

**A randomized, multicenter, open-label phase III trial
comparing 2 regimens of oral and parenteral antibiotic
prophylaxis in elective laparoscopic colorectal surgery:
The Japan-Multinational Trial Organization (JMTO) PREV
07-01.**

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Table of Contents

0. Schema

1. Purpose

2. Background and evidence

3. Drug information (also see package inserts)

4. Eligibility criteria

5. Exclusion criteria

6. Stratification factors

7. Target cases and study period

8. Study design

9. Evaluation and reporting of adverse events

10. Study schedule

11. Evaluation criteria and definition of endpoints

12. Statistical considerations

13. Ethical considerations

14. Procedure for enrollment

15. References

16. Organizations

17. Presentation and publication of study results

18. Criteria for the discontinuation of the study

19. Approval and amendment of the protocol

Appendix 1: Sample Information Sheet/Consent Form/Consent Withdrawal Form

Appendix 2: Link to package inserts: Drug Information Provision Service website

Appendix 3: ECOG Performance Status (PS) score

Appendix 4: Ethics Committee Approval Reporting Form

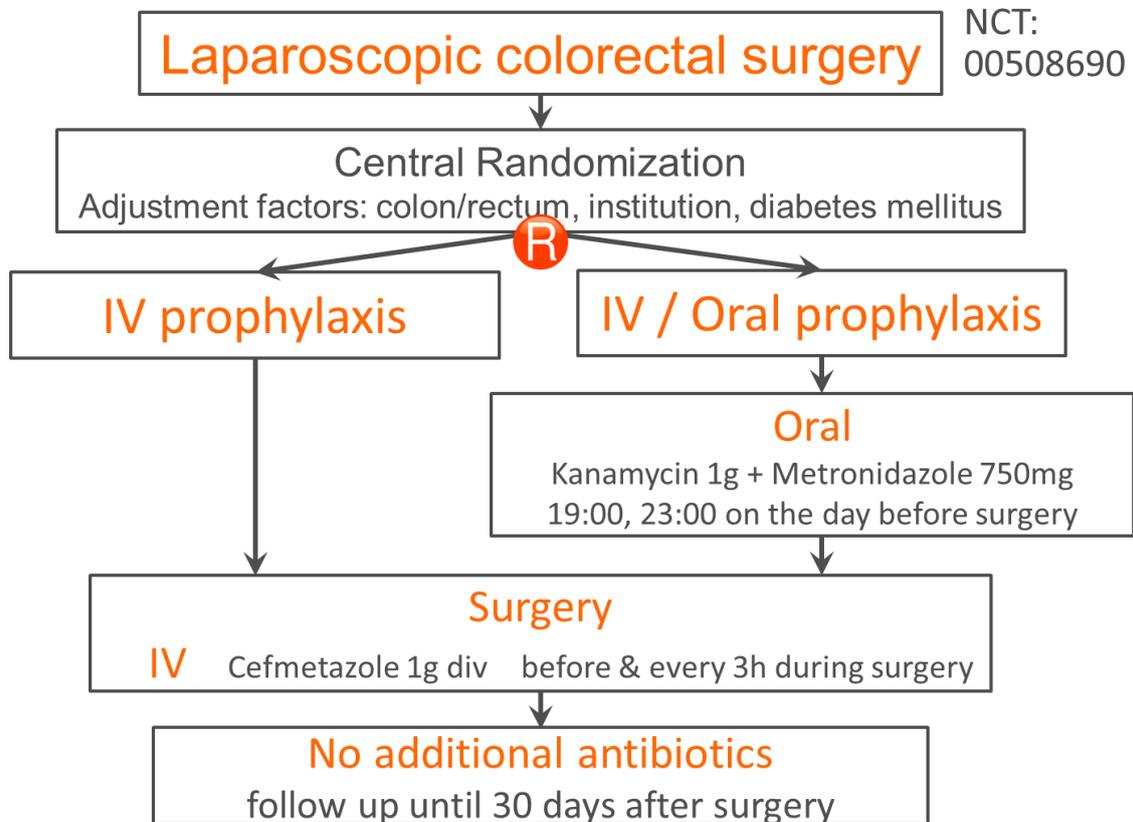
Appendix 5: Templates of Site Enrollment Completion Notification/Patient Enrollment Confirmation Form/Ineligibility Notification

Appendix 6: Patient Enrollment Form/Case Report Form

Appendix 7: NCI-CTCAE VER.3.0, Japanese version

Appendix 8: Report on Serious Adverse Events

0. Schema



1. Purpose

To demonstrate the efficacy of a combined oral and parenteral administration of the prophylactic antibiotic cefmetazole, kanamycin and metronidazole a day before the operation over parenteral antibiotic alone to facilitate the prevention of surgical site infection (SSI) after a laparoscopic-assisted colectomy.

2. Background and evidence

While a number of evidence-based studies regarding prophylactic antibiotic use in colectomy have been reported in the U.S. and Europe, such studies have not been extensively carried out in Japan. Out of 150 reported studies on prophylactic antibiotic use in colon surgery, approximately half of them included only around 100 patients and used different types of antibiotics at varying dosages, leaving a limited number of studies actually providing reliable data.

The guidelines published by the U.S. Centers for Disease Control and Prevention (CDC) in 1999 recommend that for patients undergoing elective colon surgery, prophylactic oral antibiotic administration with kanamycin plus erythromycin should be given only on the day before the operation (Evidence Level Ib).¹⁾ In Europe, it is recommended that IV administration of cefuroxime plus metronidazole or a cephem antibiotic alone should be given only before and during an operation.²⁾ In contrast, in Japan, the treatment guidelines developed by the Japanese Association for Infectious Diseases/Japanese Society of Chemotherapy discourage use of preoperative oral antibiotics due to evidence of increased MRSA infection. They instead recommend in favor of IV administration of cephem antibiotics during the period spanning right before to 3-4 days after an operation.³⁾ A meta-analysis of 134 clinical studies of prophylactic antibiotic use in colon surgery has reported the incidence of SSI to be at 11%.²⁾ In a randomized 3-year clinical study starting in 2000 and conducted by Ronald et al. on 216 patients, the incidence of SSI with oral versus oral plus IV administration of prophylactic antibiotics was 17% versus 4.8%, with a risk ratio of 0.29 and 95% CI of 0.11-0.75.⁴⁾ Although the 95% confidence interval (CI) for SSI incidence was not reported, it is expected to occur at a rough incidence of 10% after colon surgery, suggesting the need for more efforts to further reduce the occurrences.

Laparoscopic-assisted surgery is less stressful for patients, and involves smaller skin incisions with a shorter time required for extra-abdominal operations as compared to conventional laparotomy, thus posing a lower risk of SSI. However, previous studies only evaluated SSI as one of the short-term complications reported in other studies and were conducted under different conditions including different antibiotic treatment regimens. Thus, the present study is the first to evaluate SSI as the primary endpoint.⁵⁾ In addition, laparoscopic-assisted colectomy allows patients to resume oral intake the day after the operation and eliminates the need for IV infusion in most cases. It also allows patients to get out of bed and perform other activities such as taking a bath, in an early

postoperative period. In lieu of all this, the exploration of a new regimen for prophylactic antibiotic administration in laparoscopic-assisted colectomy is considered of great significance.

A comparative analysis of the relationship between prophylactic antibiotic treatment regimens and the incidence of SSI in patients who underwent laparoscopic-assisted colectomy at our hospital revealed the incidence to be 12% with a 3-day IV administration, 20% with oral administration on the day before the operation, 11% with IV administration right before and during the operation, and 3.3% with pre- and intra-operative IV with oral administration on the day before the operation. The antibiotics used were cefmetazole for IV and kanamycin plus metronidazole for oral administration. These antibiotics were selected because an increasing number of randomized clinical studies are using IV monotherapy with cephem antibiotics with an activity spectrum that includes anaerobic bacteria such as ceftiofur and cefotetan,⁶⁾ and cefmetazole is the drug kind that is most commonly used in colon surgery in Japan.⁷⁾ In addition, with respect to oral antibiotics, metronidazole has shown to exert a stronger antibacterial effect than erythromycin against anaerobic bacteria, and recent studies have demonstrated good outcomes in patients treated with a combination of kanamycin and metronidazole.⁷⁾ These findings suggest that the prophylactic pre- and intra operative IV and oral antibiotic treatment regimen given on the day before the operation prevents SSI more effectively than any other regimen recommended in the U.S., Europe, and Japan.

Based on this hypothesis, we designed a 3-phase clinical study to evaluate the efficacy of the combined prophylactic and oral antibiotic treatment regimen given a day before the operation to patients undergoing laparoscopic-assisted colectomy. In this study, the patients will be assigned to receive either IV-administered cefmetazole (IV group), which has been most commonly used as a control treatment,⁸⁾ or the same combined with oral administration of kanamycin plus metronidazole given on the day before the operation (Oral/IV group), which has been demonstrated to be effective during a meta-analysis in 2002.

The regimen recommended by the CDC guidelines, consisting of preoperative oral antibiotic alone, is not used in this study, given a low compliance to the regimen in clinical settings in the U.S. and a relatively high incidence of SSI with this regimen.⁹⁾

The regimen recommended by the Japanese guidelines, consisting of 3-4-days postoperative IV administration of antibiotics, is also not used in this study due to lack of evidence to support the regimen and absence of the postoperative continuous administration of antibiotics for prophylactic purposes outside Japan.

3. Drug information (see also package inserts)

3-1. Kanamycin sulfate (Kanamycin Capsule, Meiji Seika Kaisha, Ltd.)

3-1-1. General information

Kanamycin sulfate is an aminoglycoside antibiotic that exerts a bactericidal effect by inhibiting the

cell division/proliferation process of bacteria through the inhibition of protein synthesis. The CDC guidelines recommend the prophylactic use of non-absorbable aminoglycosides in colon surgery. Kanamycin is also extensively used in Japan for eradication of enterobacteria, especially gram-negative bacilli, in patients with hepatic encephalopathy.

3-1-2. Adverse drug reactions

Nervous system (<0.1%), kidney (<0.1%), gastrointestinal system (0.1-<0.5%): gastrointestinal symptoms, such as anorexia, nausea and diarrhea, anaphylaxis ($\geq 5\%$ or unknown frequency), vitamin deficiency (<0.1%): vitamin K deficiency, vitamin B deficiency

3-1-3. Pharmacology

(See the package insert)

3-2. Metronidazole (Flagyl Tablets, Shionogi & Co, Ltd.)

3-2-1. Information about off-label use

Metronidazole is not currently covered by the National Health Insurance in Japan for use against intestinal infections. Outside, the drug is commonly used as a first-line treatment for intra-abdominal infections including those caused by anaerobic bacteria. The drug is also frequently used in Japan for eradication of *Helicobacter pylori* and treatment of intra-abdominal infections associated with inflammatory bowel disease.¹⁰⁾ The off-label use of metronidazole is becoming increasingly common. The drug is prescribed as a treatment option for peritonitis caused by anaerobes in the current textbooks on infectious diseases. This drug was selected for use in the present study because of its unique feature of covering a broad spectrum of intestinal anaerobes.¹¹⁾

3-2-2. General information

A suggested mechanism for the antimicrobial effect of metronidazole is mediated by the reduction in the nitro group of the compound by microorganisms. The reduced product causes functional impairment of the microorganisms through such mechanisms as DNA double-strand breaks and inhibits cell division/proliferation. The literature cited in the CDC guidelines recommends the prophylactic use of metronidazole in colon surgery for its proven effectiveness against anaerobic bacteria. A meta-analysis has also demonstrated that the oral administration of metronidazole can reduce the incidence of SSI.

3-2-3. Adverse drug reactions

Adverse drug reactions (ADRs) reported at a frequency of $\geq 5\%$ or unknown include rash, leukopenia, gastrointestinal symptoms and hepatic dysfunction. For information about other ADRs, see the package insert.

3-2-4. Pharmacology

See the package insert.

3-3. Cefmetazole (Cefmetazon, Daiichi-Sankyo)

3-3-1. General information

Second-generation cephem antibiotics, including cefmetazole, are recommended for use as prophylactics in colon surgery, as their activity spectrum covers Enterobacteriaceae bacteria (e.g., E. coli) and anaerobic bacteria (e.g., Bacteroides). Cefmetazole was selected for the present study as it is commonly used in many institutions. Cefmetazole is believed to exert a bactericidal effect by strongly inhibiting the synthesis of the bacterial cell wall during the growth phase.

3-3-2. Adverse drug reactions

The incidence of ADRs has been reported to be about 3%. Major ADRs include AST (GOT) increase (0.94%), ALT (GPT) increase (0.90%), rash (0.82%) and nausea/vomiting (0.20%). For information about other ADRs, see the package insert.

3-3-3. Pharmacology

See the package insert.

4. Eligibility criteria

4-1. Eligibility criteria

- 1) Patients with colon tumor, including confirmed and suspected cases of colon cancer or colon adenoma, undergoing elective laparoscopic colorectal surgery.
- 2) Having good oral intake.
- 3) ECOG Performance Status (P.S.) of 0 or 1 (see Appendix 3).
- 4) Age \geq 20 years.
- 5) Adequate function of major organs, as evidenced by the following laboratory results obtained within 2 weeks prior to enrollment: \rightarrow within 4 weeks prior to enrollment. (2008.03.01 Partial amendment)

Leucocyte count \geq 3,000/mm³ and \leq 12,000/mm³

Hemoglobin \geq 8 g/dL

AST (GOT) \leq laboratory reference range x 2.5

ALT (GPT) \leq laboratory reference range x 2.5

Albumin \geq 3 g/dL

Creatinine \leq laboratory reference range x 1.5

HbA1c \leq 7.0 %

SpO₂ \geq 95% (room air)

- 6) Written informed consent to participate in the study.

5. Exclusion criteria

5-1. Exclusion criteria

- 1) Bowel obstruction.
- 2) Pre-operative infections.
- 3) Antibiotics use within two weeks before surgery.
- 4) Long-term treatment with corticosteroids within 6 months prior to the operation.
- 5) Neo-adjuvant radiation and/or chemotherapy.
- 6) Uncontrolled diabetes mellitus.
- 7) Pregnant or lactating woman.
- 8) History of severe drug allergy (CTCAE Grade ≥ 3).
- 9) Patients deemed unsuitable for this study by the study investigator for any other reason.

6. Stratification factors

6-1. Stratification factors

Patients will be stratified by the following factors:

- Institution.
- Operative procedure (anterior resection, abdomino-perineal resection, colectomy).
- Abnormal glucose tolerance (CTCAE Grade 0-1 or 2-3).

6-2. Randomization

Enrolled patients will be randomly assigned to the Oral/IV group or the IV group, using the method of Pocock and Simon (Pocock SJ and Simon R. Sequential assignments with balancing for prognostic factors in the controlled clinical trial. Biometrics 31: 103-115, 1975).

7. Sample size and study period

7-1. Sample size: 580 patients.

7-2. Study period: 2.5 years. → 4.5 years. (2009.05.22 Partial amendment)

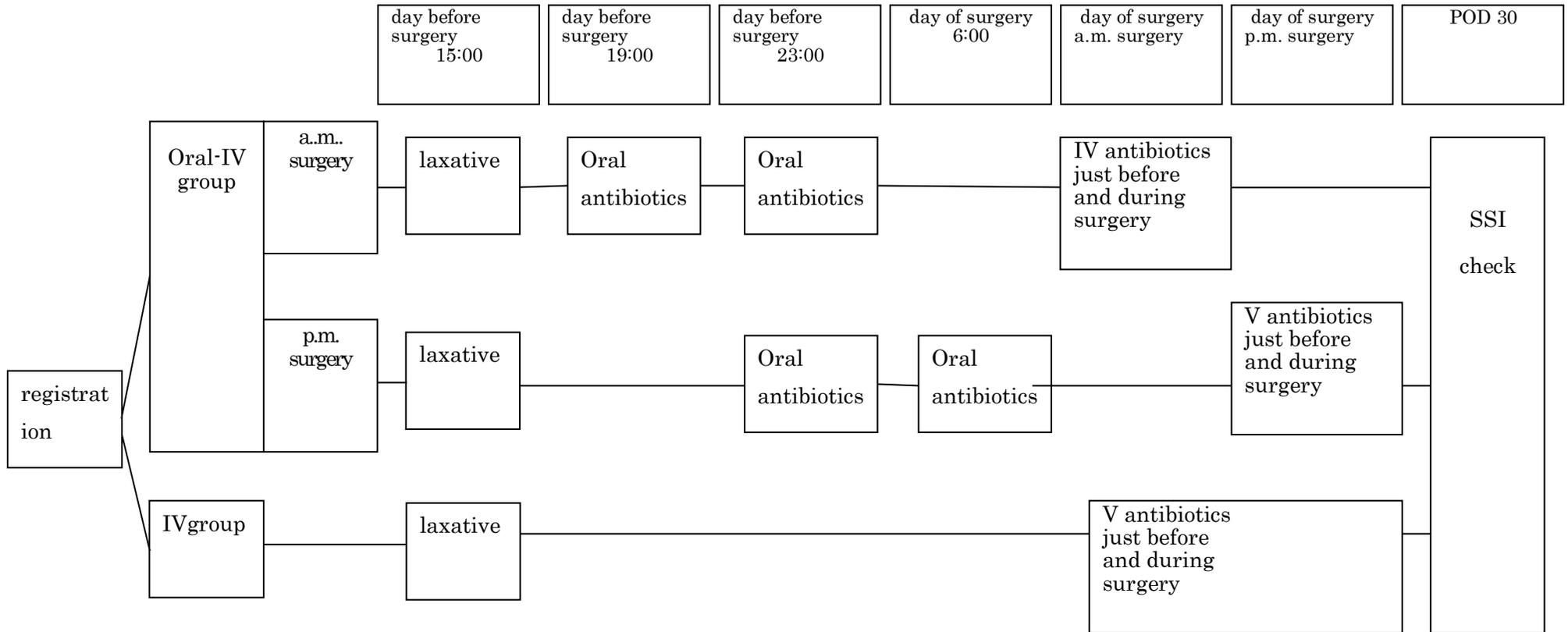
8. Study design

8-1. Study initiation.

Study will be initiated within 2 weeks of enrollment.

8-2. Study overview

Two treatment groups, the Oral/IV and IV groups, will be defined.



8-3. Preoperative study design

- 1) Patients in the IV group will be served with a formula diet along with oral administration of a laxative (magnesium citrate in 180 ml hypertonic solution (dissolve 1 bag of Magcorol P powder in 180 ml) + 10 ml sodium picosulfate solution (1 bottle of Laxoberon)) at 15:00 on the day before the operation.
- 2) Patients in the Oral/IV group will be administered with the same dosage as the patients in the IV group. Patients will also be given 2 doses of combined kanamycin (KM) 1 g and metronidazole 750 mg at 19:00 and 23:00 on the day before the operation if the operation is planned in the morning of the following day, or before going to bed on the day before the operation and at 06:00 on the day of the operation if the operation is planned in the afternoon. In the event of any adverse reactions, such as anaphylactic shock, administration will be discontinued and the reason for the occurrence of the reaction will be recorded in the case report form (CRF).

8-4. Intraoperative study design

- 1) Patients in both groups will be intravenously infused with 100 ml of cefmetazole 1 g + NS before the surgeon washes his or her hands. During the operation, the same amount of the infusion will be additionally given every 3 hours. In the event of any adverse reactions, such as anaphylactic shock, administration will be discontinued and the reason for the occurrence of the reaction will be recorded in the CRF.
- 2) The surgical wound site will be closed by the interrupted fascial suture technique with an absorbable monofilament suture. The skin will be sutured by the buried suture technique with an absorbable monofilament suture. → The skin will be sutured by the buried suture technique with an absorbable monofilament suture or closed with staples. (2008.03.01 Partial amendment.)
- 3) No indwelling drain will be used in principle. If a drain is used based on the physician's judgment, the reason will be recorded in the CRF.

8-5. Postoperative design

- 1) The surgical wound site will be covered with gauze. The gauze will not be changed on postoperative day (POD) 1 unless there is leakage of exudate. On POD 2 and thereafter, if epidermal fusion is observed, wound site protection will not be performed and the patient will be allowed to take a bath.
- 2) The worst cases of diarrhea during the first 30 days after the operation will be recorded.
- 3) In cases of clinically suspected enteritis, stool culture as well as Clostridium difficile (CD) toxin test by enzyme immunoassay will be performed.
- 4) Bacterial culture test, including anaerobes, will be performed on all confirmed or suspected cases of SSI.

9. Evaluation and reporting of adverse events

9-1. Evaluation of adverse events

1) Adverse events

The evaluation of adverse events (AEs) will be based on the study assessments defined in section 9 and performed at the specified time points. Observed AEs will be graded according to the Japanese version of the NCI-Common Terminology Criteria for Adverse Events (NCI-CTCAE) ver. 3.0.

9-2. Expected adverse events and their management

1) Kanamycin

Nervous system (<0.1%), kidney (<0.1%), gastrointestinal system (0.1-<0.5%), gastrointestinal symptoms such as anorexia, nausea and diarrhea, anaphylaxis ($\geq 5\%$ or unknown frequency), vitamin deficiency (<0.1%), etc.

2) Metronidazole

ADRs reported at a frequency of $\geq 5\%$ or of unknown frequency include rash, leukopenia, gastrointestinal symptoms and hepatic dysfunction.

3) Cefmetazole

AST (GOT) increase (0.94%), ALT (GPT) increase (0.90%), rash (0.82%), nausea/vomiting (0.20%), etc.

4) Operative procedure-related

Intraoperative injury (e.g., injury of other organs).

9-3. Emergency response

In the event of any AE associated with the investigational antibiotics during or after study, the study investigator shall give appropriate treatment and, if the AE is among the severe adverse events (SAEs) listed below, immediately notify the principal investigator (Dr. Hiroaki Hata) verbally or by telephone or FAX, regardless of the causality with the investigational antibiotics. For SAEs (severe ADRs), for which a causal relationship with the investigational antibiotics could not be ruled out (including those with unknown causality), the details of the event shall be immediately reported to the director of the medical institution, principal investigator and the Operations Office of the JMTO using the Report on Severe Adverse Events form (see Appendix 8). The manufacturer of the drug shall also be notified. Upon receipt of the report from the principal investigator, the JMTO Operations Office will immediately notify the Independent Data Monitoring Committee (IDMC). The IDMC will then discuss necessary measures and intimate the directors and representative investigators at all study sites.

(1) Death

- (2) May lead to death
- (3) Requires inpatient hospitalization or prolongation of existing hospitalization for the treatment
- (4) Disability
- (5) May lead to disability
- (6) Other (equivalent in severity to any of 1 through 5 above)
- (7) Congenital disorder/abnormality in the later generation

9-4. Emergency contact

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10. Study schedule

10-1. Pre-enrollment evaluation (within 2 weeks prior to enrollment).

1) Subject/patient background

Height, weight, age, gender, presence or absence of abnormal glucose tolerance.

2) Diagnosis, planned operative procedure.

3) Presence or absence of comorbidities and history of drug anaphylaxis, such as allergy.

4) Hematology: WBC, Hb, Plt

- 5) Biochemistry: Alb, GOT, GPT, Cr and HgA1c
- 6) Function of major organs: CXR, ECG, SpO₂

10-2. Intraoperative evaluation

- 1) Checking the administration method of laxative and presence or absence of AEs.
- 2) Checking the administration method of antibiotics and presence or absence of AEs.
- 3) Presence or absence of contamination by leakage of bowel contents.
- 4) Presence or absence of intraoperative AEs.
- 5) Operative procedure.
- 6) Operation time.
- 7) Bleeding volume
- 8) Use or non-use of blood transfusion

10-3. Post-treatment evaluation

- 1) Presence or absence of SSI.
- 2) Presence or absence of diarrhea.
- 3) Presence or absence of enteritis, results of stool culture and CD toxin test.
- 4) Presence or absence of other infectious complications.
- 5) Presence or absence of AEs.

11. Evaluation criteria and definition of endpoints

11-1. Endpoints

The primary endpoint of this study is the incidence and classification of SSI. The secondary endpoints are the incidence of enterocolitis, other infectious diseases and postoperative complications.

11-2. Evaluation of SSI

The occurrence of SSI will be diagnosed according to the definition adopted by the CDC guidelines described below. Evaluation of SSI will be performed on PODs 3, 5, 7, 14 and 30. When evaluation cannot be done on any of the specified dates, it will be done on the first day of visit after the specified date. Every occurrence of SSI will be followed by bacterial culture (including anaerobic culture). Final results of the observation will be recorded in the CRF on POD 30 and submitted to the Data Center.

11-2-1. Classification of SSI

- 1) SSI is classified into incisional SSI and organ-space SSI.

2) Incisional SSI is further classified into superficial and deep incisional SSI.

11-2-2. Superficial incisional SSI

1) Infection occurs within 30 days after an operation and involves only the skin or subcutaneous tissue of the incisional site, with at least one of the following findings:

- (1) Drainage from a superficial incision.
- (2) Pathogenic bacteria isolated from a culture of fluid or tissue aseptically obtained from a superficial incision.
- (3) At least one of the following signs or symptoms of infection are observed despite a negative culture result: pain or tenderness, localized swelling, redness, or heat, and a sutured incision is deliberately opened by a surgeon.

11-2-3. Deep incisional SSI

1) Infection occurs within 30 days after an operation, with at least one of the following findings:

- (1) Drainage from a deep incision, excluding drainage from an organ or body space in the surgical site
- (2) A deep incisional wound spontaneously dehisces, or at least one of the following signs or symptoms is observed despite a negative culture result: fever ($\geq 38^{\circ}\text{C}$), localized pain, or tenderness, and a deep incisional wound is deliberately opened by a surgeon.
- (3) An abscess or other evidence of infection in a deep incisional wound is found upon direct examination, during reoperation, or by histopathological or radiological examination.

11-2-4. Organ-space SSI

1) Infection occurs within 30 days after an operation and involves any part of the body, excluding the skin incision, which is opened or manipulated during the operation, such as organs and spaces, with at least one of the following findings:

- (1) Drainage from a drain that is placed through a stab wound into an organ/space (Note: in principle, no postoperative drain will be inserted in this study).
- (2) Pathogenic bacteria isolated from a culture of a sample aseptically obtained from an organ/space.
- (3) An abscess or other evidence of infection in an organ/space is found on direct examination, during reoperation, or by histopathological or radiological examination.

11-3. Frequency of occurrence of enteritis, type of SSI, and type of bacteria responsible for infection.

11-3-1. Frequency of occurrence of diarrhea/enteritis

- 1) The occurrence of diarrhea will be monitored during the observation period until POD 30.
- 2) Every occurrence of Grade ≥ 3 enteritis (inflammation of large or small intestine) during the observation period until POD 30 will be followed by stool culture and immunoassay-based CD toxin test and submission of the results.

11-3-2. Incidence of each type of SSI

1) In addition to each type of SSI defined according to the classification system of the CDC described above, suturing failure will also be evaluated separately.

11-3-3. Type of causative bacteria

1) The type of causative bacteria will be identified based on culture results obtained from patients who developed SSI and/or enteritis, and the incidence of MRSA, *Pseudomonas aeruginosa* and *Clostridium difficile* will be determined.

12. Statistical considerations

12-1. Rationale for the sample size

This superiority study aims to demonstrate that the incidence of SSI in the Oral/IV group is lower than that in the IV group. Given the incidence of SSI of about 10% in the IV group and 4% in the Oral/IV group, a total of 283 patients per group will be required at a 2-tailed significance level (α) of 0.05 and a type II error (β) of 0.20. These number of patients can be accrued in 2.5 years, assuming that approximately 100 patients will be treated at each study site and 80% of them will provide consent.

12-2. Interim analysis

No interim analysis will be performed.

12-3. Verification of superiority

The superiority of the Oral/IV group will be verified by comparing the incidence of SSI between the IV and Oral/IV groups using the chi-square test.

12-4. Independent Data Monitoring Committee (IDMC)

The IDMC will monitor the overall progress of the study. The committee will obtain a progress and an ADR report annually from the JMTO Data Center, and will hold a meeting every 6 months, if necessary. The committee shall have the right to decide about the discontinuation and early reporting of the study.

13. Ethical considerations

13-1. Regulations to be complied with

All individuals involved in this study must comply with the World Medical Association's Declaration of Helsinki (revised in 2004) and the Ethical Guidelines for Clinical Research (Ministry of Health, Labour and Welfare notification No. 459, dated December 28, 2004).

13-2. Preparation and revision of the information sheet, consent form and consent withdrawal form
The information sheet, consent form and consent withdrawal form will be prepared by the representative investigator at each site. The Sample Information Sheet/Consent Form/Consent Withdrawal Form (Appendix 1), prepared by the principal investigator, may be used with some modification. The prepared information sheet/consent form should be submitted to and approved by the ethical committee at each site before the study is initiated.

The information sheet must include at least the following information and should not include any statement that intentionally encourages subjects to participate in the study:

- 1) That the study involves research
- 2) The purpose of the study
- 3) The methods of the study
- 4) The planned number of subjects participating in the study
- 5) The anticipated clinical benefits and risks or inconveniences
- 6) If a patient is included as a subject of the study, whether there are alternative methods of treatment available to the patient and their important potential benefits and risks
- 7) The indemnities and treatment subjects may receive if they suffer any injury related to the study
- 8) That the subject's participation in the study is voluntary and that the subject or the subject's legally acceptable representative may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which the subject is otherwise entitled
- 9) That the subject or the subject's legally acceptable representative will be informed in a timely manner if new information becomes available that may be relevant to their willingness to continue participation in the study
- 10) That subject's confidentiality will be protected even if the results of the study are published
- 11) If there is any financial burden on the subject, the details thereof
- 12) If any payments, etc. are to be made to the subject, the details thereof
- 13) Name, title and contact information of the representative investigator or study investigator at the study site
- 14) Contact point at the study site if the patient wants further information on the study and the rights of subjects, or if any injury occurs related to the study
- 15) That patent rights, etc. may be derived from the results of the clinical study, and identification of the party who will possess such rights
- 16) Date of preparation and version of the information sheet

The consent form must include the following information:

- 1) The title of the clinical study
- 2) Date of preparation and version of the information sheet
- 3) The section in which the date of explanation and the signature or seal of the representative/study investigator will be entered
- 4) The section in which the date of consent and the signature or seal of the subject will be entered
- 5) A statement indicating that the subject understands the details of the study and consents to participate in the study
- 6) The name of the study site

The consent withdrawal form must include the following information:

- 1) The title of the clinical study
- 2) The section in which the signature or seal of the representative/study investigator will be entered
- 3) The section in which the date of consent withdrawal and the signature or seal of the subject will be entered
- 4) A statement indicating that the subject wishes to withdraw his or her consent to participate in the study
- 5) The name of the study site

The representative investigator shall revise the information sheet/consent form when new information becomes available that may be relevant to the subject's consent to participate in the study after it has been initiated and the revision of these documents is deemed necessary. Such information includes details about new adverse events related to the concerned treatment and the development of a new treatment for the concerned disease. If the content of a revision is considered significant, the revised document should be submitted to and approved by the ethics committee at the site.

13-3. Informed consent

The representative/study investigator will provide adequate explanation of the study to a subject before his or her participation in the study using the information sheet, and obtain from the subject a written voluntary consent for participation.

When obtaining a written consent from a subject, the representative/study investigator who explained the study and the subject shall fully understand the content of the information sheet and date and seal/sign the consent form.

The representative/study investigator will issue a patient's copy of the sealed or signed consent form, as well as the information sheet, to the subject. An investigator's copy of the consent form, as well as the information sheet, should be attached to the subject's medical chart and kept at the study

site.

If a major amendment has been made to the information sheet, the representative/study investigator will explain again to the subjects participating in the study using the amended information sheet, and obtain the voluntary consent of the subjects to continue participation in the study.

When a subject participating in the study wishes to withdraw his or her consent, the representative/study investigator and the subject shall date and seal or sign a document indicating the subject's will to withdraw consent (i.e., consent withdrawal form). A copy of the consent withdrawal form will be issued to the subject and the original of the form will be attached to the subject's medical chart and stored at the study site.

13-4. Protection of personal information

All personnel involved in the study shall protect the personal information of the subjects strictly in accordance with the Personal Information Protection Act.

When providing a patient enrollment form or case report form to an organization outside the study site, the representative/study investigator shall assign a new case identification number and use it to anonymize the subject's information in a linkable fashion. Any information, by which someone outside the study site can identify the subject, such as the subject's name, address and telephone number, should not be provided.

When the Data Center enquires about a subject to the study site, the subject will be identified by a case identification number kept by the representative/study investigator or a registration number issued by the Data Center.

When information obtained from the study is published by the principal investigator or other personnel, sufficient care will be taken to ensure that the subjects are not identified.

14. Procedure for enrollment

14-1. Enrollment of study sites (see Fig. 1)

The enrollment of both study subjects and sites will be centrally coordinated by the JMTO Data Center (hereinafter, referred to as "the Data Center").

- 1) After approval by the ethics committee at the study site, the investigator representing each study site (hereinafter, referred to as "the representative investigator") will fill out the Ethics Committee Approval Notification form and send it to the Data Center by fax.
- 2) The Data Center will check the completeness of the form. If the form is deemed incomplete, the representative investigator will receive an inquiry from the Data Center by fax. (The representative investigator must respond to the inquiry by fax, in principle. The site will not be enrolled unless the form is deemed complete.)

3) If the form is deemed complete, the site will receive the Site Enrollment Completion Notification from the Data Center by fax. Site enrollment is completed upon the receipt of the notification.

14-2. Enrollment of study subjects (see Fig. 2)

1) Prior to the enrollment of subjects, each site will issue case identification numbers, each of which is expressed by a 6-character alphanumeric string, to anonymize patients. (The link between the case identification numbers and each patient must be kept on file at each site, and need not be sent to the Data Center.)

2) The study investigator will fill in the Patient Enrollment Form and Patient Background forms attached to the protocol, confirm the eligibility of the patient, and send the completed forms to the Data Center by fax. (The originals of the Patient Enrollment Form and Patient Background forms should be kept until the study is completed).

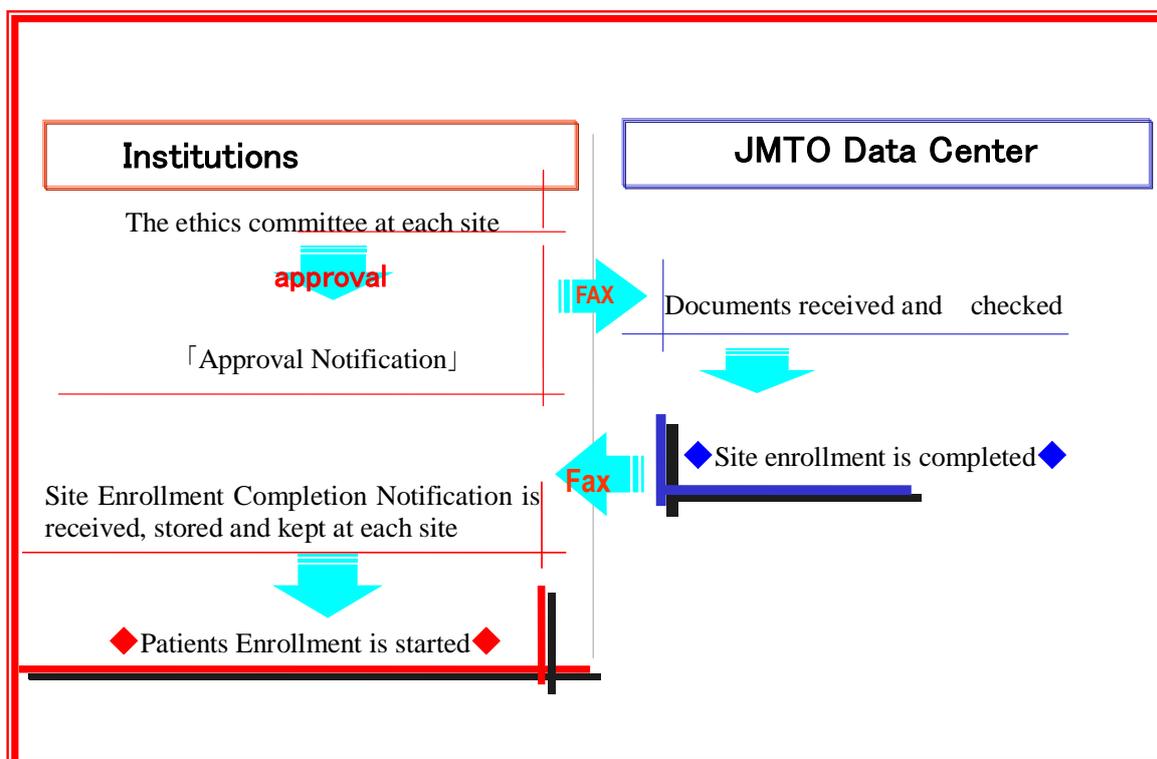


Fig. 1: Procedure for enrollment of study sites

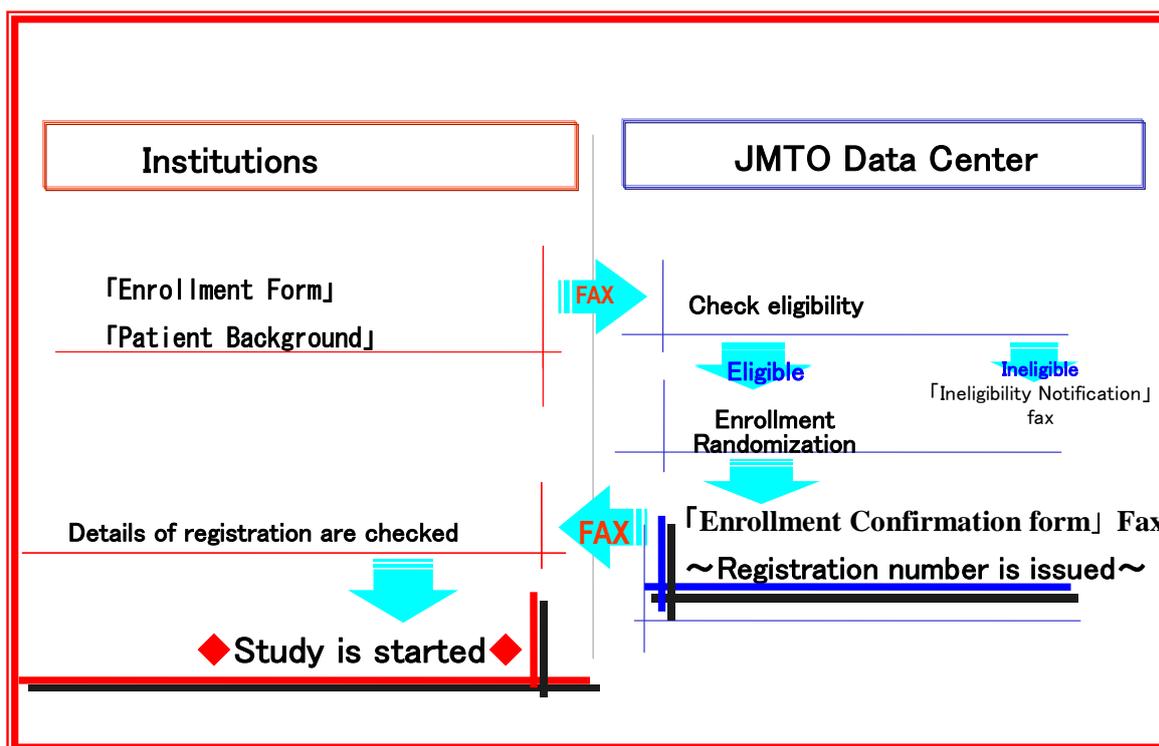


Fig. 2: Procedure for enrollment of study subjects

- 3) The Data Center will check the completeness of the submitted Patient Enrollment Form and Patient Background forms.
- 4) If the forms are deemed complete, the patient will be considered eligible. The eligible patient will be given a registration number and randomized based on stratification factors. The Data Center will prepare a Patient Enrollment Confirmation form based on the result of randomization and send it to the study investigator by fax. The registration number will be notified through the Patient Enrollment Confirmation form. If the patient is deemed ineligible, the study investigator will receive an Ineligibility Notification form from the Data Center by fax.
- 5) Patient Enrollment Confirmation forms for those enrolled between 09:00 and 12:00 will be faxed by 17:00 on the same day and by 12:00 on the following day for those enrolled between 12:00 and 17:00.
- 6) If the form is deemed incomplete, the study investigator will receive an inquiry from the Data Center by fax.

14-3. Contact for questions about enrollment of study sites/subjects

FAX: 075-241-4895

Office hours: 9:00am-5:00pm, Monday through Friday (office closed on weekends and holidays, including New Year holidays).

14-4. Preparation and submission of case report forms

The case report forms to be prepared and submitted in this study consist of the following documents:

Timing of submission	Type of document	Frequency of submission
1) <u>At enrollment</u>	Patient Enrollment Form, Patient Background	Once
2) <u>After completion of operation</u>	Operation records (1) and (2)	Once
3) <u>1 month after operation</u>	Final Adverse Events Report	Once
4) <u>Upon discontinuation of study</u>	Report on Study Discontinuation	Once at time of discontinuation

14-5. Procedure for preparation and fax submission of case report forms

1) The study investigator will fill in each case report form for submission at the specified time points. The originals of each form, (forms that are directly filled in), will be sent to the Data Center by fax. Each case report form must be submitted by fax within 2 days of the specified time of submission. The study investigator will keep the originals of the forms submitted by fax until completion of the study.

2) After receiving each case report form by fax, the Data Center will check the contents of the form and proceed with data entry if it is deemed complete. If the form is deemed incomplete, the Data Center will contact the study investigator by e-mail, fax or telephone to resolve the issue.

15. References

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- 5) Braga M, Vignali A, Gianotti L, et al. Laparoscopic versus open colorectal surgery: a randomized trial on short-term outcome. *Ann Surg* 2002; 236(6):759-66; discussion 767.
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- 9) Classen DC, Evans RS, Pestotnik SL, et al. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. *N Engl J Med* 1992; 326(5):281-6.
- 10) Takaku F, et al. *Manual of Therapeutic Agents* (2006). 2006. Igaku-Shoin. Tokyo
- 11) Fujimoto T. *Resident Manual for Infectious Diseases*. 2004. Igaku-Shoin. Tokyo

16. Organizations

Assisting organization for this study:

General Incorporated Association The Japan-Multinational Trial Organization (JMTO;

Representative Director: Hiromi Wada)

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Fax: +81-52-265-9523

mail: jmt0-adm@jmt0.org

Study sites

See the attachments

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jmto-dc@jmto.org

17. Presentation and publication of study results

The results of this study will be presented jointly by the study sites and reported in English under the joint names of the investigators from the study sites contributing to patient enrollment. The authors will be selected through discussion between the principal investigator, subinvestigator, executive secretary and person responsible for statistical analysis. The corresponding author is the principal investigator. In principle, presentations at academic meetings shall be made preferably by study sites enrolling a larger number of patients.

18. Criteria for discontinuation of the study

In principle, the study will be continued until the target sample size has been reached and assessments have been completed for all subjects. However, in the event of an unexpected serious ADR or apparent treatment-related death, the principal and representative investigator at the site will discuss whether to continue the study or not. The principal investigator will notify the JMTO Operations Office of the results of the discussion, and the office will then immediately notify the IDMC. The IDMC will then discuss necessary measures and communicate it to the directors and representative investigators at all study sites as well as the JMTO Ethics Committee.

19. Approval and amendment of the protocol

This protocol must be reviewed and approved by the ethics committees at each study site before patient enrollment is started at each site. Study sites that have no ethics committee may have the JMTO Ethics Committee review the protocol. When the need for protocol amendment arises after it has been implemented, patient enrollment will be temporarily discontinued and the decision will be communicated by the JMTO Operations Office. Patient enrollment will be resumed after the amended protocol has been reviewed and approved by the ethics committees at each site.