearson's chi-square test or Fisher's exact test for categorical outcomes and Student's t-test for continuous variables, as appropriate. For the primary analysis, which is aimed at comparing the treatment effects, the adjusted risk ratio and its 95% confidence interval will be estimated using the Mantel-Haenszel method. To test for a significant association of the primary outcome, the Mantel-Haenszel test will be applied after adjusting for allocation factors. All comparisons are planned, and all *p*-values will be two sided. *P*-values <0.05 will be considered statistically significant. All statistical analyses will be performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA). The SAP will be developed by the principal investigator and the biostatistician before completion of patient recruitment and data fixation.

ETHICS AND DISSEMINATION

Participant recruitment began in June 2018. The final results will be published in international peer-reviewed medical journals.

DISCUSSION

Although some guidelines have indicated the efficacy of chlorhexidine and povidone-iodine for reducing the SSI rate, the optimal recommendation has still not been established, and the prevalence of SSI remains high in gastrointestinal surgery. Therefore, a comparative trial between conventional antiseptics including chlorhexidine and povidone-iodine, and newly antiseptics that considers their effectiveness, toxicity, and costs is needed.[8]

We have been conducting a randomized controlled clinical trial to compare olanexidine and povidone-iodine, which is the most popular antiseptic in Japan in terms of prevalence of SSI and toxicity. The strength in this trial is that we adopted a single-blind system for diagnosing SSI in multiple centers. To maintain the quality of practices, only 4 centers, all of which are high-volume centers performing greater than 500 gastrointestinal surgeries per year, are participating in this trial. Furthermore, since the staff in each center belongs to the SSI control committee for providing unified and evidence-based counter measures against SSI in Keio University Hospital, the management of SSI in each center can be performed in almost the same manner.

This study has several limitations. First, this trial is recruiting patients with various types of gastrointestinal surgery, such as esophagectomy, gastrectomy, and cholecystectomy, and there

are differences in the prevalence of SSI according to the type of surgery. However, there is no major bias in allocation because it is randomized. Furthermore, since this is the first report using olanexidine, it is more important to include various types of surgery than limiting the study to a particular type of surgery. Second, this study is limited to a Japanese population, which could introduce an element of selection bias, because olanexidine is only commercially available in Japan.

In conclusion, the present study is assessing the efficacy of olanexidine compared to povidone-iodine for preventing SSI in gastrointestinal surgery. We expect olanexidine to be more useful for preventing SSI than povidone-iodine without increasing toxicity. Even if this expectation is not the predicted result, this trial can provide new knowledge in the aspect of antisepsis for preventing SSI. The result will also contribute to the development of new antisepsis treatment for gastrointestinal surgery.

TRIAL STATUS

As of 25 October 2018, this trial is actively recruiting patents in 3 centers with additional centers planned. Two hundred of the planned 600 participants have been enrolled.

AUTHORS' CONTRIBUTIONS

Masashi Takeuchi and Hideaki Obara contributed equally to this study. All authors made significant contribution to the conception and design of the study protocol. MT designed the study and wrote the protocol and manuscript. The protocol was reviewed by HO, HK, MS, KO, and YK. YS wrote the statistical analysis plan. All authors gave final approval of the manuscript and agree to be accountable for all aspects of the work.

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DISCLAIMER

Otsuka Pharmaceutical Factory, Inc. was not involved in the planning of the protocol or in the conduct of the trial.

COMPETING INTERESTS

YK received grant support from Otsuka Pharmaceutical Factory, Inc.

ETHICS APPROVAL

The protocol was firstly approved by the Institutional Review Board of Keio University School of Medicine, and then approved by the institutional review board of each participating site.

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FIGURE LEGEND

Figure 1

The definition of wound classes.

Figure 1

Wound Class	Definition
Class I (Clean)	An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tracts are not entered.
Class II (Clean-contaminated)	Operative wounds in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions and without unusual contamination.
Class III (Contaminated)	Includes open, fresh, accidental wounds.
Class IV (Dirty-contaminated)	Includes old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera.

Figure 1
The definition of wound classes.

338x190mm (200 x 200 DPI)

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Comparison of olanexidine versus povidone-iodine for preventing surgical site infection in gastrointestinal surgery: study protocol for a multicenter, single-blind, randomized controlled clinical trial

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ABSTRACT

Introduction: The prevalence of surgical site infection (SSI) remains higher in gastrointestinal surgery than in other surgeries. Although several guidelines have indicated the efficacy of chlorhexidine and povidone-iodine in reducing the SSI rate, the optimal recommendation has still not been established. Therefore, it is necessary to determine the more effective antiseptic for surgical site preparation. Olanexidine (1.5% Olanedine®, Otsuka Pharmaceutical Factory, Inc., Tokushima, Japan), which is a new antiseptic in Japan, has antimicrobial activity against a wide range of bacteria, including gram-positive bacteria and gram-negative bacteria. Our study will contribute to determining a new antiseptic for use in gastrointestinal and other surgeries.

Methods and analysis: We propose a multicenter, randomized controlled clinical trial for comparing two treatments, i.e., 1.5% olanexidine or 10% povidone-iodine, for surgical skin preparation to prevent SSI in clean-contaminated gastrointestinal surgeries with surgical wounds. Patients aged ≥20 years at the time of consent will be included. The primary outcome measure is the 30-day postoperative SSI rate. For the primary analysis, which is

aimed at comparing the treatment effects, the adjusted risk ratio and its 95% confidence interval will be estimated using the Mantel-Haenszel method.

Ethics and dissemination: The protocol was first approved by the Institutional Review Board of Keio University School of Medicine, followed by the institutional review board of each participating site. Participant recruitment began in June 2018. The final results will be published in international peer-reviewed medical journals.

Trial registration number: UMIN 000031560 (https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000036031)

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Article Summary

Strengths and limitations of this study

- This is the first study to evaluate the effect of olanexidine, which has been commercially available since 2015 in Japan.
- The study design is a multicenter, single-blind, randomized controlled clinical trial.
- The primary outcome measure is the 30-day postoperative SSI rate.
- This study is limited to a Japanese population, which could introduce an element of selection bias, because olanexidine is only commercially available in Japan.

INTRODUCTION

Surgical site infection (SSI) is one of the most common nosocomial infections in surgical patients.[1] Especially, the rate of SSI is higher in gastrointestinal surgery than in other surgeries, such as cardiothoracic surgery, gynecologic surgery, and neurosurgery,[2-4] and it has been reported that 10% to 30% of patients suffer from SSI after gastrointestinal surgery.[5] SSI not only causes prolonged hospitalization and delay of postoperative therapy, but it also causes increased medical costs—$1300-5000 per person for inpatient treatment including antibiotic therapy.[6,7] Therefore, prevention of SSI is extremely important to both the patient and all medical practitioners involved in the surgery.

Many perioperative measures for decreasing SSI have been reported, including enhanced nutritional support, perioperative oxygenation, surgical technique, wound dressing, and use of an antimicrobial agent.[1,8] Surgical site preparation is one of the useful procedures for preventing SSI because microorganisms are removed from the skin. Thus far, two types of preparations, povidone-iodine and chlorhexidine-alcohol,[9-12] have been commonly used as preoperative antiseptic procedures worldwide. The Centers for Disease Control and Prevention (CDC) guideline just recommends skin preparation with an alcohol-containing

agent if there are no contraindications to its use, and other guidelines do not favor one antiseptic agent over another for skin preparation.[1,13,14] Both preparations have broad-spectrum antibacterial effectiveness; however, povidone-iodine is known to decrease its activity under the presence of organic materials including blood or pus.[15] On the other hand, chlorhexidine-alcohol has high antibacterial activity against some pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA)[15] and vancomycin-resistant enterococci (VRE); nevertheless, it is associated with inflammability, more expensive than povidone-iodine, and has been linked to allergic reactions.[16,17] Therefore, it is necessary to determine the more effective antiseptic for surgical site preparation.

Olanexidine (1.5% Olanedine®; Otsuka Pharmaceutical Factory, Inc., Tokushima, Japan), which is a new antiseptic, is one of the biguanide bactericidal disinfectants that contains olanexidine gluconate as its active ingredient.[18,19] It has been commercially available since 2015 in Japan. It can disrupt membrane integrity by binding to the cell membrane; this results in irreversible leakage of intracellular components, and its bactericidal and fungicidal activities are exerted.[18] Olanexidine has antimicrobial activity against a wide range of bacteria, including gram-positive bacteria and gram-negative bacteria. Moreover, Inoue et al. reported that compared to chlorhexidine-alcohol and povidone-iodine, olanexidine showed

more potent bactericidal activity against MRSA and VRE both in vitro and in vivo.[18] Therefore, the use of olanexidine is highly expected to lead to decreases in the SSI rate. However, to date, no study has evaluated the effectiveness and safety of olanexidine compared to conventional antiseptics in large-scale clinical trials.

In this multicenter, randomized controlled clinical trial, we aim to evaluate whether olanexidine or povidone-iodine, which is the conventional skin antiseptic used in Japan, is useful for preventing SSI in gastrointestinal surgery. We hypothesize that olanexidine will be more useful for preventing SSI than povidone-iodine without increasing toxicity.

METHODS

Trial design

This trial is a multi-center, prospective, randomized, blinded-endpoint trial (PROBE) designed to assess the efficacy of 1.5% olanexidine for surgical skin preparation for preventing SSIs in gastrointestinal surgery. The trial was designed and will independently be conducted by Keio University with approval from the ethics committee of Keio University School of Medicine in accordance with the principals of the Declaration of Helsinki. All analyses will be conducted by Keio University, independent of the sponsor, according to the prespecified statistical analysis plan (SAP). As a prospective randomized controlled trial, the study strategy will be constructed and presented in accordance with the recommendations of the SPIRIT statement.

Eligibility criteria

Eligible patients are those who meet all of the following inclusion criteria and who do not have any listed exclusion criteria.

- Inclusion criteria

1) Scheduled to undergo elective gastrointestinal surgery involving the esophagus, stomach, duodenum, small intestine, colorectal, liver, biliary tract, and pancreas that has a class II surgical wound (Table 1).

2) Age ≥20 years at the time of consent by non-blinded investigators.

3) Provision of written informed consent by the patient.

- Exclusion criteria

1) Allergy to olanexidine gluconate or povidone-iodine.

2) Unable to undergo follow-up 30 days postoperatively.

3) Active bacterial infection at the time of informed consent (except for viral hepatitis).

4) Antimicrobial therapy on the day before surgery.

5) Undergoing non-elective surgery or surgery requiring antisepsis of the mucosal surfaces or surgical wound sites.

6) Unsuitable conditions for safe conduct of this trial according to the non-blinded investigators.

Intervention

Study arm A (experimental group): Surgical skin antisepsis with an aqueous formulation of

1.5% olanexidine is administered just before gastrointestinal surgery.

Study arm B (control group): Surgical skin antisepsis with an aqueous formulation of 10% povidone-iodine is administered just before gastrointestinal surgery.

Treatment protocol

The antisepsis should be applied widely in consideration of the drain site and length of the skin incision. We apply agents from the papilla (in cases of esophageal surgery; the neck) with a cranial limit and to the upper thigh with a caudal limit. After waiting 3 minutes to allow the antiseptics to dry, the operation is started. In study arm A, one olanexidine applicator will be used in surgery; however, if surgeons determine that disinfection is inadequate, an additional applicator can be added.

We used other measures to prevent SSI in our protocol as follows:

(1) Administer standard antibiotic prophylaxis before making the surgical incision,

(2) use absorbable sutures for wound closure and recommend the use of antimicrobial-coated sutures,

(3) recommend the use of a wound protector,

(4) recommend wound irrigation,

(5) use any type of immunosuppressive agent,

(6) change or retain the same gloves during the operation, and

(7) change or retain the surgical instruments.

Furthermore, we always maintain a normal body temperature by using warming devices during surgery, and do not perform hair removal before surgery.

Recruitment of study participants

The trial protocol (October 24, 2018, version 1.3) was approved by each participating institution's institutional review board and registered in the University Hospital Medical Information Network Clinical Trials Registry (number UMIN 000031560). Recruitment into the trial started in June 2018 and will continue until 600 participants are registered. All participants who meet the inclusion criteria will receive a participant information sheet from investigators before giving written informed consent. This study is being conducted in 4 general centers: Keio University Hospital (Tokyo, Japan), National Hospital Organization Tokyo Medical Center (Tokyo, Japan), Tokyo Saiseikai Central Hospital (Tokyo, Japan), and Kawasaki Municipal Hospital (Kanagawa, Japan).

Randomization

Registration and allocation of participants are generated by non-blinded investigators using the CapTool® Lite (Mebix, Inc., Tokyo, Japan). Eligible patients will be randomized to either surgical skin antisepsis with olanexidine (study arm A) or surgical skin antisepsis with povidone-iodine (study arm B) in a 1:1 replacement ratio. The random sequence will be generated from computer-generated block randomization. We designated the factor of surgical approach (laparoscopy versus laparotomy) as the allocation adjustment factor because of evidence that there is a significantly higher SSI rate in laparotomy than in laparoscopy.[20]

Blinding

Both patients and investigators will be blinded to the assigned group. Although there is a difference in color between povidone-iodine and olanexidine, it is feasible for patients to be masked because we wipe the stain of the antiseptic off their skin postoperatively. Non-blinded investigators cannot be masked because they will be in the operating room when the antiseptic is used.

Non-blinded investigators will answer the questionnaire about the wound condition; however, they do not diagnose the presence or absence of SSI. SSIs are diagnosed by investigators who

are blinded to the group allocation with reference to the questionnaire. Blinded investigators perform data entry for diagnosis of SSI, and the data analyst is blinded.

Trial visits

Generally, patients are hospitalized 1 to 4 days before surgery. We obtain informed consent and patients' background characteristics after admission. Informed consent for the operation and clinical trial is routinely obtained on the day before surgery. Thus, randomization is mainly performed on the day before surgery. The duration of observation will be 30 days postoperatively. The schedule for the trial visits and data collection is summarized in Table 2.

Outcome measures

The non-blinded investigators will observe the surgical wound site daily during admission. After discharge, participants will undergo outpatient observation at least once if it is within 30 days postoperatively. Non-blinded investigators will observe the surgical wound in the same manner as during the hospital stay. We also recommend that patients visit the outpatient clinic or an emergency department if there are any symptoms suggestive of SSI such as pain or redness. If SSI is suspected based on the clinical findings, a microbiological culture would

be collected using a cotton swab. The diagnosis of SSI will be determined by blinded investigators who will be unaware of the patients' group assignment. The investigator will verify the SSI via chart review by using the questionnaire for SSI provided by the non-blinded investigators in accordance with the CDC guideline. Moreover, blinded investigators will assess the seriousness of all adverse events and determine whether they are related to the study.

(1) Primary outcome measure

Postoperative 30-day SSI rate.

(2) Secondary outcome measures

Postoperative 30-day superficial incisional SSI rate, deep incisional SSI rate, organ/space SSI rate, rate of positive bacterial wound culture, bacterial strains, and rates of intervention-related toxicity and allergy events (e.g., erythema, pruritus, dermatitis, and other symptoms of allergy around the region disinfected by the antiseptic during surgery).

Definitions

SSIs are classified as superficial incisional SSIs, deep incisional SSIs, and organ/space SSIs based on criteria in the CDC guidelines (Supplemental Table 1).[1]

Data collection

All data will be collected and recorded into the web-based electric CRF (CapTool® Lite) by the trial or non-blinded investigators. From the electric CRF, the trial database will be established. Patients' characteristics, such as sex, age, smoking status, body mass index, the use of prophylactic antibiotics, mode of skin closure, comorbidities, such as diabetes mellitus, and steroid use, will be collected.

Data will also be collected regarding the surgical procedures such as the type of surgery, use of laparoscopy, method of wound closure, type of prophylactic antiseptic agent, repeat application of an antiseptic agent, use of sterilized sutures for wound closure, amount of intraperitoneal irrigation, amounts of wound irrigation and blood loss, and status of excision site into the electric CRF. We will confirm that personal identifying information such as patients' name and medical record identification are deleted from the data. Thereafter, a linkable anonymized number is set and stored by a personal information manager for at least 5 years after study completion.

Data monitoring

Central monitoring will be conducted with the aim of ensuring that the trials are conducted safely and in accordance with the implementation plan, and that the data collection is correct. It is conducted once a year, with 10% of registration completed in each institution. The number of consents acquired, number of patients registered, number of patients who withdraw or are loss to follow-up and their reasons, safety, compliance with eligibility criteria and exclusion criteria, accuracy of the allocation procedure, and compliance with various regulations and research plan are all evaluated by test secretariat.

Sample size calculation

In our institution, the estimated proportions of SSI in gastrointestinal surgery with wound class II are 12% (this rate was only included in a non-published Japanese report) after povidone-iodine use and 6% after olanexidine use. Assuming a group difference of 6% during the study period, 281 patients per group would provide a power over 80%, which is sufficient for detecting a difference in the proportion of SSI between olanexidine and povidone-iodine using a one-sided, chi-square test at a 5% level of significance. A dropout rate of about 5% is allowed; thus, with 300 patients required per group, a total sample size of 600 patients is required for the trial.

Patient and Public Involvement

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

Statistical analysis

We will perform the primary analyses using the full analysis set, from which patients who do not undergo surgery or who withdraw consent before assessment of the primary endpoint are excluded. In addition, we will repeat the analyses in the per-protocol set, further excluding patients with major protocol deviations. The safety analysis set will include all patients who were randomly assigned to a study group and received treatment during the study. For the baseline variables, summary statistics will be performed using frequencies and proportions for categorical data, and means and standard deviations for continuous variables. Patient characteristics will be compared using Pearson's chi-square test or Fisher's exact test for categorical outcomes and Student's t-test for continuous variables, as appropriate. For the primary analysis, which is aimed at comparing the treatment effects, the adjusted risk ratio and its 95% confidence interval will be estimated using the Mantel-Haenszel method. To test for a significant association of the primary outcome, the Mantel-Haenszel test will be applied after adjusting for allocation factors. All comparisons are planned, and all *p*-values will be two sided. *P*-values <0.05 will be considered statistically significant. All statistical analyses will be performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA). The SAP will be developed by the principal investigator and the biostatistician before completion of patient recruitment and data fixation.

ETHICS AND DISSEMINATION

Participant recruitment began in June 2018. The final results will be published in international peer-reviewed medical journals.

DISCUSSION

Although some guidelines have indicated the efficacy of chlorhexidine-alcohol and povidone-iodine for reducing the SSI rate, the optimal recommendation has still not been established, and the prevalence of SSI remains high in gastrointestinal surgery. Therefore, a comparative trial between conventional antiseptics, including chlorhexidine-alcohol and povidone-iodine, and newly antiseptics that considers their effectiveness, toxicity, and costs is needed.[8]

We have been conducting a randomized controlled clinical trial to compare olanexidine and povidone-iodine, which is the most popular antiseptic in Japan in terms of prevalence of SSI and toxicity. The strength in this trial is that we adopted blinding for diagnosing SSI in multiple centers. To maintain the quality of practices, only 4 centers, all of which are high-volume centers performing greater than 500 gastrointestinal surgeries per year, are participating in this trial. Furthermore, since the staff in each center belongs to the SSI control committee for providing unified and evidence-based counter measures against SSI in Keio University Hospital, the management of SSI in each center can be performed in almost the same manner.

In this study, we adopted povidone-iodine instead of chlorhexidine-alcohol as a control. Since inflammability is associated with chlorhexidine-alcohol, povidone-iodine is recommended and typically used for gastrointestinal surgery in Japan. In addition, chlorhexidine-alcohol with concentrations greater than 1% are not commercially available in Japan, although a concentration greater than 2% is recognized as having a bactericidal effect in international guidelines.[21-23] Moreover, considering the influence of ethnic differences including intrinsic and extrinsic ethnic factors, this comparison is a meaningful examination of SSI treatment at least in Japan. Therefore, we think that the selection of a control group is reasonable.

Although antisepsis would influence only superficial and deep SSIs, we included organ-space SSI in the endpoint. As described earlier, this is the first study to use olanexidine; therefore, it is more important to establish evidence for all types of SSI than limiting the study to superficial and deep wound infections. Some studies have investigated skin antisepsis in gastrointestinal surgery and included organ SSI as an outcome.[11,12]

This study has several limitations. First, this trial is recruiting patients with various types of gastrointestinal surgery, such as esophagectomy, gastrectomy, and cholecystectomy, and there are differences in the prevalence of SSI according to the type of surgery. However,

there is no major bias in allocation because it is randomized. Furthermore, since this is the first report using olanexidine, it is more important to include various types of surgery than limiting the study to a particular type of surgery. Second, this study is limited to a Japanese population, which could introduce an element of selection bias, because olanexidine is only commercially available in Japan.

In conclusion, the present study is assessing the efficacy of olanexidine compared to povidone-iodine for preventing SSI in gastrointestinal surgery. We expect olanexidine to be more effective for preventing SSI than povidone-iodine without increasing toxicity. In the future, we should also consider conducting another trial that compares olanexidine to an alcohol-based antiseptic agent, if superiority of olanexidine compared to povidone-iodine is proven in this trial. Even if this expectation is not the predicted result, this trial can provide new knowledge in the aspect of antisepsis for preventing SSI. The result will also contribute to the development of new antisepsis treatment for gastrointestinal surgery.

TRIAL STATUS

As of 25 October 2018, this trial is actively recruiting patents in 3 centers with additional centers planned. Two hundred of the planned 600 participants have been enrolled.

AUTHORS' CONTRIBUTIONS

Masashi Takeuchi and Hideaki Obara contributed equally to this study. All authors made significant contribution to the conception and design of the study protocol. MT designed the study and wrote the protocol and manuscript. SM, TI, KF, RN, NW, MK, HY, YA, GO, SH, MT, TI, TY, KH, YI, YS, HH, YM, MS, and TK assisted with the development of the study design and protocol. The protocol was reviewed by HO, HK, MS, KO, and YK. YS wrote the statistical analysis plan. All authors gave final approval of the manuscript and agree to be accountable for all aspects of the work.

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DISCLAIMER

Otsuka Pharmaceutical Factory, Inc. was not involved in the planning of the protocol or in the conduct of the trial.

COMPETING INTERESTS

YK received grant support from Otsuka Pharmaceutical Factory, Inc.

ETHICS APPROVAL

The protocol was firstly approved by the Institutional Review Board of Keio University School of Medicine, and then approved by the institutional review board of each participating site.

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Table 1 The definition of wound classes

Wound Class	Definition
Class I (Clean)	An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tracts are not entered.
Class II (Clean-contaminated)	Operative wounds in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions and without unusual contamination.
Class III (Contaminated)	Includes open, fresh, and accidental wounds.
Class IV (Dirty-contaminated)	Includes old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera.

Table 2 Flow chart of the trial

Time point	After admission	Before surgery	Surgery	After surgery
Informed consent	□			
Patients' background characteristics	□			
Physical examination	□			
Randomization		□		
Intervention			□	
Observation of the surgical site				□a

□a: From postoperative day 1 to postoperative day 30 (outpatient observation is performed at least once if the discharge is within 30 days postoperatively)

Supplemental Table1 Definitions of SSI

Type of SSI	Definition
Superficial incisional SSI	Superficial incisional SSI must meet the following three criteria (A, B, and C). A) Infection occurred within 30 days postoperatively. B) The infection affects only the incision in the skin and the subcutaneous tissue. C) At least one of the following is applicable: a. purulent drainage is observed from the superficial incision, b. organisms are identified from the superficial incision or subcutaneous tissue by a culture or non-culture based microbiologic testing method, and/or c. the superficial incision is deliberately opened by a nonblinded investigators, and culture or non-culture based testing is not performed. In addition, at least one of the following symptoms for infection must be applicable: pain, tenderness, localized swelling, erythema, or heat.
Deep incisional SSI	Deep incisional SSI must meet the following three criteria (A, B, and C). A) Infection occurred within 30 days postoperatively. B) The infection reaches the deep soft tissues of the incision (fascia or muscle layer). C) At least one of the following is applicable: a. purulent drainage is observed from the deep incision, b. the deep incision spontaneously dehisces, or is deliberately opened or aspirated by a nonblinded investigators, and/or

	c. an abscess or other evidence of infection is present and involves the deep incision. In addition, the organism is identified by a culture or non-culture based microbiologic testing method that is performed for purposes of clinical diagnosis or treatment, and symptoms for infection must be applicable: fever, localized pain, or tenderness. Negative finding of a culture does not meet this criterion.
Organ/space SSI	Organ/space SSI involves any part of the body other than the skin incision, fascia, or muscle layer that has been opened or manipulated during surgery. The specific site is classified as organ/space for the purpose of further identification of the infection site. Organ/space SSI must meet the following three criteria (A, B, and C). A) Infection occurred within 30 days postoperatively. B) The infection involves any part of the body that is opened or manipulated during the operative procedure (except for the facial/muscle layers). C) At least one of the following is applicable: a. purulent drainage is observed from a drain that is placed into the organ/space, b. organisms are identified from fluid or tissue in the organ/space by a culture or non-culture based microbiologic testing method, and/or c. an abscess or other evidence of infection is present and involves the organ/space.

*Erythema; the skin redness of the skin that spreads away from the incision site, localized swelling; a bulge limited to the incision site, tenderness; pressured pain beyond normal for the operation.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	ItemNo (Page No)	Description
Administrative information		
Title	1(p1)	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a (p4)	Trial identifier and registry name. If not yet registered, name of intended registry
	2b (n/a)	All items from the World Health Organization Trial Registration Data Set
Protocol version	3 (p12)	Date and version identifier
Funding	4 (p24)	Sources and types of financial, material, and other support
Roles and responsibilities	5a (p24)	Names, affiliations, and roles of protocol contributors
	5b (p2)	Name and contact information for the trial sponsor
	5c (n/a)	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
	5d (n/a)	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)
Introduction		
Background and rationale	6a (p6-8)	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
	6b (p6-8)	Explanation for choice of comparators

Objectives	7 (p6-8)	Specific objectives or hypotheses
Trial design	8 (p6-8)	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
Methods: Participants, interventions, and outcomes		
Study setting	9 (p12)	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
Eligibility criteria	10 (p9)	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a (p10)	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b (p10)	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)
	11c (n/a)	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d (p10)	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12 (p14)	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
Participant timeline	13 (p14)	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14 (p17)	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15 (p12)	Strategies for achieving adequate participant enrolment to reach target sample size
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a (p12)	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
Allocation concealment mechanism	16b (p14)	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
Implementation	16c (p12)	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a (p13)	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b (n/a)	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a (p16)	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
	18b (p16)	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
Data management	19 (p16)	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
Statistical methods	20a (p17)	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
	20b (p17)	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c (p17)	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring

Data monitoring	21a (p16)	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
	21b (p16)	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
Harms	22 (n/a)	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23 (n/a)	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24 (p19)	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25 (n/a)	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)
Consent or assent	26a (p12)	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b (n/a)	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27 (p15)	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
Declaration of interests	28 (p24)	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29 (n/a)	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30 (n/a)	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

Dissemination policy	31a (n/a)	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b (p24)	Authorship eligibility guidelines and any intended use of professional writers
	31c (n/a)	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32 (n/a)	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33 (n/a)	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

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

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Comparison of olanexidine versus povidone-iodine for preventing surgical site infection in gastrointestinal surgery: study protocol for a multicenter, single-blind, randomized controlled clinical trial

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Comparison of olanexidine versus povidone-iodine for preventing surgical site infection in gastrointestinal surgery: study protocol for a multicenter, single-blind, randomized controlled clinical trial

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ABSTRACT

Introduction: The prevalence of surgical site infection (SSI) remains higher in gastrointestinal surgery than in other surgeries. Although several guidelines have indicated the efficacy of chlorhexidine and povidone-iodine in reducing the SSI rate, the optimal recommendation has still not been established. Therefore, it is necessary to determine the more effective antiseptic for surgical site preparation. Olanexidine (1.5% Olanedine®, Otsuka Pharmaceutical Factory, Inc., Tokushima, Japan), which is a new antiseptic in Japan, has antimicrobial activity against a wide range of bacteria, including gram-positive and gram-negative bacteria. Our study will contribute to determining a new antiseptic for use in gastrointestinal and other surgeries.

Methods and analysis: We propose a multicenter, randomized controlled clinical trial for comparing two treatments, i.e., 1.5% olanexidine or 10% povidone-iodine, for surgical skin preparation to prevent SSI in clean-contaminated gastrointestinal surgeries with surgical wounds. Patients aged ≥20 years at the time of consent will be included. The primary outcome measure is the 30-day postoperative SSI rate. For the primary analysis, which is

aimed at comparing the treatment effects, the adjusted risk ratio and its 95% confidence interval will be estimated using the Mantel-Haenszel method.

Ethics and dissemination: The protocol was first approved by the Institutional Review Board of Keio University School of Medicine, followed by the institutional review board of each participating site. Participant recruitment began in June 2018. The final results will be published in international peer-reviewed medical journals.

Trial registration number: UMIN 000031560 (https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000036031)

5

Article Summary

Strengths and limitations of this study

- This is the first study to evaluate the effect of olanexidine, which has been commercially available in Japan since 2015.
- The study design is a multicenter, single-blind, randomized controlled clinical trial.
- The primary outcome measure is the 30-day postoperative SSI rate.
- This study is limited to a Japanese population, which could introduce an element of selection bias, because olanexidine is only commercially available in Japan.

INTRODUCTION

Surgical site infection (SSI) is one of the most common nosocomial infections in surgical patients.[1] The rate of SSI in gastrointestinal surgery in particular is higher than in other surgeries, such as cardiothoracic surgery, gynecologic surgery, and neurosurgery,[2-4] and it has been reported that 10% to 30% of patients suffer from SSI after gastrointestinal surgery.[5] SSI not only causes prolonged hospitalization and delay of postoperative therapy, but increased medical costs of $1300-5000 per person for inpatient treatment, including antibiotic therapy.[6,7] Therefore, prevention of SSI is extremely important for both the patient and all medical practitioners involved in the surgery.

Many perioperative measures for decreasing SSI have been reported, including enhanced nutritional support, perioperative oxygenation, surgical technique, wound dressing, and use of an antimicrobial agent.[1,8] Surgical site preparation is useful for preventing SSI because it can remove microorganisms from the skin. Thus far, two types of preparations, povidone-iodine and chlorhexidine-alcohol,[9-12] have been commonly used as preoperative antiseptic procedures worldwide. The Centers for Disease Control and Prevention (CDC) guideline only recommends skin preparation with an alcohol-containing agent if there are no

contraindications to its use, and other guidelines do not favor one antiseptic agent over another for skin preparation.[1,13,14] Both preparations have broad-spectrum antibacterial effectiveness; however, povidone-iodine's activity is known to decrease in the presence of organic materials including blood or pus.[15] In contrast, chlorhexidine-alcohol has high antibacterial activity against some pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA)[15] and vancomycin-resistant enterococci (VRE); nevertheless, it is associated with inflammability, is more expensive than povidone-iodine, and has been linked to allergic reactions.[16,17] Therefore, it is necessary to determine the more effective antiseptic for surgical site preparation.

Olanexidine (1.5% Olanedine®; Otsuka Pharmaceutical Factory, Inc., Tokushima, Japan), which is a new antiseptic, is one of the biguanide bactericidal disinfectants that contains olanexidine gluconate as its active ingredient.[18,19] It has been commercially available in Japan since 2015. It can disrupt membrane integrity by binding to the cell membrane resulting in irreversible leakage of intracellular components, which is the mechanism underlying its bactericidal and fungicidal activities.[18] Olanexidine has antimicrobial activity against a wide range of bacteria, including gram-positive and gram-negative bacteria. Moreover, Inoue et al. reported that compared to chlorhexidine-alcohol and povidone-iodine, olanexidine showed

more potent bactericidal activity against MRSA and VRE both in vitro and in vivo.[18] Therefore, the use of olanexidine is highly expected to lead to decreases in the SSI rate. However, to date, no study has evaluated the effectiveness and safety of olanexidine compared to conventional antiseptics in large-scale clinical trials.

In this multicenter, randomized controlled clinical trial, we aim to evaluate whether olanexidine or povidone-iodine, which is the conventional skin antiseptic used in Japan, is useful for preventing SSI in gastrointestinal surgery. We hypothesize that olanexidine will be more useful for preventing SSI than povidone-iodine without increasing toxicity.

METHODS

Trial design

This is a multi-center, prospective, randomized, blinded-endpoint trial (PROBE) designed to assess the efficacy of 1.5% olanexidine for surgical skin preparation for preventing SSIs in gastrointestinal surgery. The trial was designed and will be independently conducted by Keio University with approval from the ethics committee of Keio University School of Medicine in accordance with the principals of the Declaration of Helsinki. All analyses will be conducted by Keio University, independent of the sponsor, according to the prespecified statistical analysis plan (SAP). As a prospective randomized controlled trial, the study strategy will be constructed and presented in accordance with the recommendations of the SPIRIT statement.

Eligibility criteria

Eligible patients are those who meet all of the following inclusion criteria and who do not have any listed exclusion criteria.

- Inclusion criteria

1) Scheduled to undergo elective gastrointestinal surgery involving the esophagus, stomach, duodenum, small intestine, colorectal, liver, biliary tract, and pancreas that has a class II surgical wound (Table 1).

2) Age ≥20 years at the time of consent by non-blinded investigators.

3) Provision of written informed consent by the patient.

- Exclusion criteria

1) Allergy to olanexidine gluconate or povidone-iodine.

2) Unable to undergo follow-up 30 days postoperatively.

3) Active bacterial infection at the time of informed consent (except for viral hepatitis).

4) Antimicrobial therapy on the day before surgery.

5) Undergoing non-elective surgery or surgery requiring antisepsis of the mucosal surfaces or surgical wound sites.

6) Unsuitable conditions for safe conduct of this trial according to the non-blinded investigators.

Intervention

Study arm A (experimental group): Surgical skin antisepsis with an aqueous formulation of

1.5% olanexidine is administered immediately before gastrointestinal surgery.

Study arm B (control group): Surgical skin antisepsis with an aqueous formulation of 10% povidone-iodine is administered immediately before gastrointestinal surgery.

Treatment protocol

The antisepsis should be applied widely in consideration of the drain site and length of the skin incision. We apply agents from the papilla (in cases of esophageal surgery; the neck) with a cranial limit and to the upper thigh with a caudal limit. The duration of application of both antiseptics is at least 1 minute. After waiting 3 minutes to allow the antiseptics to dry, the operation is started. Olanexidine is administered by ready-to-use applicators. One olanexidine applicator will be used in surgery; however, if surgeons determine that disinfection is inadequate, an additional applicator can be added. Povidone-iodine is administered by a brush or by compression using pliers.

We used other measures to prevent SSI in our protocol as follows:

(1) Administering standard antibiotic prophylaxis before making the surgical incision

(2) Using absorbable sutures for wound closure and recommending the use of antimicrobial-coated sutures

(3) Recommending the use of a wound protector [The types used are the Alexis® wound protector (Medical Leaders Co. Ltd, Japan) or the lap protector (HAKKO Co. Ltd, Japan), which are used without anti-infective agents]

(4) Recommending wound irrigation with sterile normal saline

(5) Not restricting the type of immunosuppressive agent that can be used

(6) Changing or maintaining the same gloves during the operation

(7) Changing or maintaining the surgical instruments

Furthermore, we always maintain a normal body temperature by using warming devices during surgery, and do not perform preoperative hair removal.

Recruitment of study participants

The trial protocol (October 24, 2018, version 1.3) was approved by each participating institution's institutional review board and registered in the University Hospital Medical Information Network Clinical Trials Registry (number UMIN 000031560). Recruitment into the trial started in June 2018 and will continue until 600 participants are registered. All participants who meet the inclusion criteria will receive a participant information sheet from investigators before giving written informed consent. This study is being conducted at 4

general centers: Keio University Hospital (Tokyo, Japan), National Hospital Organization Tokyo Medical Center (Tokyo, Japan), Tokyo Saiseikai Central Hospital (Tokyo, Japan), and Kawasaki Municipal Hospital (Kanagawa, Japan).

Randomization

Registration and allocation of participants is performed by non-blinded investigators using the CapTool® Lite (Mebix Inc., Tokyo, Japan). Eligible patients will be randomized to either surgical skin antisepsis with olanexidine (study arm A) or surgical skin antisepsis with povidone-iodine (study arm B) in a 1:1 replacement ratio. The random sequence will be generated from computer-generated block randomization. We designated the factor of surgical approach (laparoscopy versus laparotomy) as the allocation adjustment factor because of evidence that there is a significantly higher SSI rate in laparotomy than in laparoscopy.[20]

Blinding

Both patients and investigators will be blinded to the assigned group. Although there is a difference in color between povidone-iodine and olanexidine, it is feasible for patients to be

masked because we wipe the stain of the antiseptic off their skin postoperatively. Non-blinded investigators cannot be masked because they will be in the operating room when the antiseptic is used.

Non-blinded investigators will answer the questionnaire about the wound condition; however, they do not diagnose the presence or absence of SSI. SSIs are diagnosed by investigators who are blinded to the group allocation with reference to the questionnaire. Blinded investigators perform data entry for diagnosis of SSI, and the data analyst is blinded.

Trial visits

Generally, patients are hospitalized 1 to 4 days before surgery. We obtain informed consent and record the patients' background characteristics after admission. Informed consent for the operation and clinical trial is routinely obtained on the day before surgery. Thus, randomization is mainly performed on the day before surgery. The duration of observation will be 30 days postoperatively. The schedule for the trial visits and data collection is summarized in Table 2.

Outcome measures

The non-blinded investigators will observe the surgical wound site daily during admission. After discharge, participants will undergo outpatient observation at least once if it is within 30 days postoperatively. Non-blinded investigators will observe the surgical wound in the same manner as during the hospital stay. We also recommend that patients visit the outpatient clinic or an emergency department if there are any symptoms suggestive of SSI such as pain or redness. If SSI is suspected based on the clinical findings, a microbiological culture would be collected using a cotton swab. The diagnosis of SSI will be determined by blinded investigators who will be unaware of the patients' group assignment. The investigator will verify the SSI via chart review by using the questionnaire for SSI provided by the non-blinded investigators in accordance with the CDC guideline. Moreover, blinded investigators will assess the seriousness of all adverse events and determine whether they are related to the study.

(1) Primary outcome measure

Postoperative 30-day SSI rate

(2) Secondary outcome measures

Postoperative 30-day superficial incisional SSI rate, deep incisional SSI rate, organ/space SSI rate, positive bacterial wound culture rate, bacterial strains, and rates of intervention-related

toxicity and allergic events (e.g., erythema, pruritus, dermatitis, and other symptoms of allergy around the region disinfected by the antiseptic during surgery).

Definitions

SSIs are classified as superficial incisional, deep incisional, and organ/space based on criteria in the CDC guidelines (Supplemental Table 1).[1]

Data collection

All data will be collected and recorded into the web-based electric case report form (CRF; CapTool® Lite) by the trial or non-blinded investigators. From the electric CRF, the trial database will be established. Patients' characteristics, such as sex, age, smoking status, body mass index, the use of prophylactic antibiotics, mode of skin closure, comorbidities, such as diabetes mellitus, and steroid use, will be collected.

Data will also be collected regarding the surgical procedures such as the type of surgery, use of laparoscopy, method of wound closure, type of prophylactic antiseptic agent, repeat application of an antiseptic agent, use of sterilized sutures for wound closure, amount of intraperitoneal irrigation, amounts of wound irrigation and blood loss, and status of excision

site, and recorded in the electric CRF. We will confirm that personal identifying information such as patient names and medical record identification are deleted from the data. Thereafter, a linkable anonymized number is set and stored by a personal information manager for at least 5 years after study completion.

Data monitoring

Central monitoring will be conducted with the aim of ensuring that the trials are conducted safely and in accordance with the implementation plan, and that the data collection is performed correctly. It is conducted once a year, with 10% of registration completed in each institution. The number of consents acquired, number of patients registered, number of patients who withdraw or are lost to follow-up and their reasons, safety, compliance with eligibility criteria and exclusion criteria, accuracy of the allocation procedure, and compliance with various regulations and research plan are all evaluated by the test secretariat.

Sample size calculation

At our institution, the estimated rate of SSI after gastrointestinal surgery with wound class II is 12% (this rate was only included in a non-published Japanese report) after povidone-iodine

use and 6% after olanexidine use. Assuming a group difference of 6% during the study period, 281 patients per group would provide a power of over 80%, which is sufficient for detecting a difference in the proportion of SSI between olanexidine and povidone-iodine using a one-sided chi-square test at a 5% level of significance. A dropout rate of about 5% is allowed; thus, with 300 patients required per group, a total sample size of 600 patients is required for the trial.

Patient and Public Involvement

The patients and the public were not involved in the design of this study.

Statistical analysis

We will perform the primary analyses using the full analysis set, from which patients who do not undergo surgery or who withdraw consent before assessment of the primary endpoint are excluded. In addition, we will repeat the analyses in the per-protocol set, further excluding patients with major protocol deviations. The safety analysis set will include all patients who were randomly assigned to a study group and received treatment during the study period. For the baseline variables, summary statistics will be performed using frequencies and proportions for categorical data and means and standard deviations for continuous variables. Patient characteristics will be compared using Pearson's chi-square test or Fisher's exact test for categorical outcomes, and Student's t-test for continuous variables,

as appropriate. For the primary analysis, which is aimed at comparing the treatment effects, the adjusted risk ratio and its 95% confidence interval will be estimated using the Mantel-Haenszel method. To test for a significant association of the primary outcome, the Mantel-Haenszel test will be applied after adjusting for allocation factors. All comparisons are planned, and all *p*-values will be two sided. *P*-values <0.05 will be considered statistically significant. All statistical analyses will be performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA). The SAP will be developed by the principal investigator and the biostatistician before completion of patient recruitment and data fixation.

ETHICS AND DISSEMINATION

Participant recruitment began in June 2018. The final results will be published in international peer-reviewed medical journals.

DISCUSSION

Although some guidelines have indicated the efficacy of chlorhexidine-alcohol and povidone-iodine for reducing the SSI rate, the optimal recommendation has still not been established, and the prevalence of SSI remains high in gastrointestinal surgery. Therefore, a comparative trial between conventional antiseptics, including chlorhexidine-alcohol and povidone-iodine, and newly developed antiseptics that considers their effectiveness, toxicity, and costs is needed.[8]

We have been conducting a randomized controlled clinical trial to compare olanexidine and povidone-iodine, which is the most popular antiseptic in Japan in terms of prevalence of SSI and its low toxicity. The strength of this trial is that we adopted blinding for diagnosing SSI at the multiple centers. To maintain the quality of practices, only 4 centers, all of which are high-volume centers performing greater than 500 gastrointestinal surgeries per year, are participating in this trial. Furthermore, since the staff in each center belongs to the SSI control committee, which provides unified and evidence-based counter measures against SSI at Keio University Hospital, the management of SSI at each center can be performed in almost the same manner.

In this study, we have used povidone-iodine instead of chlorhexidine-alcohol as a control. Since chlorhexidine-alcohol is associated with inflammation, povidone-iodine is recommended and typically used for gastrointestinal surgery in Japan. In addition, chlorhexidine-alcohol at concentrations greater than 1% is not commercially available in Japan, although a concentration greater than 2% is recognized as having a bactericidal effect in international guidelines.[21-23] Moreover, considering the influence of ethnic differences, including intrinsic and extrinsic ethnic factors, this comparison is a meaningful examination of SSI treatment, at least in Japan. Therefore, we think that the selection of the control group is reasonable.

Although antisepsis would influence only superficial and deep SSIs, we included organ-space SSI in the endpoint. As described earlier, this is the first study to use olanexidine; therefore, it is more important to establish evidence for all types of SSI than to limit the study to superficial and deep wound infections. Some studies have investigated skin antisepsis in gastrointestinal surgery and included organ SSI as an outcome.[11,12]

This study has several limitations. First, this trial is recruiting patients undergoing various types of gastrointestinal surgery, such as esophagectomy, gastrectomy, and cholecystectomy, which have different rates of SSI. However, there is no major bias in allocation because it is

randomized. Furthermore, since this is the first report using olanexidine, it is more important to include various operations than to limit the study to a particular procedure. Second, this study is limited to the Japanese population because olanexidine is only commercially available in Japan, which could introduce an element of selection bias,

In conclusion, the present study is assessing the efficacy of olanexidine compared to povidone-iodine for preventing SSI in gastrointestinal surgery. We expect olanexidine to be more effective for preventing SSI than povidone-iodine without increasing toxicity. In the future, if superiority of olanexidine compared to povidone-iodine is proven in this trial, we should also consider conducting another trial that compares olanexidine to an alcohol-based antiseptic agent. Even if this prediction is not the final result, this trial can provide new knowledge in terms of antisepsis for preventing SSI. The result will also contribute to the development of new antisepsis treatments for gastrointestinal surgery.

TRIAL STATUS

As of 25 October 2018, this trial is actively recruiting patents at 3 centers with additional centers planned. Two hundred of the planned 600 participants have been enrolled.

AUTHORS' CONTRIBUTIONS

MK and HO contributed equally to this study. All authors made significant contribution to the conception and design of the study protocol. MT designed the study and wrote the protocol and manuscript. SM, TI, KF, RN, NW, MK, HY, YA, GO, SH, MT, TI, TY, KH, YI, YS, HH, YM, MS, and TK assisted with the development of the study design and protocol. The protocol was reviewed by HO, HK, MS, KO, and YK. YS wrote the statistical analysis plan. All authors gave final approval of the manuscript and agree to be accountable for all aspects of the work.

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DISCLAIMER

Otsuka Pharmaceutical Factory Inc. was not involved in the planning of the protocol or in the conduct of the trial.

COMPETING INTERESTS

Yuko Kitagawa received grant support from Otsuka Pharmaceutical Factory Inc.

ETHICS APPROVAL

The protocol was first approved by the Institutional Review Board of Keio University School of Medicine, and then approved by the institutional review board of each participating site.

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Table 1 Definition of the wound classes

Wound Class	Definition
Class I (Clean)	An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tracts are not entered.
Class II (Clean-contaminated)	Operative wounds in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions and without unusual contamination.
Class III (Contaminated)	Includes open, fresh, and accidental wounds.
Class IV (Dirty-contaminated)	Includes old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera.

3

1

2 **Table 2** Flow chart of the trial

Time point	After admission	Before surgery	Surgery	After surgery
Informed consent	□			
Patients' background characteristics	□			
Physical examination	□			
Randomization		□		
Intervention			□	
Observation of the surgical site				□a

3 □a: From postoperative day 1 to postoperative day 30 (outpatient observation is performed at

4 least once if the discharge is within 30 days postoperatively)

Supplemental Table1 Definitions of SSI

Type of SSI	Definition
Superficial incisional SSI	Superficial incisional SSI must meet the following three criteria (A, B, and C). A) Infection occurred within 30 days postoperatively. B) The infection affects only the incision in the skin and the subcutaneous tissue. C) At least one of the following is applicable: a. purulent drainage is observed from the superficial incision, b. organisms are identified from the superficial incision or subcutaneous tissue by a culture or non-culture based microbiologic testing method, and/or c. the superficial incision is deliberately opened by a nonblinded investigators, and culture or non-culture based testing is not performed. In addition, at least one of the following symptoms for infection must be applicable: pain, tenderness, localized swelling, erythema, or heat.
Deep incisional SSI	Deep incisional SSI must meet the following three criteria (A, B, and C). A) Infection occurred within 30 days postoperatively. B) The infection reaches the deep soft tissues of the incision (fascia or muscle layer). C) At least one of the following is applicable: a. purulent drainage is observed from the deep incision, b. the deep incision spontaneously dehisces, or is deliberately opened or aspirated by a nonblinded investigators, and/or

	c. an abscess or other evidence of infection is present and involves the deep incision. In addition, the organism is identified by a culture or non-culture based microbiologic testing method that is performed for purposes of clinical diagnosis or treatment, and symptoms for infection must be applicable: fever, localized pain, or tenderness. Negative finding of a culture does not meet this criterion.
Organ/space SSI	Organ/space SSI involves any part of the body other than the skin incision, fascia, or muscle layer that has been opened or manipulated during surgery. The specific site is classified as organ/space for the purpose of further identification of the infection site. Organ/space SSI must meet the following three criteria (A, B, and C). A) Infection occurred within 30 days postoperatively. B) The infection involves any part of the body that is opened or manipulated during the operative procedure (except for the facial/muscle layers). C) At least one of the following is applicable: a. purulent drainage is observed from a drain that is placed into the organ/space, b. organisms are identified from fluid or tissue in the organ/space by a culture or non-culture based microbiologic testing method, and/or c. an abscess or other evidence of infection is present and involves the organ/space.

*Erythema; the skin redness of the skin that spreads away from the incision site, localized swelling; a bulge limited to the incision site, tenderness; pressured pain beyond normal for the operation.

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

Section/item	ItemNo (Page No)	Description
Administrative information		
Title	1(p1)	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a (p4)	Trial identifier and registry name. If not yet registered, name of intended registry
	2b (n/a)	All items from the World Health Organization Trial Registration Data Set
Protocol version	3 (p12)	Date and version identifier
Funding	4 (p24)	Sources and types of financial, material, and other support
Roles and responsibilities	5a (p24)	Names, affiliations, and roles of protocol contributors
	5b (p2)	Name and contact information for the trial sponsor
	5c (n/a)	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
	5d (n/a)	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)
Introduction		
Background and rationale	6a (p6-8)	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
	6b (p6-8)	Explanation for choice of comparators

Objectives	7 (p6-8)	Specific objectives or hypotheses
Trial design	8 (p6-8)	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
Methods: Participants, interventions, and outcomes		
Study setting	9 (p12)	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
Eligibility criteria	10 (p9)	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a (p10)	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b (p10)	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)
	11c (n/a)	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d (p10)	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12 (p14)	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
Participant timeline	13 (p14)	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14 (p17)	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15 (p12)	Strategies for achieving adequate participant enrolment to reach target sample size
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a (p12)	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
Allocation concealment mechanism	16b (p14)	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
Implementation	16c (p12)	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a (p13)	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b (n/a)	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a (p16)	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
	18b (p16)	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
Data management	19 (p16)	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
Statistical methods	20a (p17)	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
	20b (p17)	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c (p17)	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring		
Data monitoring	21a (p16)	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
	21b (p16)	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
Harms	22 (n/a)	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23 (n/a)	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval	24 (p19)	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25 (n/a)	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)
Consent or assent	26a (p12)	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b (n/a)	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27 (p15)	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
Declaration of interests	28 (p24)	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29 (n/a)	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30 (n/a)	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

Dissemination policy	31a (n/a)	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b (p24)	Authorship eligibility guidelines and any intended use of professional writers
	31c (n/a)	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32 (n/a)	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33 (n/a)	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

*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.