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A superiority trial of intraoperative wound irrigation with aqueous 10% povidone-iodine in comparison to saline for reducing surgical site infection after elective gastrointestinal surgery: Study protocol for a single institute, single blinded, randomized controlled trial

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A superiority trial of intraoperative wound irrigation with aqueous 10% povidone-iodine in comparison to saline for reducing surgical site infection after elective gastrointestinal surgery: Study protocol for a single institute, single blinded, randomized controlled trial

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ABSTRACT

Introduction: Surgical site infection (SSI) is one of the most common complications after gastrointestinal surgery. Its incidence has been reported to be approximately 10-25%, and is higher in comparison to after other types of surgery. Intraoperative wound irrigation (IOWI) is a simple intervention for SSI prevention, and recent studies reported that IOWI with aqueous povidone-iodine (PVP-I) has a significant benefit in reducing the incidence of SSI in comparison to saline. However, the evidence level of previous trials to evaluate the efficacy of aqueous PVP-I solution to prevent SSI has been low.

Methods and analysis: We propose a single institute, prospective, randomized, single-blinded trial to assess the superiority of IOWI with aqueous 10% PVP-I solution in comparison to normal saline for reducing SSI in clean-contaminated wounds after elective gastrointestinal surgery. In the study group, IOWI with 40 ml of aqueous 10% PVP-I solution is performed for one minute before skin suture, and in the control group, IOWI with 100 ml of saline is performed for one minute before skin suture. We hypothesize that IOWI with aqueous 10% PVP-I solution will achieve a 50% reduction in the incidence of SSI. The target number of cases was set at 950. The primary outcome
is the incidence of incisional SSI up to postoperative day 30, and will be analyzed in the
modified intention-to-treat set.

Ethics and dissemination: This trial was designed and conducted by Saitama Medical
Center, Jichi Medical University with approval from the Bioethics Committee for
Clinical Research, Saitama Medical Center, Jichi Medical University. Participant
Recruitment began in June 2019.

Trial registration number: UMIN 000036889
Strength and limitations of this study

This trial evaluates the superior efficacy of intraoperative wound irrigation with aqueous 10% povidone-iodine solution to reduce the incidence of SSI after gastrointestinal surgery in comparison to saline.

The study design is a single center, prospective, randomized controlled trial.

The primary outcome is the incidence of incisional surgical site infection within 30 days postoperatively.

The costs of intraoperative wound irrigation in both groups are almost the same.

The limitation is that multicenter randomized controlled trials will be necessary to generalize and substantiate the findings of this trial.
INTRODUCTION

Surgical site infection (SSI) is one of the most common complications after gastrointestinal surgery, and its incidence has been described around 10-25% in recent studies.\textsuperscript{1-3} Most recent global survey revealed that the incidence of SSI after gastrointestinal surgery has remained 9.4\% even in high-income countries.\textsuperscript{1} The incidence of SSI after gastrointestinal surgery is higher in comparison to after other types of surgery, including cardiac surgery, gynecological surgery, neurosurgery and urological surgery.\textsuperscript{4-7} SSI is harmful for patients in terms of incisional pain and is associated with increased risks of morbidity and mortality.\textsuperscript{8} SSI has also been suggested to be associated with adverse long-term outcomes in patients undergoing oncological gastrointestinal surgery.\textsuperscript{9-11} SSI was reported to be associated with adverse oncological outcomes in patients who underwent liver resection for colorectal liver metastasis,\textsuperscript{9} and postoperative infective complications, including SSI, affect long-term survival after resection for gastric cancer\textsuperscript{10} and colorectal cancer.\textsuperscript{11} SSI dramatically increases medical costs.\textsuperscript{12} Previous reports showed that when SSI occurs, that the excess hospitalization and additional medical costs were amounted to 6-10 days and $1300-6000 per patient, respectively.\textsuperscript{13-18} The most recent cohort study from the United Kingdom also showed that the National Health Service cost associated with 12 months of care for an infected
unhealed wound was approximately £8000 higher than the cost associated with care for a healed wound. Thus, reducing the rate of SSI after gastrointestinal surgery is very important for improving patient outcomes and to reducing medical costs, and reliable measures for SSI prevention are urgently needed.

National and international health organizations, such as the Centers for Disease Control and Prevention (CDC), the World Health Organization (WHO), and the National Institute for Health and Care Excellence (NICE) have proposed clinical guidelines, which are based on systemic reviews and meta-analyses, for SSI prevention. The pathogeneses of SSIs are complex; thus, the recommendations for SSI prevention include preoperative, intraoperative, and postoperative measures. Intraoperative wound irrigation (IOWI) is a simple intervention to remove tissue debris, metabolic waste, and tissue exudate from the surgical wound and to reduce bacterial effects before wound closure. A recent Cochrane review concluded that the evidence base for IOWI was of low quality, some recent meta-analyses showed that IOWI significantly reduced the rate of SSIs in comparison to no irrigation. Saline is isotonic solution without interference with wound healing and it has been widely accepted as the irrigation fluid for IOWI. However, two recent meta-analyses reported that IOWI with saline was not effective in reducing SSI, and showed that IOWI with aqueous povidone-iodine
(PVP-I) has a significant benefit in reducing SSI in comparison to saline.\textsuperscript{26-28} However, previous trials to evaluate the efficacy of aqueous PVP-I solution to prevent SSI were mostly conducted in the 1970-1980s, and the evidence level is low because heterogeneous patients were included and ununiformed definitions were used for the diagnosis of SSI.\textsuperscript{26-28} Because the evidence levels are low, the clinical guidelines of the CDC and WHO weakly recommend IOWI with aqueous PVP-I for the prevention for SSI, and suggest that IOWI with saline is not effective.\textsuperscript{20, 21} From the viewpoint of wound classification, recent meta-analyses showed that IOWI with aqueous PVP-I for the prevention of SSI had reproducible effects in clean wounds,\textsuperscript{27,28} but the findings were controversial in clean-contaminated wounds.\textsuperscript{28} The majority of wounds after gastrointestinal surgery are classified as clean-contaminated or contaminated; thus to date, there is no established evidence to support the effectiveness of IOWI with aqueous PVP-I for the prevention of SSI after gastrointestinal surgery. Furthermore, the clinical guideline of the NICE states that IOWI with aqueous PVP-I solution should be avoided to prevent local and systemic side effects.\textsuperscript{22} Thus, the lack of uniformity in clinical guidelines from the CDC, WHO, and NICE\textsuperscript{20-22} and the lack of well-established evidence to support the effectiveness of IOWI with aqueous PVP-I solution for SSI prevention\textsuperscript{26-28} may potentially confuse surgeons.
This single center, prospective, randomized controlled trial (RCT) was undertaken to evaluate the superiority of IOWI with aqueous 10% PVP-I solution for reducing the incidence of SSI after gastrointestinal surgery in comparison to saline. We hypothesize that IOWI with aqueous 10% PVP-I solution will be more useful for the prevention of SSI in clean-contaminated wounds in comparison to saline.

METHODS

Trial design

This was a single institute, prospective, randomized, single-blinded trial to assess the superiority of IOWI with aqueous 10% PVP-I solution in comparison to normal saline for reducing SSI in clean-contaminated wounds after elective gastrointestinal surgery. This trial was designed and conducted by Saitama Medical Center, Jichi Medical University with approval from the Bioethics Committee for Clinical Research, Saitama Medical Center, Jichi Medical University (S18-138).

The presented protocol follows the recommendations outlined in the Standard Protocol Items: Recommendations for Interventional Trials guidelines for RCTs.

Eligibility criteria

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

Inclusion criteria

1. Scheduled to undergo elective gastrointestinal surgery for esophagus, stomach, duodenum, jejunum, ileum, colorectal, pancreas, liver or biliary tract with a class II (clean-contaminated) surgical wound (Table 1).

2. Age > 20 years at the time that consent is obtained by non-blinded investigators.

3. Provision of written informed consent by the patient.

Exclusion criteria

1. Identification of bacterial infection in the surgical field or the use antibiotic therapy prior to the operation.

2. Presence of a contaminated abdominal cavity due to stoma, intestinal fistula or drainage tube.

3. Synchronous operation for more than 2 targeted organs.

4. Open wound management for prior operation.

5. Pregnancy.

6. Allergy to PVP-I.

7. Conditions unsuitable for the safe conduct of this trial according to the non-blinded investigators.
**Intervention**

Study group: IOWI with 40 ml of aqueous 10% PVP-I solution is performed for one minute before skin suture after elective gastrointestinal surgery.

Control group: IOWI with 100 ml of saline is performed for one minute before skin suture after elective gastrointestinal surgery.

**Treatment protocol**

IOWI describes rinsing the surface of a surgical incision before skin suture to reduce bacterial wound contamination and to clean the wound from blood and necrotic tissue.\(^{23,24}\) In a previous meta-analysis, IOWI with aqueous PVP-I solution showed no dose-response effect in reducing the incidence of SSI,\(^{27}\) and in previous RCTs, the most frequently used concentration of aqueous PVP-I solution was 10%.\(^{27,28}\) The medical costs of 100 mL of saline and 40 ml of aqueous 10% PVP-I solution are almost the same (approximately JPY 40). Thus, before skin suture, subcutaneous tissues are irrigated with surgical cotton balls for one minute with 40 mL of aqueous 10% povidone-iodine (POVIDONE-IODINE solution 10% “MEIJI”; Meiji Seika Pharma Co., Ltd., Tokyo, Japan) in the study group and same procedure is performed with 100 mL of saline (Isotonic Sodium Chloride Solution “Hikari”; Hikari Pharmaceutical Co., Ltd., Tokyo, Japan) in the control group.
In addition, the following measures are used to prevent SSI in our protocol:

1. Surgical skin antisepsis with aqueous 10% PVP-I solution is performed before skin incision.

2. Standard antibiotic prophylaxis is administered 30 minutes before making the skin incision with additional doses every 3 hours for patients with a normal renal function.

3. The use of a wound protector is recommended.

4. Surgical gloves are changed before skin suture.

5. Antimicrobial sutures coated with triclosan (PDS Plus; Ethicon, Johnson & Johnson, Somerville, NJ) are used, the abdominal fascia and peritoneum are closed with interrupted sutures, and interrupted subcutaneous sutures are used for skin closure.

6. Intraoperatively and postoperatively, a normal body temperature is maintained using warming devices and appropriate oxygenation.

7. Perioperative glycemic control is implemented with a blood glucose target level of <200 mg/dL.

**Recruitment of study participants**

This trial was approved by our institutional review board on April 11, 2019, and is registered in the University Hospital Medical Information Network Clinical Trial
Registry (part of the WHO International Clinical Trial Registry Platform) under the identification number UMIN-CTR000036889. Patient recruitment for this trial was started in June 2019 and approximately 540 participants were registered as of January 2021. Recruitment is scheduled to continue until 950 participants are recruited. All participants who meet the criteria will receive a participant information sheet from investigators before giving their written informed consent.

**Randomization**

Participants are registered, randomized, and allocated by non-blinded investigators using REDCap (Research Electronic Data Capture). REDcap is a global, standard-free electronic data capture system for investigator-initiated clinical research, which provides an intuitive interface for users to enter data, and has real-time validation rules (with automated data type and range checks) at the time of data entry. Data entered into REDCap will be password protected and will only be accessible by investigators, and all access to the secure separate database in REDCap will be monitored and logged. Permutated-block randomization with an allocation ratio of 1:1 and a block size of two is used. Gender, surgical organ (upper-gastrointestine, small bowel, colorectum, hepatobiliary-pancreas, and others), and surgical approach (laparotomy or laparoscopy) were designated as allocation adjustment factors.\(^\text{29}\)
Blinding

Patients will be blinded to the assigned group. Conversely, the operating surgeons cannot be blinded, as there is a color difference between aqueous 10% PVP-I solution and saline. The assessors can be blinded, because they are absent from the operating room and cannot access the randomization results. The data on the SSI and analyses will be entered by blinded investigators.

Trial visits

We obtain informed consent for surgery and inclusion in the clinical trial after admission, 1-2 days before surgery. We confirm and record the patient’s past medical history, allergies including povidone-iodine, and physical examination results. After their written informed consent is obtained, patients eligible for this trial will be randomized into two groups before surgery. The period of observation will be 30 days after surgery. Table 2 shows a summary of the schedule and the data collected for this trial.

Risks

No additional risks for study patients are anticipated. IOWI with aqueous 10% PVP-I solution is a manner of usage that is in line with the pharmaceutical affairs law, and is generally performed and is recommended by several guidelines as a measure to prevent
In the past, there has been concern about the potential negative effect of PVP-I on tissue regeneration and serum iodine toxicity; however, these adverse effects could not be substantiated in clinical trials. Adverse effects may be expected in the improbable event of unknown hypersensitivity to PVP-I. The potential benefits of a reduced risk of SSI outweigh the negligible potential adverse effects of PVP-I. Each participant will be provided with medical care for any potential harm from participation in the trial. The Bioethics Committee for Clinical Research, Saitama Medical Center, Jichi Medical University agreed that a data monitoring and safety committee is unnecessary.

**Outcome measures**

The non-blinded investigators will check the surgical wound and describe the medical records during hospitalization. If SSI is suspected based on the clinical findings, non-blinded investigators will collect microbiological cultures from wounds and record the treatment details and wound depth in the medical record. After discharge, participants will be referred to the outpatient department at approximately 30 days after surgery. Participants will be recommended to contact us and visit the outpatient department soon if they experience any symptoms suggesting SSI. The non-blinded investigators will examine the patients in the same way as during hospitalization. The blinded assessors
will determine the presence or absence of SSI according to clinical findings and microbiological cultures. The primary outcome is the incidence of incisional SSI up to postoperative day 30. The secondary outcomes are length of postoperative hospital stay, the positive wound bacterial test rate, and bacterial strains.

Definitions

SSI is defined according to the standard criteria devised by the CDC (Table 3).

Incisional SSI includes superficial and deep incisional SSI, which develops during the first 30 days after surgery. Superficial incisional SSI involves the skin or subcutaneous tissue at the site of the incision, and deep incisional SSI affects the more internal structures of the abdominal layer (such as the fascia or muscle).

Data collection

The investigators will obtain the participants’ information from medical records and collect the information in a password-protected file in the hospital database. The participants’ hospital identification will be anonymized. Patient characteristics, such as sex, age, body mass index, serum albumin level, comorbidities, American society of anesthesiologists-physical status classification, pre-operative treatment, will be collected. And also, surgical data, such as surgical procedures, operative time, estimated blood loss, wound classification, the length of postoperative hospital stay, will be
collected.

**Data management**

The study is conducted according to good clinical practice standards and legal regulations. Prior to inclusion, patients will be informed that any patient-related data and materials will be appropriately pseudonymized and that these data may be used for analysis and publication purposes. All information required by the study protocol and collected during this trial will be entered in the electronic case report form (CRF; encrypted Excel database) by investigators. The progress of the trial will be updated on the web page of UMIN-CTR every 6 months, and the president of Jichi Medical University and the Bioethics Committee for Clinical Research, Saitama Medical Center, Jichi Medical University monitors progress approximately every year. All data will be collected by the investigators in an anonymous and encrypted database. The confidentiality of the participants will be maintained at all times. The investigator will maintain all study-related information, including medical records, CRFs, written informed consent documents, and other pertinent data until 5 years after trial termination. After the study, all individual participant data required during the trial will be available from the corresponding author in an anonymized fashion on reasonable request.
Sample size calculation

In a retrospective cohort of patients who underwent gastrointestinal surgery and IOWI with saline at our department in 2017, the incidence of SSI was 9.4%. The most recent meta-analysis showed that IOWI with aqueous 10% PVP-I solution attribute 59% reduction of SSI in elective surgical procedures. Therefore in this trial, we hypothesize that IOWI with aqueous 10% PVP-I solution will achieve a 50% reduction in the incidence of SSI. The expected SSI rates of the study and control groups are 4.7% and 9.4%, respectively. With a two-sided alpha level of 0.05, it is estimated that a total of 930 patients will be needed in order for the trial to have 80% power to detect superiority in the reduction of the frequency of SSI. Twenty dropout cases are expected based on previous RCTs conducted by our department. Thus, the total target number of cases was set at 950.

Patient and public involvement

Patients and the public were not involved in this trial.

Statistical analysis

All analyses will be performed after the termination of the main part of the trial, that is, after the last 30-day follow-up visit has taken place. The primary and secondary outcomes will be analyzed in the modified intention-to-treat set, from which
participants who do not undergo surgery or who withdraw their consent before the assessment of the primary endpoint will be excluded. The safety analysis will be performed on the safety set, which will consist of all participants randomized into the treatment group, who received the actual treatment. Student’s \( t \)-test or the Mann-Whitney U-test will be used to compare continuous variables with normal or non-normal distribution. The chi-squared test or Fisher’s exact test will be used to compare categorical variables between the study group and the control group. \( P \) values of <0.05 are considered to indicate statistical significance. All statistical analyses will be conducted using EZR.  

**Ethics and dissemination**

This trial protocol was registered in the UMIN-CTR. Participant recruitment was started in June 2019. The final results will be reported in international peer-reviewed journals immediately after the trial is completed.

**DISCUSSION**

Recent meta-analyses suggested that IOWI with aqueous PVP-I solution has a benefit for SSI prevention\(^{26-28}\), and the clinical practice guidelines of the CDC\(^{20}\) and WHO\(^{21}\) weakly recommend IOWI with aqueous PVP-I for SSI prevention. However, previous
clinical trials to evaluate the efficacy of aqueous PVP-I solution for SSI prevention were mostly conducted in the 1970-1980s\textsuperscript{26-28}, and since then, many control measures to prevent SSI—other than IOWI—have been developed.\textsuperscript{20-22} Nowadays, preoperative surgical skin antisepsis, the administration of standard antibiotic prophylaxis, maintaining a normal body temperature, proper oxygenation during surgery, perioperative serum blood sugar control, and other measures are strongly recommended for SSI prevention in many clinical guidelines.\textsuperscript{20-22} With the development surgical technology, surgical procedures have progressed from open surgery to laparoscopic surgery since 1990s, and many clinical studies have revealed that laparoscopic surgery is associated with a significantly lower incidence of SSI in comparison to open surgery in many types of gastrointestinal surgery.\textsuperscript{31-33} Thus, it may be difficult to directly introduce clinical guidelines related to IOWI with aqueous PVP-I for SSI prevention into current surgical practice based on evidence obtained from studies from the 1970-1980s.

High-quality studies adhere to methodological principles to minimize errors in surgical trials: adequate randomization, concealment of allocation, blinding, the performance of an intention-to-treat analysis, complete follow-up, reliable accurate outcome measures, and \textit{a priori} sample size calculation\textsuperscript{34}. This trial was designed
according to these principles. RCTs in single centers tend to include more homogeneous populations (highly selected) and follow-up outcomes more completely in comparison to multicenter RCTs. Our inclusion and exclusion criteria for participants aim to select homogenous patients with clean-contaminated wounds. SSI is diagnosed according to the definition of the CDC guidelines. As mentioned above, we used multiple perioperative measures for SSI prevention according to the clinical guidelines. The ratio of the participants undergoing open surgery or laparoscopic surgery reflects the surgical practice at present. Thus, this RCT, using homogenous patient recruitment, a standardized definition of SSI, and current measures other than IOWI, will clearly establish evidence to support the efficacy of IOWI with aqueous 10% PVP-I solution in the prevention of SSI in current surgical practice.

SSI is associated with increased medical costs and imposes a huge burden on healthcare systems worldwide. When designing measures for SSI prevention significant attention should be paid to its medical cost. A recent meta-analysis revealed that the introduction of absorbable antimicrobial sutures reduced the risk of SSI and the mean savings per surgical procedure from using antimicrobial sutures was found to be significant across all wound types. In this RCT, 40 ml of aqueous 10% PVP-I solution is used for IOWI in the study group, and 100 ml of saline is used for IOWI in the
control group; the costs of IOWI in the two groups are almost same. Because IOWI with aqueous PVP-I solution showed no dose-response effect, we could set the volume of aqueous 10% PVP-I solution used for IOWI as 40 ml (approximately JPY 40), this is in line with the price of 100 mL of saline (approximately JPY 40). There is novelty in our trial setting in that the cost of IOWI for SSI prevention is taken into consideration. If this trial reveals that IOWI with aqueous 10% PVP-I solution is more useful for SSI prevention in comparison to saline, the result will also be supported from the viewpoint of medical cost.

The present study was associated with some limitations. First, all patients undergoing gastrointestinal surgery irrespective of organ, the diagnosis, and procedure, which are associated with different incidences of SSI, are considered for inclusion. Second, this trial was conducted in single center, and RCTs at single centers typically show larger treatment effects in comparison to multicenter RCTs. Well-designed multicenter RCTs will be necessary to generalize and substantiate the findings of this trial. Third, the evidence level was low, a meta-analysis suggested that IOWI with antibiotic solutions seems to be more effective than that IOWI with aqueous PVP-I solution. When this study reveals that IOWI with aqueous 10% PVP-I solution is effective for SSI prevention, it might be worth planning an RCT to compare IOWI with
aqueous 10% PVP-I solution to IOWI with antibiotic solutions in patients with clean-contaminated wounds after gastrointestinal surgery.

The results of this RCT will provide high-level evidence regarding the effectiveness of IOWI with aqueous 10% PVP-I solution for SSI prevention for clean-contaminated wounds after gastrointestinal surgery. If this trial reveals the superior efficacy of IOWI with aqueous 10% PVP-I solution for SSI prevention in comparison to saline, the evidence will strongly support the clinical CDC and WHO guidelines for SSI prevention, as well as current surgical practice. Even though this trial will be negative, the findings of this trial will contribute to the modification of future clinical guidelines in relation to IOWI for SSI prevention and will encourage the next RCT for the development of effective IOWI methods.

Trial status

Recruitment continues steadily, as of January 2021, 540 participants have been enrolled.
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Contributions.

RM and HN contributed equally to this study. RM, HN, KI, and ST participated in the trial design. All authors were responsible for the protocol development. RM wrote the manuscript. HN and TR critically revised the manuscript. All authors read and approved the final manuscript.

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Competing interests statement.

The authors declare no competing interests in association with the present study.
| Class I (clean) | An uninfected operation wound in which no inflammation is encountered and respiratory, alimentary, and genitourinary tract is not entered. |
|----------------|----------------------------------------------------------------------------------------------------------------------------------|
| Class II (clean-contaminated) | An operative wound in which the respiratory, alimentary, and genitourinary tracts are entered under controlled conditions and without unusual contamination provided no evidence of infection or major break in technique is encountered. |
| Class III (contaminated) | A wound in which gross contamination/spillage and a break in sterile technique occurs, and incision in which acute, nonpurulent inflammation is encountered. |
| Class IV (dirty-condaminated) | A wound that is already considered infected, such as old traumatic wounds with retained devitalized tissue or perforated viscera. |
Table 2. Schedule and data collection of this trial.

| STUDY PERIOD | Enrolment | Allocation | Post-allocation | Close-out |
|--------------|-----------|------------|-----------------|-----------|
| TIMEPOINT    | -1-2 days | Surgery    | POD1            | POD3      | POD4-29 | POD30 |

**ENROLMENT:**
- Informed consent
- Inclusion and exclusion criteria
- Allocation

**INTERVENTIONS:**
- Intervention A (PVP-I)
- Intervention B (saline)

**ASSESSMENTS:**
- Demographic data
- Past medical history
- Physical examination
- Blood sample*
- Type of operation
- Time of operation
- Wound classification
- Estimated blood loss
- Blood transfusion
- Stoma creation
- Documentation of SSI
- Wound swab microbiology
- Documentation of re-operation
- Documentation of AE
- Duration of hospital stay

* Includes white blood cell count, red blood cell count, hemoglobin, hematocrit, platelets, lymph cell count, total protein, albumin, bilirubin, AST, ALT, urea nitrogen, creatinine, Na, K, Cl, glucose

POD=postoperative day; PVP-I=povidone-iodine; SSI=surgical site infection; AE=adverse event; AST=aspartate aminotransferase; ALT=alanine aminotransferase; Na=sodium; K=potassium; Cl=chloride
Table 3. Definition of surgical site infection

| Superficial incisional SSI | Date of event occurs within 30 days after any NHSN operative procedure (where day 1 = the procedure date) AND involves only skin and subcutaneous tissue of the incision AND patient has at least one of the following: |
|----------------------------|---------------------------------------------------------------------------------------------------------------|
|                            | a. purulent drainage from the superficial incision.                                                          |
|                            | b. organism(s) identified from an aseptically-obtained specimen from the superficial incision or subcutaneous tissue by a culture or nonculture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment (for example, not Active Surveillance Culture/Testing (ASC/AST)). |
|                            | c. superficial incision that is deliberately opened by a surgeon, physician* or physician designee and culture or non-culture based testing of the superficial incision or subcutaneous tissue is not performed AND patient has at least one of the following signs or symptoms: localized pain or tenderness; localized swelling; erythema; or heat. |
|                            | d. diagnosis of a superficial incisional SSI by a physician* or physician designee. |

* The term physician for the purpose of application of the NHSN SSI criteria may be interpreted to mean a surgeon, infectious disease
physician, emergency physician, other physician on the case, or physician’s designee (nurse practitioner or physician’s assistant).

| Deep incisional SSI | The date of event occurs within 30 or 90 days after the NHSN operative procedure (where day 1 = the procedure date) AND involves deep soft tissues of the incision (for example, fascial and muscle layers) AND patient has at least one of the following: a. purulent drainage from the deep incision. b. a deep incision that spontaneously dehisces, or is deliberately opened or aspirated by a surgeon, physician* or physician designee AND organism(s) identified from the deep soft tissues of the incision by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment (for example, not Active Surveillance Culture/Testing (ASC/AST)) or culture or nonculture based microbiologic testing method is not performed. A culture or non-culture based test from the deep soft tissues of the incision that has a negative finding does not meet this criterion. AND patient has at least one of the following signs or symptoms: fever (>38°C); localized pain or tenderness. c. an abscess or other evidence of infection involving the deep incision that is detected on gross anatomical or histopathologic exam, or imaging test. |
|---|---|
| Organ/Space SSI | Date of event occurs within 30 or 90 days after the NHSN operative procedure (where day 1 = the procedure date) |

* The term physician for the purpose of application of the NHSN SSI criteria may be interpreted to mean a surgeon, infectious disease physician, emergency physician, other physician on the case, or physician’s designee (nurse practitioner or physician’s assistant).
involves any part of the body deeper than the fascial/muscle layers that is opened or manipulated during the operative procedure

AND

patient has at least one of the following:

a. purulent drainage from a drain that is placed into the organ/space (for example, closed suction drainage system, open drain, T-tube drain, CT guided drainage).

b. organism(s) identified from fluid or tissue in the organ/space by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment (for example, not Active Surveillance Culture/Testing (ASC/AST)).

c. an abscess or other evidence of infection involving the organ/space that is detected on gross anatomical or histopathologic exam, or imaging test evidence suggestive of infection.
SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item                      | Item No | Description                                                                                                                                                                                                 | Addressed on page number |
|-----------------------------------|---------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| Administrative information        |         |                                                                                                                                                                                                             |                          |
| Title                             | 1       | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym                                                                                                  | 1                        |
| Trial registration                | 2a      | Trial identifier and registry name. If not yet registered, name of intended registry                                                                                                                        | 12                       |
|                                  | 2b      | All items from the World Health Organization Trial Registration Data Set                                                                                                                                     | 12                       |
| Protocol version                  | 3       | Date and version identifier                                                                                                                                                                                 | Not applicable           |
| Funding                           | 4       | Sources and types of financial, material, and other support                                                                                                                                                    | 29                       |
| Roles and responsibilities        | 5a      | Names, affiliations, and roles of protocol contributors                                                                                                                                                      | 29                       |
|                                  | 5b      | Name and contact information for the trial sponsor                                                                                                                                                           | Not applicable           |
|                                  | 5c      | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | Not applicable           |
|                                  | 5d      | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | Not applicable           |
## Introduction

**Background and rationale**

6a **Description of research question and justification for undertaking the trial**, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention

5, 6, 7

6b **Explanation for choice of comparators**

10

**Objectives**

7 **Specific objectives or hypotheses**

7, 8

**Trial design**

8 **Description of trial design including type of trial** (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

8

## Methods: Participants, interventions, and outcomes

**Study setting**

9 **Description of study settings** (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained

8

**Eligibility criteria**

10 **Inclusion and exclusion criteria for participants**. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)

8, 9

**Interventions**

11a **Interventions for each group with sufficient detail to allow replication**, including how and when they will be administered

10

11b **Criteria for discontinuing or modifying allocated interventions for a given trial participant** (eg, drug dose change in response to harms, participant request, or improving/worsening disease)

13

11c **Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence** (eg, drug tablet return, laboratory tests)

Not applicable

11d **Relevant concomitant care and interventions that are permitted or prohibited during the trial**

Not applicable

**Outcomes**

12 **Primary, secondary, and other outcomes**, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended

14

**Participant timeline**

13 **Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants**. A schematic diagram is highly recommended (see Figure)

13
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations |
|-------------|----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size                                                                                                                                                                        |
| **Methods: Assignment of interventions (for controlled trials)** | **Allocation:** | **Sequence generation** 16a Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions |
| | **Allocation concealment mechanism** 16b Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned |
| | **Implementation** 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions |
| | **Blinding (masking)** 17a Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how |
| | 17b 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 Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., 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 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 |
| Section                        | Subsection | Reference | Description                                                                                                                                                                                                 |
|-------------------------------|------------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Data management               |            | 19, 15, 16| 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, 17, 18| 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, 17, 18| Methods for any additional analyses (eg, subgroup and adjusted analyses)                                                                                                                                       |
|                               |            | 20c, Not applicable | 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, Not applicable | 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, Not applicable | 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, 13, 14| 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, Not applicable | 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, 18    | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval                                                                                                                     |
| Protocol amendments          |            | 25, Not applicable | 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  Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) 11,12

26b  Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable 15,16

Confidentiality 27  How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial 15,16

Declaration of interests 28  Financial and other competing interests for principal investigators for the overall trial and each study site 29

Access to data 29  Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators 13

Ancillary and post-trial care 30  Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation  Not applicable

Dissemination policy 31a  Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions 18

31b  Authorship eligibility guidelines and any intended use of professional writers  Not applicable

31c  Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code  Not applicable.

Appendices

Informed consent materials 32  Model consent form and other related documentation given to participants and authorised surrogates  Not applicable

Biological specimens 33  Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable  Not applicable.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.
A superiority trial of intraoperative wound irrigation with aqueous 10% povidone-iodine in comparison to saline for reducing surgical site infection after elective gastrointestinal surgery: Study protocol for a randomized controlled trial

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Category of paper: Protocol

A superiority trial of intraoperative wound irrigation with aqueous 10% povidone-iodine in comparison to saline for reducing surgical site infection after elective gastrointestinal surgery: Study protocol for a randomized controlled trial

Ryo Maemoto, Hiroshi Noda, Kosuke Ichida, Sawako Tamaki, Rina Kanemitsu, Erika Machida, Nozomi Kikuchi, Ryotaro Sakio, Hidetoshi Aizawa, Taro Fukui, Nao Kakizawa, Yuta Muto, Masahiro Iseki, Rintaro Fukuda, Fumiaki Watanabe, Takaharu Kato, Masaaki Saito, Shingo Tsujinaka, Yasuyuki Miyakura, Toshiki Rikiyama.

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ABSTRACT

Introduction: Surgical site infection (SSI) is one of the most common complications after gastrointestinal surgery. Its incidence has been reported to be approximately 10-25%, and is higher in comparison to after other types of surgery. Intraoperative wound irrigation (IOWI) is a simple intervention for SSI prevention, and recent studies reported that IOWI with aqueous povidone-iodine (PVP-I) has a significant benefit in reducing the incidence of SSI in comparison to saline. However, the evidence level of previous trials to evaluate the efficacy of aqueous PVP-I solution to prevent SSI has been low.

Methods and analysis: We propose a single institute, prospective, randomized, blinded-endpoint trial to assess the superiority of IOWI with aqueous 10% PVP-I solution in comparison to normal saline for reducing SSI in clean-contaminated wounds after elective gastrointestinal surgery. In the study group, IOWI with 40 ml of aqueous 10% PVP-I solution is performed for one minute before skin suture, and in the control group, IOWI with 100 ml of saline is performed for one minute before skin suture. We hypothesize that IOWI with aqueous 10% PVP-I solution will achieve a 50% reduction in the incidence of SSI. The target number of cases was set at 950. The primary outcome is the incidence of incisional SSI up to postoperative day 30, and will be analyzed in the
modified intention-to-treat set.

**Ethics and dissemination:** This trial was designed and conducted by Saitama Medical Center, Jichi Medical University with approval from the Bioethics Committee for Clinical Research, Saitama Medical Center, Jichi Medical University. Participant Recruitment began in June 2019. The final results will be reported in international peer-reviewed journals immediately after the trial is completed.

**Trial registration number:** UMIN000036889
Strength and limitations of this study

We hypothesize that intraoperative wound irrigation with aqueous 10% povidone-iodine solution will achieve a 50% reduction in the incidence of SSI in comparison to intraoperative wound irrigation with saline.

The primary outcome is the incidence of incisional surgical site infection within 30 days postoperatively, which is defined according to the criteria of the Centers for Disease Control and Prevention.

In this trial, the cost of intraoperative wound irrigation in the study group and that in the control group were almost the same.

One limitation is that multicenter randomized controlled trials will be necessary to generalize and substantiate the findings of this trial.
INTRODUCTION

Surgical site infection (SSI) is one of the most common complications after gastrointestinal surgery, and its incidence has been described around 10-25% in recent studies.\(^1\)\(^-\)\(^3\) Most recent global survey revealed that the incidence of SSI after gastrointestinal surgery has remained 9.4% even in high-income countries.\(^1\) The incidence of SSI after gastrointestinal surgery is higher in comparison to after other types of surgery, including cardiac surgery, gynecological surgery, neurosurgery and urological surgery.\(^4\)-\(^7\) SSI is harmful for patients in terms of incisional pain and is associated with increased risks of morbidity and mortality.\(^8\) SSI has also been suggested to be associated with adverse long-term outcomes in patients undergoing oncological gastrointestinal surgery.\(^9\)-\(^11\) SSI was reported to be associated with adverse oncological outcomes in patients who underwent liver resection for colorectal liver metastasis,\(^9\) and postoperative infective complications, including SSI, affect long-term survival after resection for gastric cancer\(^10\) and colorectal cancer.\(^11\) SSI dramatically increases medical costs.\(^12\) Previous reports showed that when SSI occurs, that the excess hospitalization and additional medical costs were amounted to 6-10 days and $1300-6000 per patient, respectively.\(^13\)-\(^18\) The most recent cohort study from the United Kingdom also showed that the National Health Service cost associated with 12 months of care for an infected
unhealed wound was approximately £8000 higher than the cost associated with care for a healed wound.\textsuperscript{19} Thus, reducing the rate of SSI after gastrointestinal surgery is very important for improving patient outcomes and to reducing medical costs, and reliable measures for SSI prevention are urgently needed.  

National and international health organizations, such as the Centers for Disease Control and Prevention (CDC)\textsuperscript{20}, the World Health Organization (WHO)\textsuperscript{21}, and the National Institute for Health and Care Excellence (NICE)\textsuperscript{22} have proposed clinical guidelines, which are based on systemic reviews and meta-analyses, for SSI prevention. The pathogeneses of SSIs are complex; thus, the recommendations for SSI prevention include preoperative, intraoperative, and postoperative measures. Intraoperative wound irrigation (IOWI) is a simple intervention to remove tissue debris, metabolic waste, and tissue exudate from the surgical wound and to reduce bacterial effects before wound closure.\textsuperscript{23, 24} A recent Cochrane review concluded that the evidence base for IOWI was of low quality,\textsuperscript{25} some recent meta-analyses showed that IOWI significantly reduced the rate of SSIs in comparison to no irrigation.\textsuperscript{26-28} Saline is isotonic solution without interference with wound healing and it has been widely accepted as the irrigation fluid for IOWI.\textsuperscript{23, 24} However, two recent meta-analyses reported that IOWI with saline was not effective in reducing SSI,\textsuperscript{26, 27} and showed that IOWI with aqueous povidone-iodine
(PVP-I) has a significant benefit in reducing SSI in comparison to saline.\textsuperscript{26,27} The previous trials to evaluate the efficacy of aqueous PVP-I solution to prevent SSI were mostly conducted in the 1970-1980s, and the evidence levels are low because heterogeneous patients were included and ununiformed definitions were used for the diagnosis of SSI.\textsuperscript{26-29} A meta-analysis after the exclusion of RCTs of low or uncertain quality showed that IOWI with aqueous PVP-I solutions was not associated with a significant decrease in the incidence of SSI.\textsuperscript{28} Thus the evidence levels are low, the clinical guidelines of the CDC and WHO weakly recommend IOWI with aqueous PVP-I for the prevention for SSI, and suggest that IOWI with saline is not effective.\textsuperscript{20, 21} From the viewpoint of wound classification, recent meta-analyses showed that IOWI with aqueous PVP-I for the prevention of SSI had reproducible effects in clean wounds,\textsuperscript{27,28} but the findings were controversial in clean-contaminated wounds.\textsuperscript{28} The majority of wounds after gastrointestinal surgery are classified as clean-contaminated or contaminated; thus to date, there is no established evidence to support the effectiveness of IOWI with aqueous PVP-I for the prevention of SSI after gastrointestinal surgery. Furthermore, the clinical guideline of the NICE states that IOWI with aqueous PVP-I solution should be avoided to prevent local and systemic side effects.\textsuperscript{22} Thus, the lack of uniformity in clinical guidelines from the CDC, WHO, and NICE\textsuperscript{20-22} and the lack of
well-established evidence to support the effectiveness of IOWI with aqueous PVP-I solution for SSI prevention\textsuperscript{26-28} may potentially confuse surgeons.

This single center, prospective, randomized controlled trial (RCT) was undertaken to evaluate the superiority of IOWI with aqueous 10% PVP-I solution for reducing the incidence of SSI after gastrointestinal surgery in comparison to saline. We hypothesize that IOWI with aqueous 10% PVP-I solution will be more useful for the prevention of SSI in clean-contaminated wounds in comparison to saline.

**METHODS**

**Trial design**

This was a single institute, prospective, randomized, blinded-endpoint trial to assess the superiority of IOWI with aqueous 10% PVP-I solution in comparison to normal saline for reducing SSI in clean-contaminated wounds after elective gastrointestinal surgery. This trial was designed and conducted by Saitama Medical Center, Jichi Medical University, and the presented protocol follows the recommendations outlined in the Standard Protocol Items: Recommendations for Interventional Trials guidelines for RCTs.

**Eligibility criteria**
Patients who receive elective gastrointestinal surgery in the Department of Surgery, Saitama Medical Center, Jichi Medical University, and who are able to understand the extent and nature of this trial, will be eligible for inclusion in this study.

Inclusion criteria

1. Scheduled to undergo elective surgery for esophagus, stomach, duodenum, jejunum, ileum, colorectal, pancreas, liver or biliary tract with a class II (clean-contaminated) surgical wound (Table 1).

2. Age > 20 years at the time that consent is obtained by non-blinded investigators.

3. Provision of written informed consent by the patient. (Supplement file)

Exclusion criteria

1. Identification of bacterial infection in the surgical field or the use antibiotic therapy prior to the operation.

2. Presence of a contaminated abdominal cavity due to stoma, intestinal fistula or drainage tube.

3. Synchronous operation for more than 2 targeted organs.

4. Open wound management for prior operation.

5. Pregnancy.

6. Allergy to PVP-I.
7. Conditions that make the patient unsuitable for inclusion (e.g., thyroid disease, renal
disease, cardiac disease, etc.) according to the judgement of non-blinded
investigators,

**Intervention**

Study group: IOWI with 40 ml of aqueous 10% PVP-I solution with washing using
surgical cotton balls is performed for one minute before skin suture after elective
gastrointestinal surgery.

Control group: IOWI with 100 ml of saline with washing using surgical cotton balls is
performed for one minute before skin suture after elective gastrointestinal surgery.

**Treatment protocol**

Before skin suture, IOWI is performed for one minute with 40 mL of aqueous 10%
povidone-iodine (POVIDONE-IODINE solution 10% “MEIJI”; Meiji Seika Pharma
Co., Ltd., Tokyo, Japan) in the study group and same procedure is performed with
100 mL of saline (Isotonic Sodium Chloride Solution “Hikari”; Hikari Pharmaceutical
Co., Ltd., Tokyo, Japan) in the control group. The performance of IOWI with washing
using surgical cotton balls is associated with additional benefits in bacterial wound
contamination and cleaning blood and necrotic tissue from the wound. The medical
costs of 100 mL of saline and 40 ml of aqueous 10% PVP-I solution are almost the
same (approximately JPY 40).

In addition, the following measures are used to prevent SSI in our protocol:

1. Surgical skin antisepsis with aqueous 10% PVP-I solution is performed before skin incision.

2. Standard antibiotic prophylaxis is administered 30 minutes before making the skin incision with additional doses every 3 hours for patients with a normal renal function.

3. The use of a wound protector is recommended.

4. Surgical gloves are changed before skin suture.

5. Antimicrobial sutures coated with triclosan (PDS Plus; Ethicon, Johnson & Johnson, Somerville, NJ) are used, the abdominal fascia and peritoneum are closed with interrupted sutures, and interrupted subcutaneous sutures are used for skin closure.

6. Intraoperatively and postoperatively, a normal body temperature is maintained using warming devices and appropriate oxygenation.

7. Perioperative glycemic control is implemented with a blood glucose target level of <200 mg/dL.

**Recruitment of study participants**

This trial was approved by our institutional review board on April 11, 2019, and is
registered in the University Hospital Medical Information Network Clinical Trial Registry (part of the WHO International Clinical Trial Registry Platform) under the identification number UMIN-CTR000036889. Patient recruitment for this trial was started in June 2019 and approximately 540 participants were registered as of January 2021. Recruitment is scheduled to continue until 950 participants are recruited. All participants who meet the criteria will receive a participant information sheet from investigators before giving their written informed consent.

Randomization

Participants are registered, randomized, and allocated by non-blinded investigators. Participants’ data will be password protected and will only be accessible by investigators. All access to the secure separate database will be monitored and logged.

Permuted-block randomization with an allocation ratio of 1:1 and a block size of two is used. Gender, surgical organ (upper-gastrointestine, small bowel, colorectum, hepatobiliary-pancreas, and others), and surgical approach (laparotomy or laparoscopy) were designated as allocation adjustment factors.

Blinding

Patients will be blinded to the assigned group. Conversely, the operating surgeons cannot be blinded, as there is a color difference between aqueous 10% PVP-I solution
and saline. The assessors can be blinded, because they are absent from the operating room and cannot access the randomization results. The data on the SSI and analyses will be entered by blinded investigators.

**Trial visits**

The non-blinded investigators who received the ethics education and who were approved by the Bioethics Committee for Clinical Research, Saitama Medical Center, Jichi Medical University obtain informed consent for surgery and inclusion in the clinical trial after admission, 1-2 days before surgery. We confirm and record the patient’s past medical history, allergies including povidone-iodine, and physical examination results. After their written informed consent is obtained, patients eligible for this trial will be randomized into two groups before surgery. The period of observation will be 30 days after surgery. Table 2 shows a summary of the schedule and the data collected for this trial.

**Risks**

No additional risks for study patients are anticipated. IOWI with aqueous 10% PVP-I solution is a manner of usage that is in line with the pharmaceutical affairs law, and is generally performed and is recommended by several guidelines as a measure to prevent SSI. Adverse effects may be expected in the improbable event of unknown
hypersensitivity to PVP-I. The potential benefits of a reduced risk of SSI outweigh the
negligible potential adverse effects of PVP-I. Each participant will receive informed
consent about notification and follow-up of adverse events, and will be provided with
medical care for any potential harm from participation in the trial. The Bioethics
Committee for Clinical Research, Saitama Medical Center, Jichi Medical University
agreed that a data monitoring and safety committee is unnecessary.

Outcome measures

The non-blinded investigators will check the surgical wound and describe the medical
records during hospitalization. If SSI is suspected based on the clinical findings, non-
blinded investigators will collect microbiological cultures from wounds and record the
treatment details and wound depth in the medical record. After discharge, participants
will be referred to the outpatient department at approximately 30 days after surgery.
Participants will be recommended to contact us and visit the outpatient department soon
if they experience any symptoms suggesting SSI. The non-blinded investigators will
examine the patients in the same way as during hospitalization. The blinded assessors
will determine the presence or absence of SSI according to clinical findings and
microbiological cultures. The primary outcome is the incidence of incisional SSI up to
postoperative day 30. The secondary outcomes are length of postoperative hospital stay,
the positive wound bacterial test rate, and bacterial strains.

Definitions

SSI is defined according to the standard criteria devised by the CDC (Table 3).

Incisional SSI includes superficial and deep incisional SSI, which develops during the first 30 days after surgery. Superficial incisional SSI involves the skin or subcutaneous tissue at the site of the incision, and deep incisional SSI affects the more internal structures of the abdominal layer (such as the fascia or muscle).

Data collection

The investigators will obtain the participants’ information from medical records and collect the information in a password-protected file in the hospital database. The participants’ hospital identification will be anonymized. Patient characteristics, such as sex, age, body mass index, serum albumin level, comorbidities, American society of anesthesiologists-physical status classification, pre-operative treatment, will be collected. And also, surgical data, such as surgical procedures, operative time, estimated blood loss, wound classification, the length of postoperative hospital stay, will be collected.

Data management

The study is conducted according to good clinical practice standards and legal
regulations. Prior to inclusion, patients will be informed that any patient-related data and materials will be appropriately pseudonymized and that these data may be used for analysis and publication purposes. All information required by the study protocol and collected during this trial will be entered in the electronic case report form (CRF; encrypted Excel database) by investigators. The progress of the trial will be updated on the web page of UMIN-CTR every 6 months, and the president of Jichi Medical University and the Bioethics Committee for Clinical Research, Saitama Medical Center, Jichi Medical University monitors progress approximately every year. All data will be collected by the investigators in an anonymous and encrypted database. The confidentiality of the participants will be maintained at all times. The investigator will maintain all study-related information, including medical records, CRFs, written informed consent documents, and other pertinent data until 5 years after trial termination. After the study, all individual participant data required during the trial will be available from the corresponding author in an anonymized fashion on reasonable request.

**Sample size calculation**

In a retrospective cohort of patients who underwent gastrointestinal surgery and IOWI with saline at our department in 2017, the incidence of SSI was 9.4%. In this trial, we
hypothesize that IOWI with aqueous 10% PVP-I solution will achieve a 50% reduction in the incidence of SSI. The expected SSI rates of the study and control groups are 4.7% and 9.4%, respectively. With a two-sided alpha level of 0.05, it is estimated that a total of 930 patients will be needed in order for the trial to have 80% power to detect superiority in the reduction of the frequency of SSI. Twenty dropout cases are expected.

Thus, the total target number of cases was set at 950.

**Patient and public involvement**

Patients and the public were not involved in this trial.

**Statistical analysis**

All analyses will be performed after the termination of the main part of the trial, that is, after the last 30-day follow-up visit has taken place. The primary and secondary outcomes will be analyzed in the modified intention-to-treat set, from which participants who do not undergo surgery or who withdraw their consent before the assessment of the primary endpoint will be excluded. The safety analysis will be performed on the safety set, which will consist of all participants randomized into the treatment group, who received the actual treatment. Student’s t-test or the Mann-Whitney U-test will be used to compare continuous variables with normal or non-normal distribution. The chi-squared test or Fisher’s exact test will be used to compare
categorical variables between the study group and the control group. P values of <0.05 are considered to indicate statistical significance. All statistical analyses will be conducted using EZR.30

Ethics and dissemination

This trial was approved by the Bioethics Committee for Clinical Research, Saitama Medical Center, Jichi Medical University (S18-138), and the trial protocol was registered in the UMIN-CTR. Participant recruitment was started in June 2019. The final results will be reported in international peer-reviewed journals immediately after the trial is completed.

DISCUSSION

Recent meta-analyses suggested that IOWI with aqueous PVP-I solution has a benefit for SSI prevention26-28, and the clinical practice guidelines of the CDC20 and WHO21 weakly recommend IOWI with aqueous PVP-I for SSI prevention. However, previous clinical trials to evaluate the efficacy of aqueous PVP-I solution for SSI prevention were mostly conducted in the 1970-1980s26-28, and since then, many control measures to prevent SSI—other than IOWI—have been developed.20-22 Nowadays, preoperative surgical skin antisepsis, the administration of standard antibiotic prophylaxis,
maintaining a normal body temperature, proper oxygenation during surgery, perioperative serum blood sugar control, and other measures are strongly recommended for SSI prevention in many clinical guidelines. With the development surgical technology, surgical procedures have progressed from open surgery to laparoscopic surgery since 1990s, and many clinical studies have revealed that laparoscopic surgery is associated with a significantly lower incidence of SSI in comparison to open surgery in many types of gastrointestinal surgery. Thus, it may be difficult to directly introduce clinical guidelines related to IOWI with aqueous PVP-I for SSI prevention into current surgical practice based on evidence obtained from studies from the 1970-1980s.

High-quality studies adhere to methodological principles to minimize errors in surgical trials: adequate randomization, concealment of allocation, blinding, the performance of an intention-to treat analysis, complete follow-up, reliable accurate outcome measures, and a priori sample size calculation. This trial was designed according to these principles. RCTs in single centers tend to include more homogeneous populations (highly selected) and follow-up outcomes more completely in comparison to multicenter RCTs. Our inclusion and exclusion criteria for participants aim to select homogenous patients with clean-contaminated wounds. SSI is diagnosed according to
the definition of the CDC guidelines.\textsuperscript{20} The most recent meta-analysis showed that IOWI with aqueous 10\% PVP-I solution was associated with a 59\% reduction in the incidence of SSI in patients undergoing elective surgical procedures.\textsuperscript{28} Thus, in this trial, we hypothesized that IOWI with aqueous 10\% PVP-I solution will achieve a 50\% reduction in the incidence of SSI and calculated the target number of cases. In addition, the number of expected dropout cases could be predicted based on a previous large RCT for SSI prevention that was conducted by our department.\textsuperscript{36} Thus, the total target number of cases might be accurate. As mentioned above, we used multiple perioperative measures for SSI prevention according to the clinical guidelines.\textsuperscript{20-22} The ratio of the participants undergoing open surgery or laparoscopic surgery reflects the surgical practice at present. Thus, This RCT, using homogenous patient recruitment, a standardized definition of SSI, precise sample size calculation, and current measures other than IOWI, will clearly establish evidence to support the efficacy of IOWI with aqueous 10\% PVP-I solution in the prevention of SSI in current surgical practice.

IOWI with aqueous 10\% PVP-I solution is generally performed and is recommended by several guidelines as a measure to prevent SSI.\textsuperscript{20,21} In the past, there has been concern about the potential negative effect of PVP-I on tissue regeneration and serum iodine toxicity; however, these adverse effects could not be substantiated in
clinical trials of IOWI with aqueous 10% PVP-I solution. Furthermore, no serious harm was reported in a large meta-analysis, even when PVP-I was used for other internal tissues (e.g., irrigation of the intraperitoneal cavity, pericardial cavity, or bladder). In previous RCTs, IOWI with aqueous PVP-I solution showed no dose-response effect in reducing the incidence of SSI, and the concentration of aqueous PVP-I solution most frequently used for IOWI was 10%. Aqueous 10% PVP-I solution is easy to access in a ready-to-use fashion for preoperative surgical skin antisepsis in Japan. We also used aqueous 10% PVP-I solution for surgical skin antisepsis before skin incision in this RTC, because chlorhexidine-alcohol at a concentration of >2%, which is recommended by international clinical guidelines, is not commercially available in Japan. In the cohort prior to this RCT in our department, the standard duration of IOWI with saline was approximately one minute. PVP-I can reach antimicrobial activity within 30 seconds after application, and the duration of IOWI with aqueous PVP-I solution most frequently used in previous RCTs was one minute. Therefore, in this study, we set the duration of IOWI to one minute for both groups.

SSI is associated with increased medical costs and imposes a huge burden on healthcare systems worldwide. When designing measures for SSI prevention
significant attention should be paid to its medical cost. A recent meta-analysis revealed that the introduction of absorbable antimicrobial sutures reduced the risk of SSI and the mean savings per surgical procedure from using antimicrobial sutures was found to be significant across all wound types.\textsuperscript{39} In this RCT, 40 ml of aqueous 10\% PVP-I solution is used for IOWI in the study group, and 100 ml of saline is used for IOWI in the control group; the costs of IOWI in the two groups are almost same. Because IOWI with aqueous PVP-I solution showed no dose-response effect,\textsuperscript{27} we could set the volume of aqueous 10\% PVP-I solution used for IOWI as 40 ml (approximately JPY 40), this is in line with the price of 100 mL of saline (approximately JPY 40). There is novelty in our trial setting in that the cost of IOWI for SSI prevention is taken into consideration. If this trial reveals that IOWI with aqueous 10\% PVP-I solution is more useful for SSI prevention in comparison to saline, the result will also be supported from the viewpoint of medical cost.

The present study was associated with some limitations. First, all patients undergoing gastrointestinal surgery irrespective of organ, the diagnosis, and procedure, which are associated with different incidences of SSI, are considered for inclusion. Second, this trial was conducted in single center, and RCTs at single centers typically show larger treatment effects in comparison to multicenter RCTs.\textsuperscript{35} Well-designed
multicenter RCTs will be necessary to generalize and substantiate the findings of this trial. Third, the evidence level was low, a meta-analysis suggested that IOWI with antibiotic solutions seems to be more effective than that IOWI with aqueous PVP-I solution. When this study reveals that IOWI with aqueous 10% PVP-I solution is effective for SSI prevention, it might be worth planning an RCT to compare IOWI with aqueous 10% PVP-I solution to IOWI with antibiotic solutions in patients with clean-contaminated wounds after gastrointestinal surgery.

The results of this RCT will provide high-level evidence regarding the effectiveness of IOWI with aqueous 10% PVP-I solution for SSI prevention for clean-contaminated wounds after gastrointestinal surgery. If this trial reveals the superior efficacy of IOWI with aqueous 10% PVP-I solution for SSI prevention in comparison to saline, the evidence will strongly support the clinical CDC and WHO guidelines for SSI prevention, as well as current surgical practice. The implementation of multidisciplinary care for SSI prevention after gastrointestinal surgery has been increasingly shown to be effective since 2010s, and IOWI with aqueous PVP-I solution will be more frequently added as an important component of multidisciplinary care. Even though this trial will be negative, the findings of this trial will contribute to the modification of future clinical guidelines in relation to IOWI for SSI prevention and will encourage the next
RCT for the development of effective IOWI methods.

**Trial status**

Recruitment continues steadily, as of January 2021, 540 participants have been enrolled.

The current protocol is in operation at version 1.4. (June 11, 2020).
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**Contributions.**

RM and HN contributed equally to this study. RM, HN, KI, and ST made substantial contributions to conception and trial design. KI, RK, EM, NK, RS, HA, TF, NK, YM, MI, RF, FW, TK, MS, ST and YM were responsible for the protocol development. RM, HN and KI contributed the data management. RM and HN performed statistical analyses, and all authors interpreted the analytical results. RM and HN wrote the manuscript. HN and TR critically revised the manuscript. All authors made critical revisions and approved the final version of the manuscript.

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**Competing interests statement.**

The authors declare no competing interests in association with the present study.

**Data availability statement.**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.
Table 1 Definition of the wound classes

| Class I (clean) | An uninfected operation wound in which no inflammation is encountered and respiratory, alimentary, and genitourinary tract is not entered. |
| Class II (clean-contaminated) | An operative wound in which the respiratory, alimentary, and genitourinary tracts are entered under controlled conditions and without unusual contamination provided no evidence of infection or major break in technique is encountered. |
| Class III (contaminated) | A wound in which gross contamination/spillage and a break in sterile technique occurs, and incision in which acute, nonpurulent inflammation is encountered. |
| Class IV (dirty-condaminated) | A wound that is already considered infected, such as old traumatic wounds with retained devitalized tissue or perforated viscera. |
Table 2. Schedule and data collection of this trial.

| TIMEPOINT    | STUDY PERIOD | Enrolment | Allocation | Post-allocation | Close-out |
|--------------|--------------|-----------|------------|-----------------|-----------|
| -1-2 days    | Enrolment    | X         |            | POD1            |           |
| Surgery      |              |           |            | POD3            |           |
| POD4-29      |              | X         |            | POD30           |           |
| POD30        |              |           |            |                 |           |

**ENROLMENT:**
- Informed consent
- Inclusion and exclusion criteria
- Allocation

**INTERVENTIONS:**
- X
| Intervention A (PVP-I) | X |   |   |   |
|-----------------------|---|---|---|---|
| Intervention B (saline)| X |   |   |   |

**ASSESSMENTS:**

- Demographic data: X
- Past medical history: X
- Physical examination: X
- Blood sample*: X
- Type of operation: X
- Time of operation: X
- Wound classification: X
- Estimated blood loss: X
- Blood transfusion: X
- Stoma creation: X
- Documentation of SSI: X
- Wound swab microbiology: X
- Documentation of re-operation: X
- Documentation of AE: X
- Duration of hospital stay: X

*Includes white blood cell count, red blood cell count, hemoglobin, hematocrit, platelets, lymph cell count, total protein, albumin, bilirubin, AST, ALT, urea nitrogen, creatinine, Na, K, Cl, glucose

POD=postoperative day; PVP-I=povidone-iodine; SSI=surgical site infection; AE=adverse event; AST=aspartate aminotransferase; ALT=alanine aminotransferase; Na=sodium; K=potassium; Cl=chloride

| Table 3. Definition of surgical site infection |
|-----------------------------------------------|
| **Superficial incisional SSI** | Date of event occurs within 30 days after any NHSN operative procedure (where day 1 = the procedure date) AND involves only skin and subcutaneous tissue of the incision |
| Deep incisional SSI | The date of event occurs within 30 or 90 days after the NHSN operative procedure (where day 1 = the procedure date) |
|---------------------|--------------------------------------------------------------------------------------------------|
| AND                 | involve deep soft tissues of the incision (for example, fascial and muscle layers)                  |
| AND                 | patient has at least one of the following:                                                        |
| a. purulent drainage from the deep incision.                                                     |
| b. a deep incision that spontaneously dehisces, or is deliberately opened or aspirated by a surgeon, physician* or physician designee |
| AND                 | patient has at least one of the following signs or symptoms:                                       |
| localized pain or tenderness; localized swelling; erythema; or heat.                            |

* The term physician for the purpose of application of the NHSN SSI criteria may be interpreted to mean a surgeon, infectious disease physician, emergency physician, other physician on the case, or physician’s designee (nurse practitioner or physician’s assistant).
organism(s) identified from the deep soft tissues of the incision by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment (for example, not Active Surveillance Culture/Testing (ASC/AST)) or culture or nonculture based microbiologic testing method is not performed. A culture or non-culture based test from the deep soft tissues of the incision that has a negative finding does not meet this criterion.

**AND**

patient has at least one of the following signs or symptoms:

- fever (>38°C); localized pain or tenderness.
- c. an abscess or other evidence of infection involving the deep incision that is detected on gross anatomical or histopathologic exam, or imaging test.

* The term physician for the purpose of application of the NHSN SSI criteria may be interpreted to mean a surgeon, infectious disease physician, emergency physician, other physician on the case, or physician’s designee (nurse practitioner or physician’s assistant).

| Organ/Space SSI | Date of event occurs within 30 or 90 days after the NHSN operative procedure (where day 1 = the procedure date) |
|-----------------|-------------------------------------------------------------------------------------------------------------|
|                 | **AND**---------------------------------------------------------------------------------------------------------|
|                 | involves any part of the body deeper than the fascial/muscle layers that is opened or manipulated during the operative procedure **AND** |
|                 | patient has at least one of the following:                                                                  |
|                 | a. purulent drainage from a drain that is placed into the organ/space (for example, closed suction drainage system, open drain, T-tube drain, CT guided drainage). |
|                 | b. organism(s) identified from fluid or tissue in the organ/space by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment (for example, not Active Surveillance Culture/Testing (ASC/AST)). |
|                 | c. an abscess or other evidence of infection involving the |
organ/space that is detected on gross anatomical or histopathologic exam, or imaging test evidence suggestive of infection.
Explanation and Request for Participation in Clinical Research (Research Title: The effect of irrigation with aqueous iodophor solution on the incidence of surgical site infection after abdominal wall closure in gastrointestinal surgery: a randomized controlled trial)

We will explain the contents of the research along with the process of consent for participation, in order to request your participation in this research. Should you fully understand this explanation and are willing to participate in the research, please tick the □ for the items in the "Research Participation Agreement" that you have received explanation and understood, then sign or print your name and affix your seal.

The implementation of this clinical research has been approved by the President of Jichi Medical University, upon receipt of approval by the Clinical Research Ethics Review Committee of Saitama Medical Center, Jichi Medical University

1 Names of research institutions and researchers

The researchers conducting this research are:

Professor Toshiki Rikiyama, Department of Surgery, Saitama Medical Center, Jichi Medical University

Ryo Maemoto, Department of Surgery, Saitama Medical Center, Jichi Medical University

Hiroshi Noda, Department of Surgery, Saitama Medical Center, Jichi Medical University

2 Objective and significance of research

There are various complications that occur following surgery, one of them being surgical site infection (suppuration of the wound; hereinafter, referred to as SSI). SSI can cause high fever and pain or cause discomfort for the patient and a delay in postoperative recovery, resulting from pus buildup under and deeper in the skin. It is also problematic that the treatment requires further medical expenses. Prevention is important for SSI, with various measures having been
taken to date, including the administration of antibacterial drugs, disinfection of the skin, and control of blood sugar levels.

This time, we focused on the cleaning method when closing a wound (hereinafter, referred to as the wound) by surgical incision at the end of surgery. Overseas treatment guidelines recommend that the subcutaneous tissue be washed with an aqueous iodophor solution (so-called Isodine solution; hereinafter, referred to as the Isodine solution) before closing the wound. However, in Japan, it is often washed with saline, which is inconsistent with overseas treatment guidelines. Because the current Isodine solution does not damage tissues, it can be safely used on wounds. The results of previous studies are shown below.

| Researcher and publishing year | Subject patients and number of patients | Intervention and contrast | Infection rate (intervention : contrast) | Conclusion (Iodophor irrigation was:)
---|---|---|---|---
| Sindelar et al. 1979 | General surgery patients, 500 | Iodophor irrigation and Saline irrigation | 2.9% : 15.1% | Effective
| Roger et al. 1983 | General surgery patients, 187 | Iodophor irrigation and Saline irrigation | 4.6% : 10.9% | Cannot say it was effective

While it has been reported that irrigation with an aqueous iodophor solution reduces the
incidence of SSI, the report was made more than 40 years ago.

We believe it is meaningful to verify the effectiveness thereof, taking into consideration that it is a cleaning method not widely used in Japan, along with the fact that the research on which the overseas treatment guidelines are based on was conducted so many years ago.

3 Method of research

After suturing the muscle layer, hemostasis at the wound should be confirmed. Subsequently, we move on to cleaning the wound, at which point the cleaning method is divided into a group that is washed with normal saline (hereinafter, referred to as the control group) and a group that is washed with the povidone-iodine solution (hereinafter, referred to as the intervention group). The skin is closed after thoroughly cleaning the wound in each group. Both groups use subcutaneous sutures (suture method that does not require suture removal) to close the skin. The incidence of SSI in both groups is compared.

The group to which you belong will be randomly assigned by the Support Center for Clinical Investigation at Jichi Medical University. For the sake of fairness, you will not be informed of the group to which you belong.

SSI is determined by postoperative wound observation. The observation period is 30 days following surgery. Wound observation is performed daily by the attending physician team during hospitalization, such as during rounds, and continues until discharge. If SSI is suspected, the wound is opened or cleaned upon examination, etc., similar to daily practice. A physician other than the attending physician may see you to assess the infection. After discharge, please observe the wound yourself and contact us immediately if there is any change. You may visit the hospital for observation of the wound and treatment will be provided, if necessary. This is covered within the scope of health insurance, as the treatment is the same as regular medical care. You will be responsible for transportation expenses. Even if there is no change in the wound, the outpatient physician will perform wound observation upon the outpatient visits after
discharge.

The obtained data and the course of medical care are compiled by researchers and statistically analyzed.

Because this research is conducted within the normal insurance practice, there is no particular burden on the patient.

4 Research period

The research will be conducted from April 11, 2019 through March 31, 2023 (during this period, you will be participating for approximately a month.)

5 Reasons for being selected as a research subject

As mentioned in 2, the purpose of this research is to investigate the presence or absence of SSI; therefore, we are asking those who will undergo a gastrointestinal surgery (gastrointestinal tract, liver, gallbladder, pancreas, etc.) at our department to participate. You have:

Disease name: ________________________________________________________

and are scheduled to undergo surgery for the said disease; therefore, we are requesting your participation in this research.

6 The burden on the research subject and the expected risks and benefits

(1) Burden on research subjects

This research does not impose any particular burden on you.

(2) Expected risks and benefits
It is very unlikely that the participation in the research poses a unique risk. In rare cases, strong allergic reactions such as anaphylaxis, redness and itchiness of the skin may appear, due to the influence of the povidone-iodine solution. However, the same povidone-iodine solution is used on a daily basis for preoperative skin disinfections. Previous studies, in which we have compared the effects of povidone-iodine and saline irrigation on wounds, have not reported any adverse events due to the use of povidone-iodine.

Furthermore, this research will not benefit you in any way.

7 Participation in the research is voluntary and you will not be put at a disadvantage by not providing your consent for participation

Participation in this research is voluntary. Please decide of your own free will. Should you not agree to participate, you will not be put at a disadvantage in any way. We will provide the best medical care as usual at this hospital.

8 You will be able to withdraw consent at any time without being put at a disadvantage, even after initially consenting to participate in the research

You can withdraw your consent and cancel participation at any time without being put at a disadvantage, even if you have initially agreed to participate. Furthermore, the samples and medical records provided for this research will not be subsequently used. However, if the research results have already been published in a treatise at the time your consent is withdrawn, we may not be able to discard the research results and samples.

9 Method of disclosing information regarding the research

You can view this research plan and related materials, as long as it does not interfere with the protection of personal information of other research subjects or the securing of the originality of the research. Please let us know if you wish to view these.
The research outline and results will be registered in the database of the National University Hospital Council of Japan, etc.

10 Protection of personal information

In conducting this research, the names and addresses of the samples and medical record information provided by you will be deleted, such that no specific individual can be identified; rather, we will anonymize individuals using a symbol that is unrelated to you. The correspondence table that links you to this code is stored and strictly managed, by the principal investigator, in the locked cabinet of the physician’s room on the 5th floor of the management research building in the research laboratory of Saitama Medical Center, Jichi Medical University. By doing so, researchers who analyze samples and medical information will not know whose samples, etc. they are analyzing.

Personal information will not be provided to third parties. Research results will be reported at academic conferences and treatises in such a way that individuals cannot be identified.

11 Method of storing and disposing of samples and information

(1) Method of storing samples, information, etc.

Once the research is completed, samples and information will be stored in the locked cabinet on the 5th floor of the management research building in the research laboratory of Saitama Medical Center, Jichi Medical University. Should stored information, etc. be used for some other purpose, we will apply to the Ethics Committee again to obtain approval.

(2) Method of disposing of samples and information

They will be erased by dedicated data-erasing software.

12 Status of conflicts of interest related to research by researchers, such as research
funding sources, conflicts of interest related to research at research institutes, and personal income

(1) Funding sources

This research will be conducted using the research funds of the Department of Surgery, Saitama Medical Center, Jichi Medical University.

(2) Conflict of interest status

The status of conflicts of interest, summarized by fiscal year as stipulated in the Conflicts of Interest Management Policy, is entered and is examined by the university.

13 Financial burden or reward

There is no new financial burden on you to participate in this research. There is no reward either.

14 Attribution of intellectual property rights

Although intellectual property rights such as patent rights may arise as a result of this research, those rights belong to the university or researcher, not to you. While such rights may have financial benefits, you do not have such rights.

15 Matters related to other treatment methods, in the case of research involving medical practices that go beyond normal medical care

This research is conducted within the scope of normal practice.

16 Response to the provision of medical care to the research subjects after the research is conducted, in the case of research that involves medical practices that go beyond normal medical care

This research is conducted within the scope of normal practice.
17  Handling of research results related to research subjects, etc., in the event potential important findings regarding the health of the research subjects, along with genetic characteristics that can be inherited by their offspring, can be obtained

This research does not provide any insight concerning genetic characteristics that can be inherited by offspring.

18  Compensation for health hazards

There is no compensation associated with this research. This research will be conducted within the scope of health insurance, in the same manner as regular medical care. As health insurance will also be used to treat health problems such as side effects, you will be responsible for the copayment of the insurance.

19  Potential to use samples/information, etc. for future unspecified research, along with the potential of providing said samples/information, etc. to other research institutes

In the event of the potential for samples/information, etc. to be used for future unspecified research, we will apply to the Ethics Committee again to obtain approval.

There is no potential of providing samples/information, etc. to other research institutes.

20  Potential for viewing samples, information, etc. by persons other than researchers

There is no potential for anyone other than the researchers to view the materials, information, etc. in this research.

21  Contact details for consultations, complaints, etc.

Should you have any questions regarding this research, please contact the following principal investigator.
Principal investigator: Ryo Maemoto, Department of Surgery, Saitama Medical Center, Jichi Medical University

Address: 1-847 Amanuma-cho, Omiya-ku, Saitama-shi, Saitama Prefecture

Telephone: 048-647-2111

Should you have any complaints, please contact the General Affairs Division, Saitama Medical Center, Jichi Medical University (telephone 048-648-5225).
To: President of Jichi Medical University

With regard to "The effect of irrigation with aqueous iodophor solution on the incidence of surgical site infection after abdominal wall closure in gastrointestinal surgery: a randomized controlled trial," I have received an explanation on the following items by way of an explanatory document.

(Please tick the □ for the items you understand upon receiving explanation.)

□ Name of research institution and name of researcher
□ Objective and significance of research
□ Research method
□ Research period
□ Reasons for being selected as a research subject
□ The burden on the research subject and the expected risks and benefits
□ Participation in the research is voluntary and will not be put at a disadvantage by not providing consent to participate.
□ I am able to withdraw my consent at any time without being put at a disadvantage, even after initially consenting to participate in the research.
□ Method of disclosing information regarding the research
□ Protection of personal information
□ Method of storing and disposing of samples and information
□ Status of conflicts of interest related to research by researchers, such as research funding sources, conflicts of interest related to research at research institutes, and personal income
□ Financial burden or reward
□ Attribution of intellectual property rights
□ Matters related to other treatment methods, in the case of research involving medical practices that go beyond normal medical care
□ Response to the provision of medical care to the research subjects after the research is conducted, in the case of research that involves medical practices that go beyond normal medical care
□ Handling of research results related to research subjects, etc., in the event potential important findings regarding the health of the research subjects, along with genetic characteristics that can be inherited by offspring, can be obtained
□ Compensation for health hazards
□ Potential to use samples/information, etc. for future research without specification, along with the potential of providing the said samples/information, etc. to other research institutes
□ Potential for viewing samples, information, etc. by persons other than researchers
□ Contact details for consultations, complaints, etc.

Having fully understood the above explanation, I agree to participate in the research as a research subject.
If you agree with the following, please tick the box.

☐ I agree that the samples and information I provide for this research will be stored for a long period of time and subsequently used for new research conducted in the future with the approval of the Ethics Review Board.

Date: _____ Year _____ Month _____ Day

Address: ________________________________

Name: ________________________________

(sign or print your name and affix your seal)

【Signature line of the principal investigator physician or a member physician of the investigation】

I have fully explained this clinical research to the above patient.

Explanation date: _____ Year _____ Month _____ Day  Dept.: Surgery

Name: ________________________________(Signature)
SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item               | Item No | Description                                                                 | Addressed on page number |
|----------------------------|---------|-----------------------------------------------------------------------------|--------------------------|
| Administrative information |         |                                                                             |                          |
| Title                      | 1       | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1                        |
| Trial registration         | 2a      | Trial identifier and registry name. If not yet registered, name of intended registry | 12                       |
|                            | 2b      | All items from the World Health Organization Trial Registration Data Set     | 12                       |
| Protocol version           | 3       | Date and version identifier                                                 | 24                       |
| Funding                    | 4       | Sources and types of financial, material, and other support                 | 32                       |
| Roles and responsibilities | 5a, 5b  | Names, affiliations, and roles of protocol contributors                     | 32                       |
|                            |         | Name and contact information for the trial sponsor                          | Not applicable           |
|                            | 5c, 5d  | 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 | Not applicable           |
|                            |         | 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) | Not applicable           |
Introduction

Background and rationale

6a Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention 5-8

6b Explanation for choice of comparators 5-8

Objectives

7 Specific objectives or hypotheses 8

Trial design

8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) 8

Methods: Participants, interventions, and outcomes

Study setting

9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained 8

Eligibility criteria

10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) 8-10

Interventions

11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered 10

11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) 13, 14

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) Not applicable

11d Relevant concomitant care and interventions that are permitted or prohibited during the trial 8-10

Outcomes

12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended 14, 15

Participant timeline

13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) 13

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations |
|-------------|----|----------------------------------------------------------------------------------|
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size |

**Methods: Assignment of interventions (for controlled trials)**

**Allocation:**

| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions |
|---------------------|-----|----------------------------------------------------------------------------------|
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how |
| | 17b | 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 | 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 | 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 |
| Section                          | Code | Details                                                                 | Page(s) |
|---------------------------------|------|--------------------------------------------------------------------------|---------|
| Data management                 | 19   | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 15,16   |
| Statistical methods             | 20a  | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 17,18   |
|                                 | 20b  | Methods for any additional analyses (eg, subgroup and adjusted analyses)  | 17,18   |
|                                 | 20c  | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 17, 18  |
| **Methods: Monitoring**         |      |                                                                          |         |
| Data monitoring                 | 21a  | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | Not applicable |
|                                 | 21b  | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | Not applicable |
| Harms                           | 22   | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 13,14   |
| Auditing                        | 23   | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | Not applicable |
| **Ethics and dissemination**    |      |                                                                          |         |
| Research ethics approval        | 24   | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 18      |
| Protocol amendments             | 25   | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | Not applicable |
| Item | Description |
|------|-------------|
| Consent or assent | 26a Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) |
| | 26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable |
| Confidentiality | 27 How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial |
| Declaration of interests | 28 Financial and other competing interests for principal investigators for the overall trial and each study site |
| Access to data | 29 Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators |
| Ancillary and post-trial care | 30 Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation |
| Dissemination policy | 31a Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions |
| | 31b Authorship eligibility guidelines and any intended use of professional writers |
| | 31c Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code |
| Appendices | Informed consent materials | 32 Model consent form and other related documentation given to participants and authorised surrogates |
| | Biological specimens | 33 Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable |

*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.
A superiority trial comparing intraoperative wound irrigation with aqueous 10% povidone-iodine to saline for the purpose of reducing surgical site infection after elective gastrointestinal surgery: Study protocol for a randomized controlled trial

Journal: BMJ Open
Manuscript ID: bmjopen-2021-051374.R2
Article Type: Protocol
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| <b>Primary Subject Heading</b> | Infectious diseases |
|-------------------------------|---------------------|
| Secondary Subject Heading    | Surgery             |
| Keywords                      | Adult surgery < SURGERY, Infection control < INFECTIOUS DISEASES, WOUND MANAGEMENT |
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Category of paper: Protocol

A superiority trial comparing intraoperative wound irrigation with aqueous 10% povidone-iodine to saline for the purpose of reducing surgical site infection after elective gastrointestinal surgery: Study protocol for a randomized controlled trial

Ryo Maemoto, Hiroshi Noda, Kosuke Ichida, Sawako Tamaki, Rina Kanemitsu, Erika Machida, Nozomi Kikuchi, Ryotaro Sakio, Hidetoshi Aizawa, Taro Fukui, Nao Kakizawa, Yuta Muto, Masahiro Iseki, Rintaro Fukuda, Fumiaki Watanabe, Takaharu Kato, Masaaki Saito, Shingo Tsujinaka, Yasuyuki Miyakura, Toshiki Rikiyama.

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ABSTRACT

Introduction: Surgical site infection (SSI) is one of the most common complications after gastrointestinal surgery, with a reported incidence of approximately 10%-25%, which is higher than the rates after other types of surgery. Intraoperative wound irrigation (IOWI) is a simple intervention for SSI prevention, and recent studies have reported that IOWI with aqueous povidone-iodine (PVP-I) is significantly more effective at reducing the incidence of SSI than saline. However, the evidence level of previous trials evaluating the efficacy of aqueous PVP-I solution for preventing SSI has been low.

Methods and analyses: We propose a single-institute, prospective, randomized, blinded-endpoint trial to assess the superiority of IOWI with aqueous 10% PVP-I solution compared to normal saline for reducing SSI in clean-contaminated wounds after elective gastrointestinal surgery. In the study group, IOWI with 40 ml of aqueous 10% PVP-I solution is performed for one minute before skin suture, and in the control group, IOWI with 100 ml of saline is performed for 1 minute before skin suture. We hypothesize that IOWI with aqueous 10% PVP-I solution will achieve a 50% reduction in the incidence of SSIs. The target number of cases is set at 950. The primary outcome is the incidence of incisional SSI up to postoperative day 30 and will be analyzed in the modified intention-to-treat set.

Ethics and dissemination: This trial was designed and is being conducted by Saitama Medical Center, Jichi Medical University, with approval from the Bioethics Committee for...
Clinical Research, Saitama Medical Center, Jichi Medical University. Participant Recruitment began in June 2019. The final results will be reported in international peer-reviewed journals immediately after trial completion.

**Trial registration number:** UMIN000036889
Strength and limitations of this study

- Our inclusion and exclusion criteria strictly select homogenous patients with clean-contaminated wounds after gastrointestinal surgery.

- We are using the criteria established by the Centers for Disease Control and Prevention to diagnose surgical site infection (SSI), as the evidence levels of previous studies concerning the efficacy of intraoperative wound irrigation (IOWI) with aqueous povidone-iodine solution for preventing SSI have been low due to non-uniform definitions of SSI.

- In our sample size calculation, the number of expected dropout cases is expected to be accurate, as we can predict dropouts based on a previous large-scale randomized controlled trial (RCT) for SSI prevention conducted by our department.

- As significant attention should be paid to associated cost when developing measures for SSI prevention, our trial setting is novel, since the costs of IOWI in the study group and those in the control group were almost the same.

- One limitation is that multicenter RCTs will be necessary to generalize and substantiate the findings of this trial.
INTRODUCTION

Surgical site infection (SSI) is one of the most common complications after gastrointestinal surgery, with a reported incidence of around 10%-25% in recent studies.\textsuperscript{1-3} A recent global survey revealed that the incidence of SSI after gastrointestinal surgery has remained at 9.4%, even in high-income countries.\textsuperscript{1} The incidence of SSI after gastrointestinal surgery is higher than that after other types of surgery, including cardiac surgery, gynecological surgery, neurosurgery and urological surgery.\textsuperscript{4-7}

SSIs are harmful to patients, inducing incisional pain, and are associated with increased risks of morbidity and mortality.\textsuperscript{8} SSIs have also been suggested to be associated with adverse long-term outcomes in patients undergoing oncological gastrointestinal surgery.\textsuperscript{9-11} SSIs were reported to be associated with adverse oncological outcomes in patients who underwent liver resection for colorectal liver metastasis,\textsuperscript{9} and postoperative infective complications, including SSI, reportedly affect the long-term survival after resection for gastric cancer\textsuperscript{10} and colorectal cancer.\textsuperscript{11}

Furthermore, SSIs dramatically increase medical costs.\textsuperscript{12} Previous reports have shown that when SSIs occur, the excess hospitalization duration and additional medical costs amounted to 6-10 days and $1300-$6000 US per patient, respectively.\textsuperscript{13-18} A recent cohort study from the United Kingdom also showed that the National Health Service cost associated with 12 months of care for an infected unhealed wound was approximately £8000 higher than
the cost associated with care for a healed wound.\textsuperscript{19} Thus, reducing the rate of SSI after gastrointestinal surgery is very important for improving patient outcomes and reducing medical costs, and reliable measures for SSI prevention are urgently needed.

National and international health organizations, such as the Centers for Disease Control and Prevention (CDC)\textsuperscript{20}, World Health Organization (WHO)\textsuperscript{21}, and National Institute for Health and Care Excellence (NICE)\textsuperscript{22} have proposed clinical guidelines based on systemic reviews and meta-analyses for SSI prevention. The pathogeneses of SSIs are complex; recommendations for SSI prevention thus include preoperative, intraoperative, and postoperative measures. Intraoperative wound irrigation (IOWI) is a simple intervention to remove tissue debris, metabolic waste, and tissue exudate from the surgical wound and to reduce bacterial effects before wound closure.\textsuperscript{23, 24} A recent Cochrane review concluded that the evidence base for IOWI was of a low quality,\textsuperscript{25} but some recent meta-analyses showed that IOWI significantly reduced the rate of SSIs compared with no irrigation.\textsuperscript{26-28}

Saline is an isotonic solution that does not interfere with wound healing and has been widely accepted as appropriate irrigation fluid for IOWI.\textsuperscript{23, 24} However, two recent meta-analyses reported that IOWI with saline was not effective in reducing SSIs\textsuperscript{26, 27} that IOWI with aqueous povidone-iodine (PVP-I) had a significant benefit in reducing SSIs compared with saline.\textsuperscript{26, 27} Previous trials to evaluate the efficacy of aqueous PVP-I solution to prevent SSI were mostly conducted in the 1970-1980s, and the evidence levels were low, as
heterogeneous patients were included and non-uniform definitions were used for the
diagnosis of SSI.26-29 A meta-analysis after the exclusion of RCTs of low or uncertain quality
showed that IOWI with aqueous PVP-I solutions was not associated with a significant
decrease in the incidence of SSIs.28 Thus, the evidence levels have been low, the clinical
guidelines of the CDC and WHO weakly recommend IOWI with aqueous PVP-I for the
prevention for SSI, thereby suggesting that IOWI with saline is not effective.20, 21 From the
viewpoint of wound classification, recent meta-analyses showed that IOWI with aqueous
PVP-I for the prevention of SSI had reproducible effects on clean wounds,27, 28 but the
findings for clean-contaminated wounds were controversial.28 The majority of wounds after
gastrointestinal surgery are classified as clean-contaminated or contaminated; thus, at present,
there is no established evidence supporting the effectiveness of IOWI with aqueous PVP-I for
the prevention of SSI after gastrointestinal surgery. Furthermore, the clinical guideline of the
NICE states that IOWI with aqueous PVP-I solution should be avoided in order to prevent
local and systemic side effects.22 Thus, the lack of uniformity in clinical guidelines from the
CDC, WHO, and NICE20-22 as well as the lack of well-established evidence supporting the
effectiveness of IOWI with aqueous PVP-I solution for SSI prevention26-28 may confuse
surgeons.

This single-center, prospective, randomized controlled trial (RCT) is being performed
to evaluate the superiority of IOWI with aqueous 10% PVP-I solution for reducing the
incidence of SSI after gastrointestinal surgery compared with saline. We hypothesize that IOWI with aqueous 10% PVP-I solution will be more useful than saline for the prevention of SSI in clean-contaminated wounds.

METHODS

Trial design

This is a single institute, prospective, randomized, blinded-endpoint trial being conducted to assess the superiority of IOWI with aqueous 10% PVP-I solution compared with normal saline for reducing SSI in clean-contaminated wounds after elective gastrointestinal surgery. This trial was designed and is being conducted by Saitama Medical Center, Jichi Medical University, and the present protocol follows the recommendations outlined in the Standard Protocol Items: Recommendations for Interventional Trials guidelines for RCTs.

Eligibility criteria

Patients who receive elective gastrointestinal surgery in the Department of Surgery, Saitama Medical Center, Jichi Medical University, and who are able to understand the extent and nature of this trial are eligible for inclusion in this study.

- Inclusion criteria

1. Scheduled to undergo elective surgery for esophagus, stomach, duodenum, jejunum, ileum, colorectal, pancreas, liver, or biliary tract with a class II (clean-contaminated)
surgical wound (Table 1).

2. Age > 20 years old at the time that consent is obtained by non-blinded investigators.

3. Provided written informed consent (Supplement file)

   • Exclusion criteria

1. Identification of bacterial infection in the surgical field or the use antibiotic therapy prior to the operation.

2. Presence of a contaminated abdominal cavity due to stoma, intestinal fistula, or drainage tube.

3. Synchronous operation for more than two targeted organs.

4. Open wound management for prior operation.

5. Pregnancy.

6. Allergy to PVP-I.

7. Conditions that make the patient unsuitable for inclusion (e.g. thyroid disease, renal disease, cardiac disease, etc.) according to the judgement of non-blinded investigators,

Intervention

• Study group: IOWI with 40 ml of aqueous 10% PVP-I solution with washing using surgical cotton balls is performed for 1 minute before skin suture after elective gastrointestinal surgery.

• Control group: IOWI with 100 ml of saline with washing using surgical cotton balls is
performed for 1 minute before skin suture after elective gastrointestinal surgery.

_Treatment protocol_

Before skin suture, IOWI is performed for 1 minute with 40 mL of aqueous 10% povidone-iodine (POVIDONE-IODINE solution 10% “MEIJI”; Meiji Seika Pharma Co., Ltd., Tokyo, Japan) in the study group, and the same procedure is performed with 100 mL of saline (Isotonic Sodium Chloride Solution “Hikari”; Hikari Pharmaceutical Co., Ltd., Tokyo, Japan) in the control group. The performance of IOWI with washing using surgical cotton balls is associated with additional benefits in preventing bacterial wound contamination and helps clean blood and necrotic tissue from the wound. The medical costs of 100 mL of saline and 40 mL of aqueous 10% PVP-I solution are almost the same (approximately JPY 40).

In addition, the following measures are used to prevent SSI in our protocol:

1. Surgical skin antisepsis with aqueous 10% PVP-I solution is performed before skin incision.

2. Standard antibiotic prophylaxis is administered 30 minutes before making the skin incision with additional doses every 3 h for patients with a normal renal function.

3. The use of a wound protector is recommended.

4. Surgical gloves are changed before skin suture.

5. Antimicrobial sutures coated with triclosan (PDS Plus; Ethicon, Johnson & Johnson, Somerville, NJ, USA) are used, the abdominal fascia and peritoneum are closed with
interrupted sutures, and interrupted subcutaneous sutures are used for skin closure.

6. Intraoperatively and postoperatively, a normal body temperature is maintained using warming devices and appropriate oxygenation.

7. Perioperative glycemic control is implemented with a blood glucose target level of <200 mg/dL.

Recruitment of study participants

This trial was approved by our institutional review board on April 11, 2019 and is registered in the University Hospital Medical Information Network Clinical Trial Registry (part of the WHO International Clinical Trial Registry Platform) under the identification number UMIN-CTR000036889. Patient recruitment for this trial was started in June 2019, and approximately 540 participants have been registered as of January 2021. Recruitment is scheduled to continue until 950 participants are recruited. All participants who meet the criteria will receive a participant information sheet from investigators before giving their written informed consent.

Randomization

Participants are being registered, randomized, and allocated by non-blinded investigators. Participants’ data will be password protected and will only be accessible by investigators. All access to the secure separate database will be monitored and logged. Permuted-block randomization with an allocation ratio of 1:1 and a block size of two is used. Gender, surgical
organ (upper gastrointestinal, small bowel, colorectum, hepato-biliary-pancreas, and others),
and surgical approach (laparotomy or laparoscopy) are designated as allocation adjustment
factors.

**Blinding**

Patients will be blinded to their assigned group. However, the operating surgeons cannot be
blinded, as there is a difference in color between aqueous 10% PVP-I solution and saline. The
assessors will be blinded, as they will not be in the operating room and cannot access the
randomization results. The data on SSIs and analyses will be entered by blinded investigators.

**Trial visits**

Non-blinded investigators who received ethics education and were approved by the Bioethics
Committee for Clinical Research, Saitama Medical Center, Jichi Medical University will
obtain informed consent for surgery and inclusion in the clinical trial after admission, one to
two days before surgery. We will confirm and record each patient’s medical history, allergies
(including povidone-iodine), and physical examination results. After their written informed
consent has been obtained, patients eligible for this trial will be randomized into two groups
before surgery. The period of observation will be 30 days after surgery. Table 2 shows a
summary of the schedule and the data collected for this trial.

**Risks**

No additional risks for study patients are anticipated. IOWI with aqueous 10% PVP-I
solution is a manner of usage that is in line with the pharmaceutical affairs law and is
generally performed and recommended by several guidelines as a measure to prevent SSI.
Adverse effects may be expected in the improbable event of unknown hypersensitivity to
PVP-I. The potential benefits of a reduced risk of SSI outweigh the negligible potential
adverse effects of PVP-I. Each participant will receive informed consent about notification
and follow-up of adverse events and will be provided with medical care for any potential
harm stemming from their participation in the trial. The Bioethics Committee for Clinical
Research, Saitama Medical Center, Jichi Medical University agree that a data monitoring and
safety committee is unnecessary.

*Outcome measures*

The non-blinded investigators will check the surgical wound and describe the medical
records during hospitalization. If an SSI is suspected based on the clinical findings, non-
blinded investigators will collect microbiological cultures from wounds and record the
treatment details and wound depth in the medical record. After discharge, participants will be
referred to the outpatient department at approximately 30 days after surgery. Participants will
be recommended to contact us and visit the outpatient department soon if they experience any
symptoms suggesting an SSI. The non-blinded investigators will examine the patients in the
same way as during hospitalization. The blinded assessors will determine the presence or
absence of an SSI according to the clinical findings and microbiological cultures. The
primary outcome is the incidence of incisional SSI up to postoperative day 30. The secondary outcomes are the length of postoperative hospital stay, positive wound bacterial test rate, and bacterial strains.

Definitions

SSI is defined according to the standard criteria devised by the CDC (Table 3). Incisional SSI includes superficial and deep incisional SSI that develops during the first 30 days after surgery. Superficial incisional SSI involves the skin or subcutaneous tissue at the site of the incision, and deep incisional SSI affects the more internal structures of the abdominal layer (such as the fascia or muscle).

Data collection

The investigators will obtain the participants’ information from medical records and collect the information in a password-protected file in the hospital database. The participants’ hospital identification will be anonymized. Patient characteristics, such as sex, age, body mass index, serum albumin level, comorbidities, American Society of Anesthesiologists-physical status classification, and pre-operative treatment, will be collected. In addition, surgical data, such as surgical procedures, operative time, estimated blood loss, wound classification, and length of postoperative hospital stay, will also be collected.

Data management

The study will be conducted according to good clinical practice standards and legal
regulations. Prior to inclusion, patients will be informed that any patient-related data and materials will be appropriately pseudonymized and that these data may be used for analysis and publication purposes. All information required by the study protocol and collected during this trial will be entered in the electronic case report form (CRF; encrypted Excel database) by investigators. The progress of the trial will be updated on the web page of UMIN-CTR every six months, and the president of Jichi Medical University and the Bioethics Committee for Clinical Research, Saitama Medical Center, Jichi Medical University will monitor progress approximately every year.

All data will be collected by the investigators in an anonymous and encrypted database. The confidentiality of the participants will be maintained at all times. The investigator will maintain all study-related information, including medical records, CRFs, written informed consent documents, and other pertinent data, for five years after trial termination. After the study, all individual participant data required during the trial will be available from the corresponding author in an anonymized fashion on reasonable request.

Sample size calculation

In a retrospective cohort of patients who underwent gastrointestinal surgery and IOWI with saline at our department in 2017, the incidence of SSI was 9.4%. In this trial, we hypothesize that IOWI with aqueous 10% PVP-I solution will achieve a 50% reduction in the incidence of SSI. The expected SSI rates of the study and control groups are 4.7% and 9.4%, respectively.
With a 2-sided alpha level of 0.05, it is estimated that a total of 930 patients will be needed in order for the trial to have 80% power to detect superiority in the reduction of the frequency of SSI. Twenty dropout cases are expected, so the total target number of cases is set at 950.

**Patient and public involvement**

Neither patients nor the public are involved in this trial.

**Statistical analyses**

All analyses will be performed after the termination of the main part of the trial, i.e. after the last 30-day follow-up visit has taken place. The primary and secondary outcomes will be analyzed in the modified intention-to-treat set, from which participants who do not undergo surgery or who withdraw their consent before the assessment of the primary endpoint will be excluded. The safety analysis will be performed on the safety set, which will consist of all participants randomized into the treatment group who received the actual treatment. Student’s $t$-test or the Mann-Whitney U-test will be used to compare continuous variables with a normal or non-normal distribution. The chi-squared test or Fisher’s exact test will be used to compare categorical variables between the study group and control group.

P values of $<0.05$ are considered to indicate statistical significance. All statistical analyses will be conducted using EZR.$^{30}$

**Ethics and dissemination**

This trial was approved by the Bioethics Committee for Clinical Research, Saitama Medical
Center, Jichi Medical University (S18-138), and the trial protocol was registered in the UMIN-CTR. Participant recruitment was started in June 2019. The final results will be reported in international peer-reviewed journals immediately after the trial is completed.

**DISCUSSION**

Recent meta-analyses have suggested that IOWI with aqueous PVP-I solution has a benefit for SSI prevention, and the clinical practice guidelines of the CDC and WHO weakly recommend IOWI with aqueous PVP-I for SSI prevention. However, previous clinical trials evaluating the efficacy of aqueous PVP-I solution for SSI prevention were largely conducted in the 1970s and 80s, and since then, many control measures for preventing SSIs other than IOWI have been developed. Nowadays, preoperative surgical skin antisepsis, the administration of standard antibiotic prophylaxis, maintaining a normal body temperature, proper oxygenation during surgery, perioperative serum blood sugar control, and other measures are strongly recommended for SSI prevention in many clinical guidelines. With the development of surgical technology, surgical procedures have progressed from open surgery to laparoscopic surgery since the 1990s, and many clinical studies have shown that laparoscopic surgery is associated with a significantly lower incidence of SSI than open surgery in many types of gastrointestinal surgery. Thus, it may be difficult to directly introduce clinical guidelines related to IOWI with aqueous PVP-I for SSI prevention into
current surgical practice based on evidence obtained from studies from the 1970s and 80s.

High-quality studies adhere to methodological principles to minimize errors in surgical trials, including adequate randomization, concealment of allocation, blinding, performance of an intention-to-treat analysis, complete follow-up, reliable accurate outcome measures, and a priori sample size calculation. The present trial is designed according to these principles. RCTs in single centers tend to include more homogeneous populations (highly selected) and follow outcomes more completely than multicenter RCTs. Our inclusion and exclusion criteria for participants aim to select homogenous patients with clean-contaminated wounds. SSIs are diagnosed according to the definition of the CDC guidelines. A recent meta-analysis showed that IOWI with aqueous 10% PVP-I solution was associated with a 59% reduction in the incidence of SSI in patients undergoing elective surgical procedures. Thus, in the present trial, we hypothesize that IOWI with aqueous 10% PVP-I solution will achieve a 50% reduction in the incidence of SSI and calculated the target number of cases for such an outcome. In addition, the number of expected dropout cases was able to be predicted based on a previous large RCT for SSI prevention that was conducted by our department. Thus, we are confident that the total target number of cases is accurate. As mentioned above, we use multiple perioperative measures for SSI prevention, according to the clinical guidelines. The ratio of participants undergoing open surgery or laparoscopic surgery reflects the surgical practice at present. Thus, our RCT using homogenous patient
recruitment, a standardized definition of SSI, precise sample size calculation, and current measures other than IOWI will clearly establish evidence to support the efficacy of IOWI with aqueous 10% PVP-I solution in preventing SSI in current surgical practice.

IOWI with aqueous 10% PVP-I solution is generally performed and recommended by several guidelines as a measure to prevent SSI.\textsuperscript{20, 21} In the past, there has been concern about the potential negative effects of PVP-I on tissue regeneration and serum iodine toxicity; however, these adverse effects were not substantiated in clinical trials of IOWI with aqueous 10% PVP-I solution.\textsuperscript{26-28} Furthermore, no serious harm was reported in a large meta-analysis, even when PVP-I was used for other internal tissues (e.g. irrigation of the intraperitoneal cavity, pericardial cavity, or bladder).\textsuperscript{29, 37, 38} In previous RCTs, IOWI with aqueous PVP-I solution showed no dose-response effect in reducing the incidence of SSI, and the concentration of aqueous PVP-I solution most frequently used for IOWI was 10%. Aqueous 10% PVP-I solution is easy to access in a ready-to-use fashion for preoperative surgical skin antisepsis in Japan. We will also use aqueous 10% PVP-I solution for surgical skin antisepsis before skin incision in this RTC, as chlorhexidine-alcohol at >2%, which is recommended by international clinical guidelines,\textsuperscript{20-22} is not commercially available in Japan. In the cohort prior to this RCT in our department, the standard duration of IOWI with saline was approximately one minute. PVP-I can induce antimicrobial activity within 30 seconds after application,\textsuperscript{38} and the duration of IOWI with aqueous PVP-I solution most frequently used in
previous RCTs was 1 minute. Therefore, in the present study, the duration of IOWI has been set to one minute for both groups.

SSI is associated with increased medical costs and imposes a huge burden on healthcare systems worldwide. When designing measures for SSI prevention, significant attention should be paid to its medical cost. A recent meta-analysis revealed that the introduction of absorbable antimicrobial sutures reduced the risk of SSI, and the mean savings per surgical procedure from using antimicrobial sutures was found to be significant across all wound types. In the present RCT, 40 ml of aqueous 10% PVP-I solution is being used for IOWI in the study group, and 100 ml of saline is being used for IOWI in the control group; the costs of IOWI in the two groups are almost the same. Because IOWI with aqueous PVP-I solution showed no dose-response effect, we will set the volume of aqueous 10% PVP-I solution used for IOWI at 40 ml (approximately JPY 40), which is in line with the price of 100 mL of saline (approximately JPY 40). There is novelty in our trial setting in that the cost of IOWI for SSI prevention is being carefully considered. If this trial reveals that IOWI with aqueous 10% PVP-I solution is more useful for SSI prevention than saline, the result will also be supported from a medical cost perspective.

Several limitations associated with the present study warrant mention. First, all patients undergoing gastrointestinal surgery, irrespective of the organ, diagnosis, or procedure, which are all associated with differing incidences of SSI, are being considered for
inclusion. Second, this trial is being conducted at a single center, and RCTs at single centers typically show larger treatment effects than multicenter RCTs. Well-designed multicenter RCTs will be necessary to generalize and substantiate the findings of this trial. Third, the evidence level is low. A meta-analysis suggested that IOWI with antibiotic solutions seems to be more effective than that with aqueous PVP-I solution. Should the present study reveal that IOWI with aqueous 10% PVP-I solution is effective for SSI prevention, it might be worth planning an RCT to compare IOWI with aqueous 10% PVP-I solution to that with antibiotic solutions in patients with clean-contaminated wounds after gastrointestinal surgery.

The results of the present RCT will provide high-level evidence regarding the effectiveness of IOWI with aqueous 10% PVP-I solution for SSI prevention for clean-contaminated wounds after gastrointestinal surgery. Should this trial reveal the superior efficacy of IOWI with aqueous 10% PVP-I solution for SSI prevention compared with saline, the evidence will strongly support the clinical CDC and WHO guidelines for SSI prevention as well as current surgical practice. The implementation of multidisciplinary care for SSI prevention after gastrointestinal surgery has been increasingly shown to be effective since the 2010s, and IOWI with aqueous PVP-I solution is being increasingly frequently incorporated as an important component of multidisciplinary care. Even if this trial produces negative results, our findings will contribute to the modification of future clinical guidelines in relation to IOWI for SSI prevention and support future RCTs exploring the development of effective
IOWI methods.

**Trial status**

Recruitment is continuing steadily, and as of January 2021, 540 participants have been enrolled. The current protocol is in operation at version 1.4 (June 11, 2020).
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Contributions.

RM and HN contributed equally to this study. RM, HN, KI, and ST made substantial contributions to conception and trial design. KI, RK, EM, NK, RS, HA, TF, NK, YM, MI, RF, FW, TK, MS, ST and YM were responsible for the protocol development. RM, HN and KI contributed the data management. RM and HN performed statistical analyses, and all authors interpreted the analytical results. RM and HN wrote the manuscript. HN and TR critically revised the manuscript. All authors made critical revisions and approved the final version of the manuscript.

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Competing interests statement.

The authors declare no competing interests in association with the present study.

Data availability statement.

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.
Table 1 Definition of the wound classes

| Class I (clean) | An uninfected operation wound in which no inflammation is encountered and respiratory, alimentary, and genitourinary tract is not entered. |
|----------------|----------------------------------------------------------------------------------------------------------------------------------|
| Class II (clean-contaminated) | An operative wound in which the respiratory, alimentary, and genitourinary tracts are entered under controlled conditions and without unusual contamination provided no evidence of infection or major break in technique is encountered. |
| Class III (contaminated) | A wound in which gross contamination/spillage and a break in sterile technique occurs, and incision in which acute, nonpurulent inflammation is encountered. |
| Class IV (dirty-contaminated) | A wound that is already considered infected, such as old traumatic wounds with retained devitalized tissue or perforated viscera. |
Table 2. Schedule and data collection of this trial.

| STUDY PERIOD | ENROLMENT: | INTERVENTIONS: | ASSESSMENTS: |
|--------------|------------|----------------|--------------|
|              |            | Intervention A (PVP-I) | Demographic data |
|              |            | Intervention B (saline) | Past medical history |
|              |            |                     | Physical examination |
|              | ENROLMENT: |                     |              |
| TIMEPOINT    | -1-2 days  | Surgery            |              |
|              |            | POD1               |              |
|              |            | POD3               |              |
|              |            | POD4-29            |              |
|              |            | POD30              |              |
| ENROLMENT:   | X          |                     |              |
| Informed consent | X   |                     |              |
| Inclusion and exclusion criteria | X |                     |              |
| Allocation   | X          |                     |              |
| INTERVENTIONS: | X      |                     |              |
| Intervention A (PVP-I) | X |                     |              |
| Intervention B (saline) | X |                     |              |
| ASSESSMENTS: | X          |                     |              |
| Demographic data | X |                     |              |
| Past medical history | X |                     |              |
| Physical examination | X |                     |              |
|                        | X | X | X |   |
|------------------------|---|---|---|---|
| Blood sample*          | X |   |   |   |
| Type of operation      | X |   |   |   |
| Time of operation      | X |   |   |   |
| Wound classification   | X |   |   |   |
| Estimated blood loss   | X |   |   |   |
| Blood transfusion      | X |   |   |   |
| Stoma creation         | X |   |   |   |
| Documentation of SSI   | X | X | X | X |
| Wound swab microbiology| X | X | X | X |
| Documentation of re-operation | X | X | X | X |
| Documentation of AE    |   |   |   | X |
| Duration of hospital stay |   |   |   |   |

* Includes white blood cell count, red blood cell count, hemoglobin, hematocrit, platelets, lymph cell count, total protein, albumin, bilirubin, AST, ALT, urea nitrogen, creatinine, Na, K, Cl, glucose

POD=postoperative day; PVP-I=povidone-iodine; SSI=surgical site infection;
Table 3. Definition of surgical site infection

| Superficial incisional SSI          | Date of event occurs within 30 days after any NHSN operative procedure (where day 1 = the procedure date) AND involves only skin and subcutaneous tissue of the incision AND patient has at least one of the following: a. purulent drainage from the superficial incision. b. organism(s) identified from an aseptically-obtained specimen from the superficial incision or subcutaneous tissue by a culture or nonculture based microbiologic testing |

AE = adverse event; AST = aspartate aminotransferase; ALT = alanine aminotransferase; Na = sodium; K = potassium; Cl = chloride
method which is performed for purposes of clinical diagnosis

or treatment (for example, not Active Surveillance Culture/Testing (ASC/AST)).

c. superficial incision that is deliberately opened by a surgeon, physician* or physician designee and culture or non-culture based testing of the superficial incision or subcutaneous tissue is not performed

**AND**

patient has at least one of the following signs or symptoms:

localized pain or tenderness; localized swelling; erythema;

or

heat.

d. diagnosis of a superficial incisional SSI by a physician* or physician designee.

* The term physician for the purpose of application of the NHSN SSI criteria may be interpreted to mean a surgeon, infectious disease physician, emergency physician, other
| Deep incisional SSI | The date of event occurs within 30 or 90 days after the NHSN operative procedure (where day 1 = the procedure date) 

**AND** 

involves deep soft tissues of the incision (for example, fascial and muscle layers) 

**AND** 

patient has at least one of the following: 

a. purulent drainage from the deep incision. 

b. a deep incision that spontaneously dehisces, or is deliberately opened or aspirated by a surgeon, physician* or physician designee 

**AND** 

organism(s) identified from the deep soft tissues of the incision by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical
diagnosis or treatment (for example, not Active Surveillance
Culture/Testing (ASC/AST)) or culture or nonculture based
microbiologic testing method is not performed. A culture
or
non-culture based test from the deep soft tissues of the
incision that has a negative finding does not meet this
criterion.

AND

patient has at least one of the following signs or symptoms:
fever (>38°C); localized pain or tenderness.
c. an abscess or other evidence of infection involving the deep
incision that is detected on gross anatomical or
histopathologic exam, or imaging test.

* The term physician for the purpose of application of the
NHSN SSI criteria may be interpreted to mean a surgeon,
infectious disease physician, emergency physician, other
| Organ/Space SSI | Date of event occurs within 30 or 90 days after the NHSN operative procedure (where day 1 = the procedure date) AND involves any part of the body deeper than the fascial/muscle layers that is opened or manipulated during the operative procedure AND patient has at least one of the following:  
  a. purulent drainage from a drain that is placed into the organ/space (for example, closed suction drainage system, open drain, T-tube drain, CT guided drainage).  
  b. organism(s) identified from fluid or tissue in the organ/space by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment (for example, not Active Surveillance) |
|---|---|
| physician on the case, or physician’s designee (nurse practitioner or physician’s assistant). |
Culture/Testing (ASC/AST)).

c. an abscess or other evidence of infection involving the organ/space that is detected on gross anatomical or histopathologic exam, or imaging test evidence suggestive of infection.
Explanation and Request for Participation in Clinical Research (Research Title: The effect of irrigation with aqueous iodophor solution on the incidence of surgical site infection after abdominal wall closure in gastrointestinal surgery: a randomized controlled trial) 

We will explain the contents of the research along with the process of consent for participation, in order to request your participation in this research. Should you fully understand this explanation and are willing to participate in the research, please tick the □ for the items in the "Research Participation Agreement" that you have received explanation and understood, then sign or print your name and affix your seal.

The implementation of this clinical research has been approved by the President of Jichi Medical University, upon receipt of approval by the Clinical Research Ethics Review Committee of Saitama Medical Center, Jichi Medical University

1 Names of research institutions and researchers

The researchers conducting this research are:

Professor Toshiki Rikiyama, Department of Surgery, Saitama Medical Center, Jichi Medical University

Ryo Maemoto, Department of Surgery, Saitama Medical Center, Jichi Medical University

Hiroshi Noda, Department of Surgery, Saitama Medical Center, Jichi Medical University

2 Objective and significance of research

There are various complications that occur following surgery, one of them being surgical site infection (suppuration of the wound; hereinafter, referred to as SSI). SSI can cause high fever and pain or cause discomfort for the patient and a delay in postoperative recovery, resulting from pus buildup under and deeper in the skin. It is also problematic that the treatment requires further medical expenses. Prevention is important for SSI, with various measures having been
taken to date, including the administration of antibacterial drugs, disinfection of the skin, and control of blood sugar levels.

This time, we focused on the cleaning method when closing a wound (hereinafter, referred to as the wound) by surgical incision at the end of surgery. Overseas treatment guidelines recommend that the subcutaneous tissue be washed with an aqueous iodophor solution (so-called Isodine solution; hereinafter, referred to as the Isodine solution) before closing the wound. However, in Japan, it is often washed with saline, which is inconsistent with overseas treatment guidelines. Because the current Isodine solution does not damage tissues, it can be safely used on wounds. The results of previous studies are shown below.

| Researcher and publishing year | Subject patients and number of patients | Intervention and contrast | Infection rate (intervention : contrast) | Conclusion (Iodophor irrigation was:)|
|-------------------------------|----------------------------------------|--------------------------|----------------------------------------|------------------------------------|
| Sindelar et al. 1979          | General surgery patients, 500          | Iodophor irrigation and Saline irrigation | 2.9% : 15.1%                           | Effective                           |
| Roger et al. 1983             | General surgery patients, 187          | Iodophor irrigation and Saline irrigation | 4.6% : 10.9%                           | Cannot say it was effective         |

While it has been reported that irrigation with an aqueous iodophor solution reduces the
incidence of SSI, the report was made more than 40 years ago.

We believe it is meaningful to verify the effectiveness thereof, taking into consideration that it is a cleaning method not widely used in Japan, along with the fact that the research on which the overseas treatment guidelines are based on was conducted so many years ago.

3 Method of research

After suturing the muscle layer, hemostasis at the wound should be confirmed. Subsequently, we move on to cleaning the wound, at which point the cleaning method is divided into a group that is washed with normal saline (hereinafter, referred to as the control group) and a group that is washed with the povidone-iodine solution (hereinafter, referred to as the intervention group). The skin is closed after thoroughly cleaning the wound in each group. Both groups use subcutaneous sutures (suture method that does not require suture removal) to close the skin. The incidence of SSI in both groups is compared.

The group to which you belong will be randomly assigned by the Support Center for Clinical Investigation at Jichi Medical University. For the sake of fairness, you will not be informed of the group to which you belong.

SSI is determined by postoperative wound observation. The observation period is 30 days following surgery. Wound observation is performed daily by the attending physician team during hospitalization, such as during rounds, and continues until discharge. If SSI is suspected, the wound is opened or cleaned upon examination, etc., similar to daily practice. A physician other than the attending physician may see you to assess the infection. After discharge, please observe the wound yourself and contact us immediately if there is any change. You may visit the hospital for observation of the wound and treatment will be provided, if necessary. This is covered within the scope of health insurance, as the treatment is the same as regular medical care. You will be responsible for transportation expenses. Even if there is no change in the wound, the outpatient physician will perform wound observation upon the outpatient visits after
discharge.

The obtained data and the course of medical care are compiled by researchers and statistically analyzed.

Because this research is conducted within the normal insurance practice, there is no particular burden on the patient.

4 Research period

The research will be conducted from April 11, 2019 through March 31, 2023 (during this period, you will be participating for approximately a month.)

5 Reasons for being selected as a research subject

As mentioned in 2, the purpose of this research is to investigate the presence or absence of SSI; therefore, we are asking those who will undergo a gastrointestinal surgery (gastrointestinal tract, liver, gallbladder, pancreas, etc.) at our department to participate. You have:

Disease name: ______________________________________________________

and are scheduled to undergo surgery for the said disease; therefore, we are requesting your participation in this research.

6 The burden on the research subject and the expected risks and benefits

(1) Burden on research subjects

This research does not impose any particular burden on you.

(2) Expected risks and benefits
It is very unlikely that the participation in the research poses a unique risk. In rare cases, strong allergic reactions such as anaphylaxis, redness and itchiness of the skin may appear, due to the influence of the povidone-iodine solution. However, the same povidone-iodine solution is used on a daily basis for preoperative skin disinfections. Previous studies, in which we have compared the effects of povidone-iodine and saline irrigation on wounds, have not reported any adverse events due to the use of povidone-iodine.

Furthermore, this research will not benefit you in any way.

7 Participation in the research is voluntary and you will not be put at a disadvantage by not providing your consent for participation

Participation in this research is voluntary. Please decide of your own free will. Should you not agree to participate, you will not be put at a disadvantage in any way. We will provide the best medical care as usual at this hospital.

8 You will be able to withdraw consent at any time without being put at a disadvantage, even after initially consenting to participate in the research

You can withdraw your consent and cancel participation at any time without being put at a disadvantage, even if you have initially agreed to participate. Furthermore, the samples and medical records provided for this research will not be subsequently used. However, if the research results have already been published in a treatise at the time your consent is withdrawn, we may not be able to discard the research results and samples.

9 Method of disclosing information regarding the research

You can view this research plan and related materials, as long as it does not interfere with the protection of personal information of other research subjects or the securing of the originality of the research. Please let us know if you wish to view these.
The research outline and results will be registered in the database of the National University Hospital Council of Japan, etc.

10 Protection of personal information

In conducting this research, the names and addresses of the samples and medical record information provided by you will be deleted, such that no specific individual can be identified; rather, we will anonymize individuals using a symbol that is unrelated to you. The correspondence table that links you to this code is stored and strictly managed, by the principal investigator, in the locked cabinet of the physician’s room on the 5th floor of the management research building in the research laboratory of Saitama Medical Center, Jichi Medical University. By doing so, researchers who analyze samples and medical information will not know whose samples, etc. they are analyzing.

Personal information will not be provided to third parties. Research results will be reported at academic conferences and treatises in such a way that individuals cannot be identified.

11 Method of storing and disposing of samples and information

(1) Method of storing samples, information, etc.

Once the research is completed, samples and information will be stored in the locked cabinet on the 5th floor of the management research building in the research laboratory of Saitama Medical Center, Jichi Medical University. Should stored information, etc. be used for some other purpose, we will apply to the Ethics Committee again to obtain approval.

(2) Method of disposing of samples and information

They will be erased by dedicated data-erasing software.

12 Status of conflicts of interest related to research by researchers, such as research
funding sources, conflicts of interest related to research at research institutes, and personal income

(1) Funding sources

This research will be conducted using the research funds of the Department of Surgery, Saitama Medical Center, Jichi Medical University.

(2) Conflict of interest status

The status of conflicts of interest, summarized by fiscal year as stipulated in the Conflicts of Interest Management Policy, is entered and is examined by the university.

13 Financial burden or reward

There is no new financial burden on you to participate in this research. There is no reward either.

14 Attribution of intellectual property rights

Although intellectual property rights such as patent rights may arise as a result of this research, those rights belong to the university or researcher, not to you. While such rights may have financial benefits, you do not have such rights.

15 Matters related to other treatment methods, in the case of research involving medical practices that go beyond normal medical care

This research is conducted within the scope of normal practice.

16 Response to the provision of medical care to the research subjects after the research is conducted, in the case of research that involves medical practices that go beyond normal medical care

This research is conducted within the scope of normal practice.
17 Handling of research results related to research subjects, etc., in the event potential important findings regarding the health of the research subjects, along with genetic characteristics that can be inherited by their offspring, can be obtained

This research does not provide any insight concerning genetic characteristics that can be inherited by offspring.

18 Compensation for health hazards

There is no compensation associated with this research. This research will be conducted within the scope of health insurance, in the same manner as regular medical care. As health insurance will also be used to treat health problems such as side effects, you will be responsible for the copayment of the insurance.

19 Potential to use samples/information, etc. for future unspecified research, along with the potential of providing said samples/information, etc. to other research institutes

In the event of the potential for samples/information, etc. to be used for future unspecified research, we will apply to the Ethics Committee again to obtain approval.

There is no potential of providing samples/information, etc. to other research institutes.

20 Potential for viewing samples, information, etc. by persons other than researchers

There is no potential for anyone other than the researchers to view the materials, information, etc. in this research.

21 Contact details for consultations, complaints, etc.

Should you have any questions regarding this research, please contact the following principal investigator.
Principal investigator: Ryo Maemoto, Department of Surgery, Saitama Medical Center, Jichi Medical University

Address: 1-847 Amanuma-cho, Omiya-ku, Saitama-shi, Saitama Prefecture

Telephone: 048-647-2111

Should you have any complaints, please contact the General Affairs Division, Saitama Medical Center, Jichi Medical University (telephone 048-648-5225).
To: President of Jichi Medical University

With regard to "The effect of irrigation with aqueous iodophor solution on the incidence of surgical site infection after abdominal wall closure in gastrointestinal surgery: a randomized controlled trial," I have received an explanation on the following items by way of an explanatory document.

(Please tick the □ for the items you understand upon receiving explanation.)

- Name of research institution and name of researcher
- Objective and significance of research
- Research method
- Research period
- Reasons for being selected as a research subject
- The burden on the research subject and the expected risks and benefits
- Participation in the research is voluntary and will not be put at a disadvantage by not providing consent to participate.
- I am able to withdraw my consent at any time without being put at a disadvantage, even after initially consenting to participate in the research.
- Method of disclosing information regarding the research
- Protection of personal information
- Method of storing and disposing of samples and information
- Status of conflicts of interest related to research by researchers, such as research funding sources, conflicts of interest related to research at research institutes, and personal income
- Financial burden or reward
- Attribution of intellectual property rights
- Matters related to other treatment methods, in the case of research involving medical practices that go beyond normal medical care
- Response to the provision of medical care to the research subjects after the research is conducted, in the case of research that involves medical practices that go beyond normal medical care
- Handling of research results related to research subjects, etc., in the event potential important findings regarding the health of the research subjects, along with genetic characteristics that can be inherited by offspring, can be obtained.
Compensation for health hazards

Potential to use samples/information, etc. for future research without specification, along with the potential of providing the said samples/information, etc. to other research institutes

Potential for viewing samples, information, etc. by persons other than researchers

Contact details for consultations, complaints, etc.

Having fully understood the above explanation, I agree to participate in the research as a research subject.

If you agree with the following, please tick the box.

I agree that the samples and information I provide for this research will be stored for a long period of time and subsequently used for new research conducted in the future with the approval of the Ethics Review Board.

Date: _____ Year _____ Month _____ Day

Address: ________________________________

Name: ________________________________

(sign or print your name and affix your seal)

Signature line of the principal investigator physician or a member physician of the investigation

I have fully explained this clinical research to the above patient.

Explanation date: _____ Year _____ Month _____ Day Dept.: Surgery

Name: ________________________________ (Signature)
# SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item             | Item No | Description                                                                                                                                                                                                 | Addressed on page number |
|--------------------------|---------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| **Administrative information** |         |                                                                                                                                                                                                          |                          |
| Title                    | 1       | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym                                                                                               | 1                        |
| Trial registration       | 2a      | Trial identifier and registry name. If not yet registered, name of intended registry                                                                                                                      | 11                       |
|                          | 2b      | All items from the World Health Organization Trial Registration Data Set                                                                                                                                  | 11                       |
| Protocol version         | 3       | Date and version identifier                                                                                                                                                                               | 22                       |
| Funding                  | 4       | Sources and types of financial, material, and other support                                                                                                                                             | 29                       |
| Roles and responsibilities| 5a      | Names, affiliations, and roles of protocol contributors                                                                                                                                                  | 29                       |
|                          | 5b      | Name and contact information for the trial sponsor                                                                                                                                                       | Not applicable          |
|                          | 5c      | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | Not applicable          |
|                          | 5d      | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | Not applicable          |
**Introduction**

**Background and rationale**

6a Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention 5-8

6b Explanation for choice of comparators 5-8

**Objectives**

7 Specific objectives or hypotheses 8

**Trial design**

8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) 8

**Methods: Participants, interventions, and outcomes**

**Study setting**

9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained 8

**Eligibility criteria**

10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) 8, 9

**Interventions**

11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered 9, 10

11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) 12, 13

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) Not applicable

11d Relevant concomitant care and interventions that are permitted or prohibited during the trial 8, 9

**Outcomes**

12 Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended 13, 14

**Participant timeline**

13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) 12
| Sample size | 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 | Strategies for achieving adequate participant enrolment to reach target sample size                                                                                                                                 |

**Methods: Assignment of interventions (for controlled trials)**

**Allocation:**

| Sequence generation | 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 | 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 | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions |

**Blinding (masking):**

| Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Not applicable                                                                                                                                                                                                                                                |                                                                                                                                                                                                     |

**Methods: Data collection, management, and analysis**

| Data collection methods | 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                    | 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 |
| Section             | Number | Description                                                                                                                                                                                                 |
|---------------------|--------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Data management     | 19     | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol |
| Statistical methods | 20a    | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol                                                |
|                     | 20b    | Methods for any additional analyses (eg, subgroup and adjusted analyses)                                                                                                                                      |
|                     | 20c    | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) |
| Methods: Monitoring |        |                                                                                                                                                                                                             |
| Data monitoring     | 21a    | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed |
|                     | 21b    | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial                                               |
| Harms               | 22     | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct                                |
| Auditing            | 23     | 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    | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval                                                                                                                      |
| Protocol amendments | 25     | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) |
|------------------|-----|--------------------------------------------------------------------------------------------------|
|                   | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable |

**Confidentiality**

| 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**

| Financial and other competing interests for principal investigators for the overall trial and each study site |
| 29 |

**Access to data**

| Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators |
| 29 |

**Ancillary and post-trial care**

| Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation |
| Not applicable |

**Dissemination policy**

| 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 |
| 16, 17 |

| Authorship eligibility guidelines and any intended use of professional writers |
| 29 |

| Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code |
| Not applicable. |

**Appendices**

| Model consent form and other related documentation given to participants and authorised surrogates |
| 9 |

| Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable |
| Not applicable |

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