A multi-center, randomized controlled trial comparing early versus elective colonoscopy in outpatients with acute lower gastrointestinal bleeding

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Principal Investigators: Kazuhiko Koike, Atsuo Yamada
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List of ABBREVIATIONS

AE	Adverse Event
DCC	Data Coordinating Center
EDC	Electronic Data Capture
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IRB	Investigational Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
PI	Principal Investigator
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
UP	Unanticipated Problem

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with *ICH E6 (R2)*, and *Ethical Guidelines for Medical and Health Research Involving Human Subjects (Japan)*. The Principal Investigator will ensure that no deviation from, or changes to, the protocol will take place without prior agreement from the sponsor and documented approval from the institutional review board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator: Kazuhiko Koike

Principal Investigator: Atsuo Yamada

Date: 2016/6/9

PROTOCOL SUMMARY

Title: A multi-center randomized controlled trial comparing early versus elective colonoscopy in outpatients with acute lower gastrointestinal bleeding.

Précis: This multi-center, randomized controlled trial study is planned to include 162 outpatients with onset of acute lower gastrointestinal bleeding to compare the rate of identification of stigmata of recent hemorrhage (SRH), and other clinical outcomes, including the 30-day rebleeding rate, between 'early' colonoscopy, performed within 24 h of arrival at the hospital and 'elective' colonoscopy, within 96 h.

Objectives

Primary Objective: To evaluate whether early colonoscopy improved the identification rate of SRH versus elective colonoscopy.

Secondary Objectives: To evaluate whether early colonoscopy improved clinical outcomes, including 30-day rebleeding, success rate of endoscopic treatment, need for additional endoscopic examinations, need for interventional radiology, need for surgery, need for transfusion during hospitalization, length of stay, 30-day thrombosis events, and 30-day mortality, compared with elective colonoscopy.

Endpoints

Primary Endpoint: Identification of SRH

Secondary Endpoints: Thirty-day rebleeding, success rate of endoscopic treatment, need for additional endoscopic examination, need for interventional radiology, need for surgery, need for transfusion during hospitalization, length of stay, 30-day thrombosis events, 30-day mortality, preparation-related adverse events, and colonoscopy-related adverse events.

Population: In total, 162 males or females aged $\geq$ 20 years presenting with moderate-to-severe hematochezia or melena within 24 h of arrival at 15 Japanese hospitals.

Number of Sites Enrolling Participants: 15

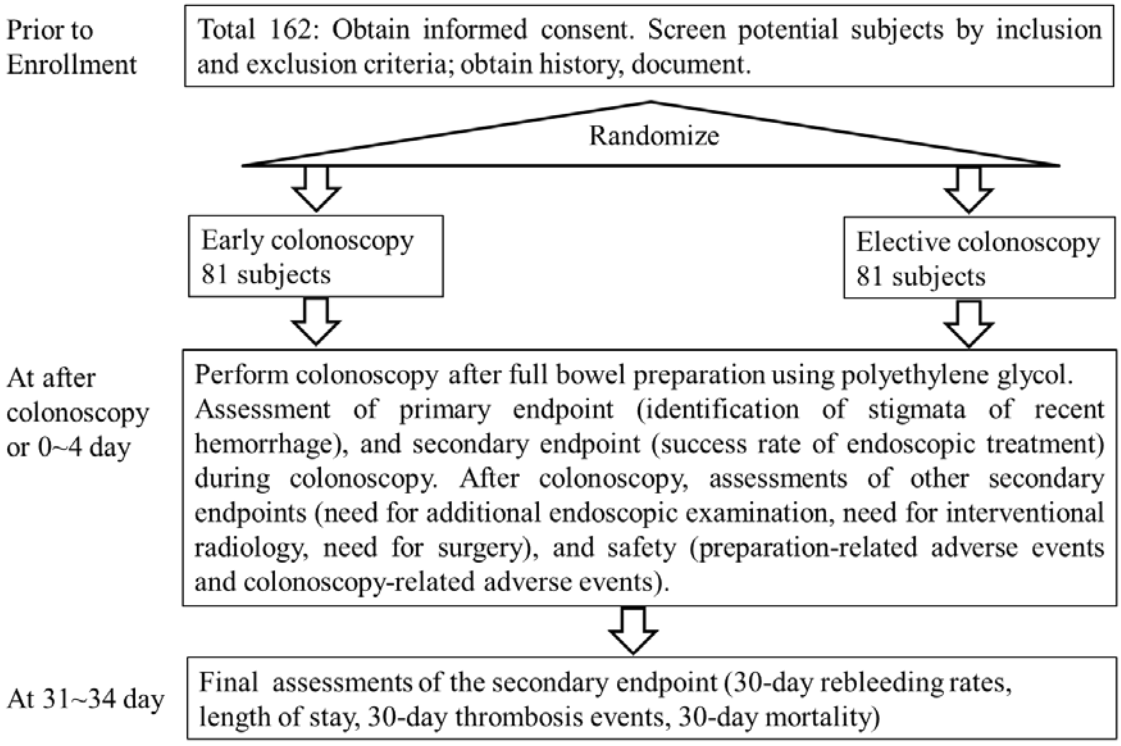
Description of Study Participants: Males or Females aged $\geq$ 20 years, presenting with moderate-to-severe hematochezia or melena within 24 h of arrival at a hospital.

Describe the intervention: Early colonoscopy is performed within 24 h of the initial visit. All colonoscopies are performed using an electronic video endoscope after 2-4 L of oral bowel preparation was administrated. If patients have not completely ingested oral bowel preparation solution until the effluent is free of fecal material, enema will be added for these patients.

Study Duration: 3 years

Participant Duration: 30 days

SCHEMATIC OF STUDY DESIGN



1 KEY ROLES

Funder

The Japanese Gastroenterological Association
Dr Kazuma Fujimoto
The Japanese Gastroenterological Association Director
2-1-1 Suido, Bunkyo-ku, Tokyo
Telephone: +81-3-5840-6338 Email: jga-secretariat@keiso-comm.com

Principal Investigators

Dr. Kazuhiko Koike
Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo, Japan
Telephone: +81-3-3815-5411 Email: kkoike-tky@umin.ac.jp

Dr. Atsuo Yamada
Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo, Japan
Telephone: +81-3-3815-5411 Email: yamada-a@umin.ac.jp

Project Manager

Dr. Ryota Niikura
Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo, Japan
Telephone: +81-3-3815-5411 Email: rniikura@triton.ocn.ne.jp

Site Investigator

Dr. Naoyoshi Nagata
Department of Gastroenterology and Hepatology, National Center for Global Health and Medicine center hospital
1-21-1 Toyama, Shinjuku-ku, Tokyo, Japan
Telephone: +81-3-3202-7181 Email: nnagata_ncgm@yahoo.co.jp

Dr. Hisashi Doyama

Department of Gastroenterology, Ishikawa prefectural central hospital
Kuratsuki-Higashi 2-1, Kanazawa city, Ishikawa, Japan
Telephone: +81-76-237-8211 Email: doyama.134@ipch.jp

Dr. Yasutoshi Shiratori
Department of Gastroenterology, St. Luke's International Hospital
9–1 Akashi-cho, Chuo-ku, Tokyo, Japan
Telephone: +81-3-3541-5151 Email: naoishi@luke.ac.jp

Dr. Tomoyuki Yada
Department of Gastroenterology and Hepatology, National Center for Global Health and Medicine kohnodai hospital
1-7-1 Kohnodai, ichikawa-shi, Chiba, Japan
Telephone: +81-47-372-3501 Email: tomoyuki0618@yahoo.co.jp

Dr. Tomoki Fujita
Department of Gastroenterology, Otaru Ekisaikai Hospital
1-4-1 Inaho, Otaru-shi, Hokkaido, Japan
Telephone: +81-134-24-0325 Email: tomoki-fujita@otaru-ekisaikai.jp

Dr. Tsutomu Nishida
Department of Gastroenterology, Toyonaka Municipal Hospital
4-14-1 Shibaharacho, Toyonaka-shi, Osaka, Japan
Telephone: +81-6-6843-0101 Email: tnishida.gastro@gmail.com

Dr. Katsuhiro Mabe
Department of Gastroenterology, National Hospital Organization Hakodate Hospital
18-16 Kawaharachou, Hakodate-shi, Hokkaido, Japan
Telephone: +81-138-51-6281 Email: kmabe@hnh.hosp.go.jp

Dr. Tetsuya Sumiyoshi
The Center for Digestive Disease, Tonan Hospital
Kita 1, Nishi 6, Chuo-ku, Sapporo-shi, Hokkaido, Japan
Telephone: +81-11-231-2121 Email: t-sumiyoshi@tonan.gr.jp

Dr. Kenkei Hasatani

Department of Gastroenterology, Fukui prefectural hospital
2-8-1, Yotsui, Fukui-shi, Fukui, Japan
Telephone: +81-776-54-5151 Email: hasatani9@yahoo.co.jp

Dr. Tatsuya Mikami
Division of Endoscopy, Hirosaki University Hospital
53, Honcho, Hirosaki-shi, Aomori, Japan
Telephone: +81-172-39-5053 Email: tmika@hirosaki-u.ac.jp

Dr. Kazuo Hara
Department of Gastroenterology, Aichi Cancer Center Hospital
1-1 Kanokoden, Chikusa-ku, Nagoya-shi, Aichi, Japan
Telephone: +81-52-762-6111 Email: khara@aichi-cc.jp

Dr. Tetsuro Honda
Department of Gastroenterology, Nagasaki Harbor Medical Center City Hospital
6-39, Shinchimachi, Nagasaki-shi, Nagasaki, Japan
Telephone: +81-95-822-3251 Email: tetsupeacevo@yahoo.co.jp

Dr. Shu Kiyotoki
Department of Gastroenterology, Shuto General Hospital
1000-1 Kogaisaku, Yanai-shi, Yamaguchi, Japan
Telephone: +81-820-22-3456 Email: shu2026eb@hi.enjoy.ne.jp

Dr. Katsumi Yamamoto
Department of Gastroenterology, Japan Community Healthcare Organization Osaka Hospital
4-2-78, Fukushima, Fukushima-shi, Osaka, Japan
Telephone: +81-6-6441-5451 Email: katsumiy770@yahoo.co.jp

Biostatistician
Tomohiro Shinozaki
Department of Biostatistics, School of Public Health, the University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo, Japan
Telephone: +81-3-3815-5411 Email: shinozaki@epistat.m.u-tokyo.ac.jp

Data Coordinating Center and Manager

Dr. Munenori Takata
Mariko Takeda
Department of Clinical Research Support Center, The University of Tokyo Hospital
7-3-1 Hongo, Bunkyo-ku, Tokyo, Japan
Telephone: +81-3-5800-9762 Email: takatam-tky@umin.ac.jp

Medical Monitor

Yumi Tanaka
Department of Clinical Research Support Center, The University of Tokyo Hospital
7-3-1 Hongo, Bunkyo-ku, Tokyo, Japan
Telephone: +81-3-5800-9762 Email: tanakaym-tky@umin.ac.jp

Regulatory Specialist Regrading Safety

Ikue Wada
Department of Clinical Research Support Center, The University of Tokyo Hospital
7-3-1 Hongo, Bunkyo-ku, Tokyo, Japan
Telephone: +81-3-5800-9762 Email: iwada-tky@umin.ac.jp

Audit

Yuki Kusaka
Department of Clinical Research Governance, The University of Tokyo Hospital
7-3-1 Hongo, Bunkyo-ku, Tokyo, Japan
Telephone: +81-3-5800-9051 Email: ykusaka-tky@umin.ac.jp

Independent Effect Judgment Committee

Dr. Shiro Oka
Department of Endoscopy, Hiroshima University Hospital, Hiroshima, Japan
1-2-3 Kasumi, Minami, Hiroshima-shi, Hiroshima, Japan
Telephone: +81-82-257-5555 Email: oka4683@hiroshima-u.ac.jp

Dr. Hirotsugu Watabe
Wakamiya Watabe Clinic
3-3-16, Wakamiya, Ichihara-shi, Chiba, Japan
Telephone: +81- 436-43-0609 Email: hwatabegi@gmail.com

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

Acute lower gastrointestinal bleeding (ALGIB) is a common disease, the incidence of which has recently increased. The estimated annual incidence of ALGIB hospitalization was 21 per 100,000 in the United States in 1997.[1] In Japan, a nationwide study reported that in 2015, 30,846 ALGIB patients required hospitalization: of them, 26% required transfusion and 2.5% suffered in-hospital mortality.[2] Another observational study showed that the incidence of severe ALGIB, requiring hospitalization, has been increasing in Japan.[3]

2.2 RATIONALE

Efficacy of colonoscopy for patients with ALGIB

Colonoscopy is a widely used examination technique worldwide and is an essential tool for the optimal management for ALGIB.[4,5] Colonoscopy provides advantages in both diagnosis and immediate therapy (hemostasis)[6]. Colonoscopy has higher diagnostic accuracy than radiological examination and can identify 75-100% of the causes of ALGIB, such as diverticular bleeding, rectal ulcers, ischemic colitis, and infectious colitis[7-11]. Thus, using colonoscopy, 50-100% successful endoscopic hemostasis can be achieved in patients.[8,10,12,13] Endoscopic hemostasis potentially reduces the need for transfusion, rebleeding, and length of stay.[12,14]

Safety of colonoscopy in ALGIB

Colonoscopy includes the potential for both preparation- and procedure-related adverse events. However, a previous study reported that these adverse event rates were low and the procedure was safe in patients with non-gastrointestinal bleeding.[15] Preparation-related adverse events include vomiting, aspiration phenomena, heart failure, and hypotension.[16] Colonoscopy-related adverse events include cerebrocardiovascular events, perforation, and sepsis.[15] In reviews of non-gastrointestinal bleeding patients in the literature, preparation-related adverse events have been reported: 13 cases of heart failure, and 4 cases of aspiration pneumonia.[17,18] Colonoscopy-related adverse events have been reported: 5-7% for hypotension,[19] 0.60-1.18 events per 1000 examinations for perforation,[20-25] and 0.22 events per 1000 for cerebrovascular events.[20,21,26]

Evidence on the safety of colonoscopy limited to patients with ALGIB is limited. Thus, we previously considered adverse event rates during bowel preparation and colonoscopy in acute LGIB and non-GIB patients and compared these between the

groups.[27] Emergency hospitalized LGIB patients (*n* = 161) and age- and sex-matched non-GIB controls (*n* = 161) were selected. During bowel preparation, 12 (7%) and 4 (2%) LGIB patients experienced hemodynamic instability and vomiting, respectively, while 19 (12%) and 3 (2%) non-GIB controls experienced these adverse events. Although none of the LGIB patients experienced volume overload, aspiration pneumonia or loss of consciousness, 12 (7%) had hypotension and 4 (2%) vomited. However, there was no significant difference in five bowel-preparation-related adverse events between LGIB and non-GIB patients.

During colonoscopy, no LGIB patient suffered perforation or sepsis; however, 23 (14%) had hypotension and 2 (1%) experienced a cerebrocardiovascular event. In non-GIB patients, 17 (11%) had hypotension and none experienced a cerebrocardiovascular event. There was no significant difference in the four colonoscopy-related adverse events between LGIB and non-GIB patients. Two LGIB patients who experienced cerebrocardiovascular events recovered after treatment, and none died during hospitalization. That study showed that colonoscopy performed during acute LGIB did not increase adverse events compared with those of non-GIB patients.

Clinical Uncertainty about Colonoscopy in ALGIB

One of the most important issues in ALGIB treatment is that 10-40% of patients suffer from rebleeding and require transfusion within 48 h after the initial bleeding.[28,29] The reason is the low identification rate of stigmata of recent hemorrhage (SRH) and the poor rate of successful hemostasis. If clinicians can identify SRH accurately, they can provide effective endoscopic hemostasis, and subsequently improve important clinical outcomes, such as the prevention of rebleeding. However, accurate identification of SRH is difficult. To date, there is no reliable method for identifying SRH. An observational study found that the timing of colonoscopy was associated with the identification rate of SRH.[30] Indeed, the SRH identification rate was higher in the early colonoscopy (22%) group than in the 24-48 h group (2.9%), with a statistically significant decrease with time.[30] ‘Early’ colonoscopy was defined as performing a prepared colonoscopy within 24 h of arrival and ‘elective’ colonoscopy was performed between 24 and 96 h.[9] The main area of uncertainty has been whether the timing of colonoscopy improves clinical outcomes, such as the identification rate of SRH and the success of hemostasis. The issue remains controversial.

Issues regarding previous randomized control trials (RCTs) of early colonoscopy in patients with ALGIB

Two RCTs of whether early colonoscopy improves identification rates of SRH and clinical outcomes have been reported.[9,31] Green et al. performed an open-label RCT between early and elective colonoscopy in 100 ALGIB patients, and reported that early colonoscopy improved the identification rate of SRH compared with that of elective colonoscopy, although it did not improve clinical outcomes, including rebleeding, transfusion, and mortality.[9] In contrast, Laine et al. performed an open-label RCT between early and elective colonoscopy in 72 ALGIB patients, and reported no difference in identification rates of SRH, rebleeding, transfusion, or length of stay.[31] However, these studies were terminated before reaching the originally planned sample size, and were unable to demonstrate the superiority of early colonoscopy.

We performed a retrospective propensity-score-matched analysis to compare identification rates of SRH and clinical outcomes, such as the success rate of endoscopic hemostasis, 30-day rebleeding, and length of stay, between early and elective colonoscopy.[32] Early colonoscopy was associated with an increased identification rate of SRH (26%) compared with elective colonoscopy (9%), as well as a higher success rate for endoscopic hemostasis and decreased length of stay, but unmeasured confounders limited the significance of the findings. These findings further highlight the need for a multi-center RCT to determine the benefits and risks of early colonoscopy in ALGIB.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

Potential sources of harm from early colonoscopy include exacerbated bleeding, due to preparation, and various adverse events such as hemorrhagic shock, thrombotic embolism, and death. Other possible mechanisms of patient harm include the possibility that poor visualization because of bleeding may lead to underestimation in the identification of SRH.[10]

2.3.2 KNOWN POTENTIAL BENEFITS

Several single-arm studies in various populations (notably, severe ALGIB) have suggested an association between early colonoscopy and improved patient outcomes, including identification rates of SRH.[4,5,8-10,12,33] Additionally, a non-randomized study suggested that early colonoscopy improved both identification rates of SRH and success rates of hemostasis, resulting in a decreased rebleeding rate.[12]

2.4. Justification for Choice of Thresholds in this Trial

Early colonoscopy for ALGIB remains controversial and people may argue for early colonoscopy, as do clinicians in clinical practice. Early colonoscopy was chosen in this trial based on evidence that has identified a key area of clinical uncertainty in daily practice. Early colonoscopy is based on the following considerations:

- As mentioned above, no high-quality evidence supports the suggestion that early colonoscopy improves identification of SRH, or clinical outcomes compared with those of elective colonoscopy in ALGIB patients. This is a controversial clinical question that should be addressed.
- If this study can 'solve' the clinical question, ALGIB patients may have decreased transfusion requirements, rebleeding rates, and lengths of stay. Subsequently, early colonoscopy may become more widespread in clinical practice.
- An observational study reported that early colonoscopy was performed in 40% of ALGIB patients.[30] Another questionnaire survey in 37 major hospitals in Japan, showed that 64% of these hospitals performed early colonoscopy.[38] In clinical practice, early colonoscopy in ALGIB is feasible for many endoscopists.
- Although patients potentially experience a slight risk of preparation- and colonoscopy-related adverse events, a Japanese observational study showed that colonoscopy in ALGIB did not increase adverse events compared with those in non-GIB patients.[27]

2.5. Summary of evidence and the need for a trial

Based on existing evidence and our preliminary work, we have identified a lack of high-quality evidence regarding the optimal timing of colonoscopy in ALGIB, with widely varying clinical use of early colonoscopy throughout Japan and a patient population for whom a RCT may address a key area of clinical uncertainty.

This trial will build upon collaborations between major hospitals in Japan, to deliver a study that may begin to inform the rational use of early colonoscopy for patients admitted with ALGIB. A RCT design is justified to demonstrate that early colonoscopy can be implemented at a hospital-wide level, to reduce contamination between the trial interventions, and to aid in operational aspects of the trial delivery. This is acceptable ethically, given that both early and elective colonoscopies are within the realms of normal practice in Japan and that all clinicians have the discretion to perform a colonoscopy in contravention of the policy if they think it is necessary, thereby ensuring patient safety is not compromised. We believe the study may also help inform the wider debate about the use of early colonoscopy.

3 OBJECTIVES AND PURPOSE

To compare the identification rates of SRH for ‘early’ versus ‘elective’ colonoscopy in outpatients with ALGIB.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

Parallel, randomized, open-label, superiority trial

Two arms

Multi-center

Early colonoscopy (performance of prepared colonoscopy within 24 h of arrival) versus elective colonoscopy (performance of prepared colonoscopy between 24 and 96 h after arrival).

One-to-one allocation

No stratification.

4.2 STUDY ENDPOINTS

4.2.1 PRIMARY ENDPOINT

- SRH identification rate in the lower gastrointestinal tract.

  We will define SRH based on colonoscopic visualization of lesions, such as diverticulosis, tumor, ulcer, hemorrhoid, angioectasia, and polyps exhibiting active bleeding,[34,35] a visible vessel,[34,36] or an adherent clot.[37]

  We will also evaluate inter-observer agreement in SRH diagnoses between site investigators and an Independent-Effect Judgment Committee using endoscopic images.

4.2.2 SECONDARY ENDPOINTS

- Success rate of endoscopic treatment
- Need for additional endoscopic examinations
- Need for interventional radiology
- Need for surgery
- Thirty-day rebleeding rates
- Need for transfusion during hospitalization
- Length of stay
- Thirty-day thrombosis events
- Thirty-day mortality

- Preparation-related adverse events
- Colonoscopy-related adverse events (hemorrhagic shock, and perforation).

4.2.3 Outcome Definitions

Outcome	Definitions
Success rate of endoscopic treatment	Success rate will be defined as the number achieving hemostasis per total number of attempts at endoscopic hemostasis during colonoscopy examination.
Need for transfusion during hospitalization	Transfusion will be performed when the hemoglobin level falls to < 7 g/dL in patients, according to the guidelines of the Ministry of Health, Labour, and Welfare.
Thirty-day rebleeding	Rebleeding will be defined as significant fresh blood loss after an initial colonoscopy with any of the following criteria: i) Hemorrhagic shock, including cold sweat, nausea, syncope, or systolic blood pressure ≤ 90 mmHg. ii) Need for transfusion, according to the guidelines of the Ministry of Health, Labour, and Welfare. iii) Further colonoscopy identifies blood pooling, or iv) SRH in the lower gastrointestinal tract. v) Contrast-enhanced CT identifies extravasation in the colorectal region. However, these examinations will not be performed routinely if rebleeding occurs in the study period.
Thirty-day thrombosis events	Thrombosis events will include acute coronary syndromes, including angina pectoris and myocardial infarction, stroke, including cerebrovascular infarction, cerebral hemorrhage, and transient ischemic attacks, deep vein thrombosis, and pulmonary embolism.
Preparation-related adverse events	Preparation-related adverse events will

	include nausea, vomiting, abdominal pain, volume overload, aspiration pneumonia, hemorrhagic shock, exacerbation bleeding, and ileus
Colonoscopy-related adverse events	Colonoscopy-related adverse events will include hemorrhagic shock, and perforation.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

1. Males or females aged $\geq$ 20 years, presenting with moderate-to-severe hematochezia or melena within 24 h of arrival, defined as (i) more than three occurrences of hematochezia within 8 h, (ii) hemorrhagic shock, or (iii) requiring transfusion.
2. Provision of signed and dated informed consent form.
3. Stated willingness to comply with all study procedures and availability for the duration of the study.

5.2 PARTICIPANT EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Patients with hematemesis, black vomiting, or melena.
2. Patients with upper gastrointestinal bleeding, diagnosed by nasogastric tube or upper endoscopy.
3. Patients who impossible consumed the oral bowel preparation solution.
4. Patients who have undergone computed tomography.
5. Patients who have been diagnosed with peptic ulcer diseases within the previous 10 days.
6. Ulcerative colitis or Crohn’s disease patients.
7. Patients who have undergone abdominal surgery within the previous 10 days.
8. Patients who have undergone polypectomy, endoscopic mucosal resection, or endoscopic submucosal dissection of the lower gastrointestinal tract within the previous 10 days.
9. Patients with suspected perforation or peritonitis.
10. Patients with suspected intestinal obstruction.

11. Patients with hemorrhagic shock refractory to infusion or blood transfusion.
12. Patients who have undergone total colectomy.
13. Patients with suspected disseminated intravascular coagulation.
14. Patients with end-stage malignant disease.
15. Patients with severe cardiac failure.
16. Patients with active thrombosis.
17. Patients with severe respiratory failure.
18. Pregnant patients.

5.3 PARTICIPANT WITHDRAWAL OR TERMINATION

5.3.1 REASONS FOR WITHDRAWAL OR TERMINATION

Participants will be free to withdraw from participation in the study at any time upon request.

An investigator may terminate participation in the study if:

- The participant meets an exclusion criterion (newly developed or not previously recognized) that precludes further study participation.
- Any clinical adverse event (AE), or other medical condition or situation occurs such that continued participation in the study would not be in the best interests of the participant.
- Trial termination occurs due to a safety problem.

5.3.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

Participants will be free to withdraw consent at any stage of data collection and follow-up, without having to provide any reason for their decision. However, such patients should continue to be managed in accordance with the safety and effects policy. Data including date and reason for withdrawal and clinical course will be recorded in the electronic data capture (EDC) system. If the withdrawal occurs due to AEs, site investigators will need to help the patient to recover to the previous state, as far as is possible.

5.4 PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for such a study suspension or termination will be provided by the suspending or terminating party to the investigator and the IRB. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reasons for the termination or

suspension. Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants.
- Data that are not sufficiently complete and/or evaluable.
- If the IRB suggests a change of protocol, and it is difficult to accept this change.

6 STUDY PROCEDURES AND SCHEDULE

6.1 STUDY PROCEDURES/EVALUATIONS

6.1.1 STUDY-SPECIFIC PROCEDURES

- Medical histories will be obtained by interview or from medical records and examine: ischemic heart disease, chronic pulmonary disease, peptic ulcer, liver cirrhosis, diabetes mellitus, chronic heart failure, cerebrovascular disease, dementia, collagen diseases, chronic kidney disease, leukemia, malignant lymphoma, malignancy, malignancy with metastasis, acquired immune deficiency syndrome, hemiplegia, lower gastrointestinal bleeding, and peripheral vascular disease.
- Medication history will include only medications currently taken, prescription and over-the-counter medications at the first visit, on performing a colonoscopy, and at the final visit (Visit 1): non-steroidal anti-inflammatory drugs, low-dose aspirin, thienopyridine, cilostazol, other anti-platelet drugs, such as eicosapentaenoic acid, sarpogrelate, beraprost, limaprost, dilazep, dipyridamole, ozagrel, non-vitamin K antagonist oral antagonists (NOACs), such as dabigatran, rivaroxaban, apixaban, and edoxaban, and warfarin.
- Physical examination will include height, weight, body mass index at initial visit, and systolic and diastolic blood pressures and pulse rate at the initial visit and on performing a colonoscopy.
- ‘Early’ colonoscopy will be performed within 24 h of the initial visit: All colonoscopies will be performed using an electronic video endoscope (Olympus Optical, Tokyo, Japan or Fujifilm Corporation, Tokyo, Japan) after 2-4 L of oral bowel preparation was administrated. If patients who have not completely ingested oral bowel preparation until the effluent is free of fecal material, enema will be added for these patients.

  An antispasmodic agent, such as scopolamine butylbromide or glucagon, will be injected intramuscularly or intravenously just before the colonoscopy. Midazolam with or without diazepam and/or pentazocine hydrochloride and/or pethidine titrated will be used for sedation during colonoscopy.

  A water-jet device (Olympus Flushing Pump; Olympus Optical, Tokyo, Japan) and

attachment cap will be used to obtain better visualization[30].

Colonoscopy assessment will include: (i) preparation-related adverse events such as nausea, vomiting, abdominal pain, heart failure, aspiration pneumonia, hemorrhagic shock, bleeding per rectum, and ileus; (ii) effectiveness: etiology of lower gastrointestinal bleeding, such as definitive diverticular bleeding, presumptive diverticular bleeding, rectal ulcer, colorectal cancer, ischemic colitis, infectious colitis, radial colitis, polyp bleeding, post-endoscopic-treatment bleeding, non-specific colorectal ulcer, and non-specific colitis; and hemorrhoids, stigmata of recent hemorrhage, endoscopic hemostasis, such as clipping, band ligation, injection of hypertonic saline, epinephrine solution, electrocautery coagulation, and argon plasma coagulation, success of endoscopic hemostasis, experience of the endoscopist (an 'expert' colonoscopist is defined as having conducted > 1000 colonoscopies and performing endoscopic hemostasis), use of attachment cap, use of water-jet device, cecal insertion, insertion time, and inspection time; and (iii) colonoscopy-related adverse events: hemorrhagic shock and perforation

- Laboratory evaluations, including blood hemoglobin at the initial visit and on performing a colonoscopy.

6.1.2 STANDARD OF CARE STUDY PROCEDURES

Elective colonoscopy will be performed between 24 and 96 h after the initial visit. All colonoscopies will be performed using an electronic video endoscope (Olympus Optical, Tokyo, Japan or Fujifilm Corporation, Tokyo, Japan) after 2-4 L of oral bowel preparation was administrated. If patients have not completely ingested oral bowel preparation solution until the effluent is free of fecal material, enema will be added for these patients.

An antispasmodic agent, such as scopolamine butylbromide or glucagon, will be injected intramuscularly or intravenously just before the colonoscopy. Midazolam with or without diazepam and/or pentazocine hydrochloride and/or pethidine titrated will be used for sedation during colonoscopy.

A water-jet device (Olympus Flushing Pump; Olympus Optical, Tokyo, Japan) and attachment cap will be used to obtain better visualization[30].

6.2 STUDY SCHEDULE

6.2.1 SCREENING

Screening Visit (Day 0)

- Obtain informed consent of potential participant, verified by signature on written

informed consent.

- Review medical history and medication history to determine eligibility based on inclusion/exclusion criteria.
- Perform medical examinations needed to determine eligibility based on inclusion/exclusion criteria.
- Collect blood for hemoglobin measurement.

6.2.2 ENROLLMENT/BASELINE

- Obtain informed consent of potential participant verified by signature on study informed consent form.
- Verify inclusion/exclusion criteria.
- Obtain demographic information, medical history, medication history.
- Record vital signs, results of examinations, other assessments.
- Collect blood for baseline hemoglobin laboratory tests required for the study.
- Administer the study treatment.

6.2.3 FOLLOW-UP

Final Study Visit (Visit 1, Day 31+/3)

- Record adverse events, as reported by participant or observed by investigator.
- Record need for additional endoscopy examination, need for interventional radiology, need for surgery, transfusion during hospitalization, date of meal starting, length of stay, medication history at final visit, 30-day rebleeding, 30-day thromboembolism events, including angina pectoris, myocardial infarction, cerebrovascular events, deep vein thrombosis, and pulmonary embolism, and 30-day mortality.

  If patient cannot visit, site investigators will perform a telephone interview.

6.2.3 EARLY TERMINATION VISIT

- Record vital signs
- Collect blood for hemoglobin

6.2.4 SCHEDULE OF EVENTS TABLE

Procedures	Screening	Enrollment	Preparation	Colonoscopy	Final study visit
Informed consent	X				
Demographics	X				
Medical history	X			X	X
Randomization	X				
Physical exam	X				
Vital signs	X		X	X	
Complete blood count [a]	X				
Early or elective colonoscopy				X	
Adverse event evaluation	X—				

[a] hemoglobin

6.2.5 JUSTIFICATION FOR SENSITIVE PROCEDURES

Not-applicable.

6.2.6 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

Not-applicable.

6.2.7 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

Not-applicable.

6.2.8 RESCUE THERAPY

If a patient presents with persistent severe bleeding in the elective-colonoscopy group, a physician will be able to deviate from the allocation and perform an early colonoscopy and hemostatic intervention, as needed according to the criteria: (i) presenting with hemorrhagic shock despite performing transfusion and infusion, or (ii) the need for transfusion of more than 6 U MAP.

6.2.9 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

Not-applicable.

7 ASSESSMENT OF SAFETY

7.1 SPECIFICATION OF SAFETY PARAMETERS

7.1.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event will mean any untoward medical occurrence associated with the use of an intervention in humans, regardless of whether considered intervention related.

7.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAEs)

An AE or suspected adverse reaction will be considered "serious" if, in the view of the investigator or monitor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, which complies with *ICH E6(R2)* and the *Ethical Guidelines for Medical and Health Research Involving Human Subjects (Japan).*

7.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The IRB considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given
  - (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and
  - (b) the characteristics of the participant population being studied.
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This study will use the IRB definition of UP. This definition can include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or

application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

7.2 CLASSIFICATION OF AN ADVERSE EVENT

7.2.1 SEVERITY OF EVENT

- Mild: Events that require minimal or no treatment and do not interfere with the patient undergoing the study procedure.
- Moderate: Events that require transfusion of saline or blood but do not interfere with the patient undergoing the study procedure.
- Severe: Events that interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

7.2.2 RELATIONSHIP TO STUDY PROCEDURE

The clinician's assessment of an AE's relationship to the study procedure is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. All AEs must have their relationship to study procedure assessed.

- Related: The AE is known to occur with the study procedure, there is a reasonable possibility that the study procedure caused the AE, or there is a temporal relationship between the study procedure and the event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study procedure and the AE.
- Not related: There is not a reasonable possibility that administration of the study procedure caused the event, there is no temporal relationship between the study procedure and event onset, or an alternate etiology has been established.

7.2.3 EXPECTEDNESS

Preparation- and colonoscopy-related adverse events will be responsible for determining whether an AE is expected or unexpected. Expected AEs in this trial include nausea and vomiting, abdominal pain, heart failure, aspiration pneumonia, gastrointestinal hemorrhage with or without hemorrhagic shock, ileus, and gastrointestinal perforation. The definitions of these AEs are provided above (4.2.3 Outcome Definitions). An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedure.

7.3 PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND

FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs will be captured on the appropriate EDC. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make such a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

The investigator will record all reportable events with start dates that occur at any time after informed consent has been obtained until the end of the study for AEs and SAEs after the last day of study participation (30 days after performing colonoscopy).

7.4 REPORTING PROCEDURES

7.4.1 ADVERSE EVENT REPORTING

The study clinician will complete an AE Form within the following timelines:

- All AEs regardless of relationship will be submitted in an AE report to EDC as soon as possible after site awareness.

7.4.2 SERIOUS ADVERSE EVENT REPORTING

The study clinician will complete an SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE form of the EDC and submitted to the IRB as soon as possible. All SAE information must be shared among all investigators within 24 h of site awareness using e-mail or telephone. If there is a 'reasonable possibility' that the study procedure caused the 'unanticipated' SAEs, the director of The University of Tokyo Hospital will report the SAEs to Ministry of Health, Labour, and Welfare, Japan. All SAEs will be collected through SAE may come to the attention of study personnel during study visits, and or interviews of from a study participant presenting for medical care, or upon review by a study monitors; and should monitor. All SAEs will be followed to adequate resolution.

7.4.3 UNANTICIPATED PROBLEM REPORTING

Incidents or events that meet the IRB criteria for UPs require the creation and completion of a report. It is the site investigator's responsibility to report UPs to their IRB and to the Ministry of Health, Labour, and Welfare, as needed. All UPs will be reported using AE/SAE reporting timelines. The UP report will include the following information:

- Protocol-identifying information: protocol title and number, PI's name, and the IRB project number.
- A detailed description of the event, incident, experience, or outcome.
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP.
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB as soon as possible after the investigator becomes aware of the event.
- Any other UP will also be reported to the IRB as soon as possible after the investigator becomes aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), and the supporting agency head (or designee), as soon as possible after the IRB's receipt of the report of the problem from the investigator.

7.4.4 EVENTS OF SPECIAL INTEREST

Not applicable.

7.4.5 REPORTING OF PREGNANCY

The patient will be excluded from the study.

7.5 STUDY HALTING RULES

Early colonoscopy will be halted when unexpected, significant, or unacceptable risk events occur. AEs determined to be "related" are to be reported to the data coordinating center (DCC). When an unexpected, significant, or unacceptable risk event is reported,

the DCC will recommend that investigators immediately stop enrollment of new study participants. The PI will inform the IRB as soon as possible of this occurrence and will provide the IRB with AE listing reports. The IRB will convene an *ad hoc* meeting as soon as possible. The IRB will provide recommendations for proceeding with the study to the PI. The PI will inform the Ministry of Health, Labour, and Welfare of the temporary halt and the disposition of the study.

7.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a risk-based monitoring team, composed of individuals with the appropriate expertise, including a biostatistician, a data coordinating center and manager, a medical monitor, and a regulatory specialist regarding safety. The risk-based monitoring team will meet at least semi-annually to assess safety and efficacy data in each arm of the study. The risk-based monitoring team will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the IRB. At this time, each data element that the IRB needs to assess will be defined clearly. The risk-based monitoring team will provide its input to the PI.

8 CLINICAL MONITORING

Clinical site monitoring will be conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendments, with GCP, and with applicable regulatory requirements.

- The risk-based monitoring team of the University of Tokyo Hospital, which consists of the Principal investigator, Project Manager, Medical Monitor, Data Managers, and Biostatistician, will conduct an early targeted review of certain data monitoring, including onsite, centralized, statistical monitoring for initial assessment and training.
- Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL AND ANALYTICAL PLAN (SAP)

This study has a separate formal SAP, which includes a more detailed analysis of populations, summary of statistical strategies. The SAP will complete prior to database lock.

9.2 STATISTICAL HYPOTHESES

- Primary efficacy endpoint: The rate of identification of SRH.
  Null hypothesis: No significant difference in the SRH identification rates between early and elective colonoscopy.
- Secondary efficacy endpoints: Success rate of endoscopic treatment, need for additional endoscopic examination, need for interventional radiology, need for surgery, need for transfusion during hospitalization, 30-day rebleeding rates, preparation-related adverse events, colonoscopy-related adverse events, 30-day thrombosis events, 30-day mortality, and length of stay.
  Null hypothesis: No significant difference in secondary outcomes is found between early and elective colonoscopy.

9.3 ANALYSIS DATASETS

- Intention-to-treat (ITT) analysis dataset: All randomized participants, excluding patients 1) who did not satisfy the enrollment criteria after randomization, 2) who provided no post-randomization data, and 3) who did not undergo colonoscopy.
- Per-protocol analysis dataset: A subset of the participants in the ITT set who complied with the protocol treatments.

9.4 DESCRIPTION OF STATISTICAL METHODS

9.4.1 GENERAL APPROACH

- For descriptive statistics, data will be summarized by treatment group. *n*, mean, standard deviation, minimum, and maximum will summarize continuous efficacy variables, whereas number and percent will summarize categorical efficacy variables.
- For inferential tests, the p-value for statistical significance (Type I error) will be < 0.05, two-tailed.
- Covariates will be pre-specified in the sections below.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT

- Define the measurement: SRH identification in lower gastrointestinal tract.
- The scale: Binary/categorical.
- The χ^2 test will be used to analyze the primary endpoint: results will be presented as prevalence rates and number-needed-to-treat.
- Missing data will be removed in the primary analysis, and primary endpoint analysis

will be performed by a complete case analysis. In sensitivity analysis, primary endpoint analysis will be performed by an imputation method.

9.4.3 ANALYSIS OF SECONDARY ENDPOINTS

- Define the measurement: Success rate of endoscopic treatment, need for additional endoscopic examination, need for interventional radiology, need for surgery, 30-day rebleeding rates, need for transfusion during hospitalization, length of stay, 30-day thrombosis events, 30-day mortality, preparation-related adverse events, and colonoscopy-related adverse events. Each outcome has been defined previously (see Section 4.2.3 Outcome Definitions).

- The scale:
  Binary/categorical: success rate of endoscopic treatment, need for additional endoscopic examination, need for interventional radiology, need for surgery, 30-day rebleeding rates, need for transfusion during hospitalization, 30-day thrombosis events, 30-day mortality, preparation-related adverse events, and colonoscopy-related adverse events.
- Interval:
  Length of stay.
- The χ^2 test or Fisher's exact test will be used to analyze the secondary endpoints of success rate of endoscopic treatment, need for additional endoscopic examination, need for interventional radiology, need for surgery, 30-day rebleeding rates, need for transfusion during hospitalization, 30-day thrombosis events, 30-day mortality, preparation-related adverse events, and colonoscopy-related adverse events as appropriate, and results will be presented as prevalence rates and number needed to treat.
  Wilcoxon's rank-sum test will be used to analyze the secondary endpoint of length of stay, and results will be presented as means with standard errors.
- Missing data will be removed in the primary analysis, and secondary endpoint analysis will be performed by complete case analysis. In sensitivity analysis, secondary endpoint analysis will be performed by an imputation method.

9.4.4 SAFETY ANALYSES

Safety endpoints (preparation- and colonoscopy-related adverse events) will be analyzed as summary statistics during preparation and colonoscopy.

AEs will be coded based on the Medical Dictionary for Regulatory Activities/Japanese

version (MedDRA/J)) and counted once only for a given participant. Evaluated start date, stop date, severity, relationship, outcome, and duration; and presented severity, frequency, and relationship of AEs to preparation and colonoscopy will be presented by system organ class (SOC) and preferred term groupings.

9.4.5 ADHERENCE AND RETENTION ANALYSES

Adherence to the protocol (e.g., performing colonoscopy) will be assessed and calculated. Similarly, study retention/loss to follow-up, and frequency of, and reasons for, discontinuation of the intervention will be assessed and calculated.

9.4.6 BASELINE DESCRIPTIVE STATISTICS

For descriptive statistics, data will be summarized by treatment group. Number, mean, standard deviation, minimum and maximum will summarize continuous efficacy variables, whereas number and percent will summarize categorical efficacy variables. Inferential statistics will not be used.

9.4.7 PLANNED INTERIM ANALYSES

Not-applicable.

9.4.8 ADDITIONAL SUB-GROUP ANALYSES

The primary endpoint will be analyzed based on subgroups of patients with colonic diverticular bleeding, patients terminated because of inadequate bowel preparation, patients who underwent endoscopic hemostasis, patients with colonic diverticular bleeding and who underwent endoscopic hemostasis, patients who underwent colonoscopy by an expert, each site, and patients who underwent colonoscopy within 24 h of onset of hematochezia.

9.4.9 MULTIPLE COMPARISON/MULTIPLICITY

Not applicable.

9.4.10 EXPLORATORY ANALYSES

Not applicable.

9.5 SAMPLE SIZE

- Outcome measure used for calculations: Identification rate of SRH.
- Test statistic: The χ^2 test comparing two independent proportions.

- Null and alternate hypotheses: Early colonoscopy improves the identification rate of SRH compared with elective colonoscopy.
- Type I error rate (α): 0.05
- Power level (e.g., 80% power): 80%
- Assumed event rate for dichotomous outcome for each study arm, justified and referenced by historical data as much as possible: Previous studies reported that early colonoscopy identified SRH in 26% of patients with ALGIB, while elective colonoscopy identified 9%.[32] Assuming an elective colonoscopy identified SRH in 9% of patients with ALGIB, $\alpha = 0.05$ (two-sided), and $\beta = 0.1$, 142 patients (2×71) will be needed to show a 17 % absolute identification rate of SRH increase or decrease in the primary outcome measure. To account for the possibility that the observed difference may be diminished by patient noncompliance and/or dropout, an additional 20 patients will be recruited to correct for these effects, resulting in 162 patients.
- Assumed dropout rates, withdrawal, cross-over to other study arms, missing data, etc., also justified: Not applicable.
- Approach to handling withdrawals and protocol violations: Participants with withdrawals and protocol violations will be included in the “intent-to-treat” population.
- Statistical method used to calculate the sample size, with a reference for it and for any software used: nQuery + nTerim 4.0.
- Method for adjusting: Not applicable.

9.6 MEASURES TO MINIMIZE BIAS

9.6.1 ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

ENROLLMENT

Plans for the maintenance of trial randomization codes will be discussed. The timing and procedures for planned and unplanned breaking of randomization codes will be included.

RANDOMIZATION

In real clinical practice, timing of colonoscopy differs between physicians. To reduce this bias, this study will perform randomization and perform a centralized effectiveness assessment to reduce diagnostic bias among the endoscopists.

MASKING PROCEDURES

It will not be feasible to perform blinding because a physician will perform the medical examination and the same physician will perform the endoscopy. Thus, the physician will be aware of patient allocation.

9.6.2 EVALUATION OF SUCCESS OF BLINDING

Not applicable.

9.6.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE

Not applicable.

10 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

“Source data” are all information, original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to: hospital records; clinical and office charts; laboratory notes; memoranda; participant’s memory aid or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate and complete; microfiches, photographic negatives, microfilm or magnetic media; X-rays; and participant files and records kept at the pharmacy, at laboratories, and medico-technical departments involved in the clinical trial. It is acceptable to use these data as source documents. Medical monitors and audit can access these data for a patient participating in this clinical trial.

11 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control (QC) procedures will be implemented, beginning with the data entry system, and data QC checks that will be run on the EDC will be generated. Any missing data or data anomalies will be communicated to the sites for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, recorded, and reported in compliance with the protocol, *GCP*, and *Ethical Guidelines for Medical and Health Research Involving Human Subjects (Japan)*. The investigational site will provide direct access to all trial-related sites, source documents, and reports for the purpose of monitoring and auditing by the PI, and inspection by local and regulatory authorities.

12 ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 ETHICAL STANDARDS

The investigator will ensure that this study is conducted in full conformity with the *Declaration of Helsinki*, and *Ethical Guidelines for Medical and Health Research Involving Human Subjects (Japan).*

12.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent forms, recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study. All changes to the consent form will be IRB approved: a determination will be made regarding whether participants who previously consented need to consent again.

12.3 INFORMED CONSENT PROCESS

12.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing early colonoscopy in detail and associated risks will be given to all participants and written documentation of informed consent will be required prior to starting the intervention study product. The following consent materials are submitted with this protocol:

- Written informed consent form (Japanese, non-Braille, non-audio recording).

12.3.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to an individual agreeing to participate in a study and continues throughout the individual’s study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study, and of their rights as research participants. Participants will have the opportunity to review the written consent form carefully and ask questions before signing. The participants will have the opportunity to discuss the study with their surrogates or think about it before agreeing to participate.

The participant will sign the informed consent document prior to any procedure that is specifically for the study. The participant may withdraw consent at any time during the course of the trial. A copy of the informed-consent document will be given to all participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

12.4 PARTICIPANT AND DATA CONFIDENTIALITY

Participant confidentiality will be held strictly in trust by the participating investigators and their staff. The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the IRB. The study monitor, other authorized representatives of the PI, or representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participants' contact information will be stored securely at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long as dictated by local IRB and institutional regulations.

Study participant research data, which are for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at Tokyo University Hospital. These will not include the participants' contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Tokyo University Hospital research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at Tokyo University Hospital.

12.4.1 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS OR DATA

- Intended use: Data collected under this protocol may be used for study. No genetic testing will be performed.
- Storage: Data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to data.

- Tracking: Data will be tracked using the EDC.
- Disposition at the completion of the study: All stored data will be sent to the biostatistician. Study participants who request destruction of samples will be notified of compliance with such a request and all supporting details will be maintained for tracking.

12.5 FUTURE USE OF STORED SPECIMENS

Data collected for this study will be analyzed and stored at Tokyo University Hospital. After the study has been completed, the de-identified, archived data will be transmitted to, and stored at, Tokyo University Hospital, under the supervision of a data manager, for use by other researchers, including those outside the study.

With the participants' approval, and as approved by local IRBs, de-identified data will be stored at each site. These data could be used for research into the causes of complications and other conditions for which individuals are at increased risk, and to improve treatment. The data will also be provided with a code-link that will allow linking the biological specimens to the phenotypic data from each participant, maintaining the masking of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have data stored for future research. However, withdrawal of consent with regard to data storage will not be possible after the study has been completed.

When the study is completed, access to study data will be provided through Tokyo University Hospital.

13. DATA HANDLING AND RECORD KEEPING

13.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

The EDC will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the EDC derived from source documents should be consistent with the source documents or discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse

reactions' data) and clinical laboratory data will be entered into the EDC, a 21 CFR Part 11-compliant data capture system provided by the DCC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

13.2 STUDY RECORDS RETENTION

Study documents will be retained for either a minimum of 5 years after the end of the study or 3 years after publication.

13.3 PROTOCOL DEVIATIONS

A "protocol deviation" is any non-compliance with the clinical trial protocol, GCP, or MOP requirements. The non-compliance may be on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with *ICH E6 (R2)*:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations as soon as possible after identification of the protocol deviation, or the scheduled protocol-required activity.

All deviations must be addressed in study source documents. Protocol deviations must be sent to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to the IRB requirements.

13.4 PUBLICATION AND DATA SHARING POLICY

This study will ensure that the public has access to the published results of the research. It will require scientists to submit final peer-reviewed journal manuscripts that arise to the digital archive "PubMed Central" upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome.

Medical interventions include endoscopic procedures. Health outcomes include

any biomedical or health-related measures pertaining to patients or participants, including adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry, such as the UMIN Clinical Trials Registry.

The data from all sites will be analyzed together and the results will be published as soon as possible after trial completion. Individual PIs at each site must not publish or divulge any report or result from the trial until the main trial results have been published. A publication committee will be formed for this purpose by the PI, which will include key members of the trial management group.

The publication committee will oversee the timely analysis, writing up, and publication of the main trial results. Investigators and the independent-effect judgment committee must be given the opportunity to read and comment on the main trial findings before submission for publication. For the main report of this study submitted for publication, together with associated methodology and health economic papers, we will use the International Committee of Medical Journal Editors' definitions of authorship and contributorship http://www.icmje.org/ethical_1author.html). The publication committee should be listed with their affiliations in the acknowledgements/appendix of the main publication and the support of the clinical studies support staff, and funder acknowledged.

14. CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Thus, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. All study group members are to disclose all conflicts of interest and a mechanism for the management of all reported dualities of interest will be established.

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Appendix Statistical Analysis Plan

Statistical Analysis Plan (SAP)

A multi-center, randomized controlled trial comparing early versus elective colonoscopy in outpatients with acute lower gastrointestinal bleeding

Version: 1.0

Author: Tomohiro Shinozaki, Department of Biostatistics, School of Public Health, the University of Tokyo

Date: 20-10-2015

1. INTRODUCTION

Acute lower gastrointestinal bleeding (ALGIB) is a common disease, the incidence of which has recently increased.[1] 'Early' colonoscopy, performed within 24 h of arrival, potentially improves clinical outcomes, such as the identification of stigmata of recent hemorrhage (SRH) and rebleeding compared with 'elective' colonoscopy, performed between 24 and 96 h.

However, we have identified a lack of high-quality evidence regarding the optimal timing of colonoscopy in ALGIB.[2-4] There is widely varying clinical use of early colonoscopy throughout Japan, and a randomized controlled trial (RCT) in a patient population will address a key area of clinical uncertainty. [6]

This trial may begin to inform the rational use of early colonoscopy for patients admitted with ALGIB. A RCT design is justified to demonstrate that early colonoscopy can be implemented at a hospital-wide level, to reduce contamination between the trial interventions, and to aid in operational aspects of the trial delivery. This is acceptable ethically, given that both 'early' and 'elective' colonoscopies are within the realms of normal practice in Japan and that all clinicians have the discretion to perform a colonoscopy in contravention of the policy if they think it is necessary, thereby ensuring patient safety is not compromised.[5] We believe the study may also help to inform the wider debate regarding the use of early colonoscopy.

The objective of the study is to compare the SRH identification rates of 'early' versus 'elective' colonoscopy in outpatients with ALGIB.

2 DATA SOURCE

All data to be analyzed are obtained from "A multi-center, randomized controlled trial comparing early versus elective colonoscopy in outpatients with acute lower gastrointestinal bleeding." Variables to be measured are specified in the protocol. Datasets are produced in compliance with the Clinical Data Monitoring Plan.

3 ANALYSIS OBJECTIVES

- Primary efficacy endpoint: The rate of identification of stigmata of recent hemorrhage (SRH).

  Null hypothesis: No significant difference in the SRH identification rates is found between early and elective colonoscopy.
- Secondary efficacy endpoints: Success rate of endoscopic treatment, need for additional endoscopic examination, need for interventional radiology, need for surgery, need for transfusion during hospitalization, 30-day rebleeding rates,

preparation related adverse events, colonoscopy-related adverse events, 30-day thrombosis events, 30-day mortality, and length of stay.

Null hypothesis: No significant difference in secondary outcomes is found between early and elective colonoscopy.

4 ANALYSIS SETS/ POPULATIONS/SUBGROUPS

- ANALYSIS SETS

The following two analysis sets will be analyzed: modified intention-to-treat (ITT) and per-protocol analysis sets. A genuine ITT analysis set includes the data of all patients participating in the trial, but a modified ITT analysis set excludes patients 1) who did not fulfill the enrollment criteria after randomization, 2) who provide no post-randomization data, and 3) who do not undergo colonoscopy (i.e., 'early' nor 'elective'). In both analysis sets, treatments are compared according to the initially randomized groups.

- PARTICIPANT INCLUSION CRITERIA

1. Males or females aged ≥ 20 years, presenting with moderate-to-severe hematochezia or melena within 24 h of arrival, defined as (i) more than three occurrences of hematochezia within 8 h, (ii) hemorrhagic shock, or (iii) requiring transfusion.
2. Provision of signed and dated informed consent form.
3. Stated willingness to comply with all study procedures and availability for the duration of the study.

- PARTICIPANT EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Patients with hematemesis, black vomiting, or melena.
2. Patients with upper gastrointestinal bleeding, diagnosed by nasogastric tube or upper endoscopy.
3. Patients who have impossible consumed the oral bowel preparation solution.
4. Patients who have undergone computed tomography.
5. Patients in whom peptic ulcer diseases have been diagnosed within the previous 10 days.
6. Ulcerative colitis or Crohn's disease patients.
7. Patients who have undergone abdominal surgery within the previous 10 days.
8. Patients who have undergone polypectomy, endoscopic mucosal resection, or

endoscopic submucosal dissection of the colon within the previous 10 days.

9. Patients with suspected perforation or peritonitis.
10. Patients with suspected intestinal obstruction.
11. Patients with hemorrhagic shock refractory to infusion or blood transfusion.
12. Patients who have undergone a total colectomy.
13. Patients with suspected disseminated intravascular coagulation.
14. Patients with end-stage malignant disease.
15. Patients with severe cardiac failure.
16. Patients with active thrombosis.
17. Patients with severe respiratory failure.
18. Pregnant patients.

- SUBGROUP ANALYSES

The primary endpoint will be analyzed based on subgroups of patients with colonic diverticular bleeding, patients terminated for inadequate bowel preparation, patients who underwent endoscopic hemostasis, patients with colonic diverticular bleeding and who underwent endoscopic hemostasis, patients who underwent colonoscopy by an expert, each site, and patients who underwent colonoscopy within 24 h of onset of hematochezia.

5 ENDPOINTS AND COVARIATES

- PRIMARY ENDPOINT

Identification rate of SRH in lower gastrointestinal tract.

We will define SRH based on colonoscopic visualization of lesions, such as diverticulosis, tumor, ulcer, hemorrhoid, angioectasia, and polyps exhibiting active bleeding, a visible vessel, or an adherent clot. We will also evaluate inter-observer agreement of SRH diagnoses among site investigators and an independent-effect judgment committee using endoscopic images.

- SECONDARY ENDPOINTS

1. Success rate of endoscopic treatment
2. Need for additional endoscopic examination
3. Need for interventional radiology
4. Need for surgery
5. Thirty-day rebleeding rates

6. Need for transfusion during hospitalization
7. Length of stay
8. Thirty -day thrombosis events
9. Thirty -day mortality
10. Preparation-related adverse events
11. Colonoscopy-related adverse events

6 HANDLING OF MISSING VALUES AND OTHER DATA CONVENTIONS

The primary analysis for both primary and secondary endpoints, will be performed by complete case analysis, which excludes patients whose data are missing. As a sensitivity analysis, missing data will be substituted by a multiple imputation method. Models and auxiliary variables for the imputation will be assessed by the trial investigators after fixing a dataset.

7.1 STATISTICAL PROCEDURES

- ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT

Definition of the measurement: Identification rate of SRH in lower gastrointestinal tract.
The scale: Binary/categorical.
The χ^2 test will be used to analyze the primary endpoint, and results presented will be prevalence rates and number needed to treat.

- ANALYSIS OF THE SECONDARY ENDPOINTS

Definition of the measurement: success rate of endoscopic treatment, need for additional endoscopic examination, need for interventional radiology, need for surgery, 30-day rebleeding rates, need for transfusion during hospitalization, length of stay, 30-day thrombosis events, 30-day mortality, preparation-related adverse events, and colonoscopy-related adverse events. Each outcome is defined in the Appendix.

The scale:
Binary/categorical: success rate of endoscopic treatment, need for additional endoscopic examination, need for interventional radiology, need for surgery, 30-day rebleeding rates, need for transfusion during hospitalization, 30-day thrombosis events, 30-day mortality, preparation-related adverse events, and colonoscopy-related adverse events (hemorrhagic shock, and perforation).
Interval: Length of stay.

The χ^2 test or Fisher's exact test will be used to analyze the secondary endpoints of success rate of endoscopic treatment, need for additional endoscopic examination, need for interventional radiology, need for surgery, 30-day rebleeding rates, need for transfusion during hospitalization, 30-day thrombosis events, 30-day mortality, preparation-related adverse events, and colonoscopy-related adverse events, as appropriate, and results will be presented as prevalence rates and number needed to treat.

Wilcoxon's rank-sum test will be used to analyze the secondary endpoint of length of stay. Results will be presented as means with standard errors or medians with percentiles, or both.

- SAFETY ANALYSES

Safety endpoints (preparation- and colonoscopy-related adverse events) will be analyzed as summary statistics during preparation and colonoscopy.

AEs will be coded based on the Medical Dictionary for Regulatory Activities/Japanese version (MedDRA/J)) and counted once only for a given participant. Evaluated start date, stop date, severity, relationship, outcome, and duration; and presented severity, frequency, and relationship of AEs to preparation and colonoscopy will be presented by system organ class (SOC) and preferred term groupings.

- ADHERENCE AND RETENTION ANALYSES

Adherence to the protocol (e.g., performing colonoscopy) will be assessed and calculated. Similarly, study retention/loss to follow-up, and frequency of, and reasons for, discontinuation of the intervention will be assessed and calculated.

- BASELINE DESCRIPTIVE STATISTICS

For descriptive statistics, data will be summarized by treatment group. Number, mean, standard deviation, minimum and maximum will summarize continuous efficacy variables, whereas number and percent will summarize categorical efficacy variables. Inferential statistics will not be used.

7.2 MEASURES TO ADJUST FOR MULTIPLICITY, CONFOUNDERS, HETEROGENEITY, ETC.

No adjustment will be made for multiplicity and confounders in the primary analysis. Heterogeneity for each endpoint is assessed by subgroup analyses (as described in Section 4), using (approximate) interaction tests based on the difference in

effect-measures among subgroups.

8 SENSITIVITY ANALYSES

As described in Section 6, sensitivity analysis for missing data will be performed by a multiple imputation method.

9 QC PLANS

Quality control (QC) procedures will be implemented, beginning with the data entry system, and data QC checks that will be run on an electronic data capture (EDC) system will be generated. Any missing data or data anomalies will be communicated to the sites for clarification/resolution.

Following written standard operating procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated, recorded, and reported in compliance with the protocol, *GCP*, and *Ethical Guidelines for Medical and Health Research Involving Human Subjects (Japan).*

The investigational site will provide direct access to all trial-related sites, source documents, and reports for the purpose of monitoring and auditing by the principal investigator (PI), and inspection by local and regulatory authorities.

10 PROGRAMMING PLANS

A Statistician (TS) writes SAS code for all planned analyses before linking a dataset to randomization labels (i.e., ‘early’ versus ‘elective’). Statistical computations and figures in tables are generated using SAS software, version 9.4 (SAS, Cary, NC).

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Appendix Clinical Data Monitoring Plan (CDMoP)

CLINICAL DATA MONITORING PLAN (CDMoP)

A multi-center, randomized controlled trial comparing early versus elective colonoscopy in outpatients with acute lower gastrointestinal bleeding

Sponsor: Graduate School of Medicine, The University of Tokyo
Funded by: The Japanese Gastroenterological Association
Draft or Version Number: v.1.0. 9 June 2016

1. PURPOSE

The purpose of this document is to specify all study-specific monitoring requirements for a multi-center, randomized controlled trial comparing early versus elective colonoscopy in outpatients with acute lower gastrointestinal bleeding protocol that ensures that the clinical sites comply with the study protocol and regulatory requirements.

2. TOOLS AND PROCESSES

2.1 Study Data

This study will use direct data entry of clinical trial data. This process will allow a clinical study site to perform direct data entry of original data into an electronic data capture (EDC) system at the time of the subject's hospital visit, and for the original data to be stored in the access-controlled data repository, access to which will be controlled by the clinical investigator. These original data will be stored in the Hospital Information System prior to the data being transmitted to the EDC database.

3. Risk Mitigation Strategy

Category	Risk	Impact	Probability	Detectability	RPE*	Risk Mitigation
Trial outcome	Missing identification rate of stigmata of recent hemorrhage	High	Medium	High	High	100% SDV and SDR (on site monitoring)
Subject safety	Risk is greater in the elective group than early group	High	Low	High	Low	Planned sample size will provide sufficient statistical power including patients with protocol violations
Subjectssafety	Specific reporting requirements for severe adverse events (SAE)	High	Low	High	High	When an SAE occurs, information is automatically transmitted from the EDC system to stakeholders
Subject registration	Violation of eligibility	High	Low	High	High	100% SDV and SDR (onsite monitoring)
Subject registration	Allocation	High	Low	High	High	All allocation is performed by the EDC system
Subjects' demographic data	Concomitant Medication	Low	Low	High	Low	Central monitoring confirms data inconsistency
Subjects' demographic data	Past history of Illness	Low	Low	High	Low	Using Charson Comorbidity Index, central monitoring confirms data inconsistency
Procedure	Data collection	Low	Low	High	Low	Vital signs, laboratory data and other

						continuous variables are extracted from the EDC system; a biostatistician performs central statistical monitoring and detects inaccurate data
Procedure	Colonoscopy	Low	Low	High	Low	All facilities are endoscopic special facilities, which have many endoscopists to complete colonoscopy procedures in compliance with the protocol
Discontinuation	Discontinuation of study subjects	High	Low	High	High	Central monitoring confirms data
Facility selection	Facility selection for this study	Low	Low	Low	Low	All facilities have own institutional review board and share study aims. Thus, these facilities are able to recruit the planned number of subjects

***** RPE, Risk priority number

4. SOURCE DOCUMENTS

1. Source data/records contain all information necessary for the reconstruction and evaluation of the study. Source data/records include original records, certified copies of original records, observations, and laboratory reports and/or data sheets. In addition, with the use of direct data entry, the access-controlled data repository will serve as an original record.

2. At the time of the first monitoring visit or during the initiation visit, the source of original data, whether it is being collected in electronic or paper format, will be identified for each site.

5. MONITORING

Onsite monitoring visits will focus on ensuring that the clinical site understands and is following the protocol, reviewing completeness and accuracy of informed consent forms, risk-based source document verification (SDV) of original records, and other issues that may occur during the course of the clinical trial.

Central monitoring will focus on assessment of the "reasonableness" of data entered into EDC system and data quality management metrics. Central statistical monitoring will focus on assessment of the veracity of data entered into the EDC system using statistical methods.

5.1 Onsite Monitoring

For each site, the responsible monitor will schedule the first onsite monitoring visit to confirm the informed consent (Day 0) of any of the first three subjects. Based on the findings at this visit, coupled with central monitoring findings, the monitor will decide when to schedule the next monitoring visit.

For each site, the monitor will schedule a monitoring visit immediately prior to, or coinciding with, the first subject's final study visit (Day 31+/3). The purpose of this visit will be primarily to retrain the site personnel on the relevant study procedures.

Interim monitoring visits will include review of the following:

1. Informed consent process and forms (100%)
2. Study conduct and protocol adherence
3. Subject eligibility (100%)
4. Adverse events (100%)
5. Personnel delegation and signature log
6. Patient medical records

7. Protocol deviations and violations
8. Follow-up of outstanding issues
9. The certification process of data originally collected on paper and subsequently entered into the EDC system

Where a site maintains patient records that duplicate information captured in the EDC system, the monitor will review those records specified below, to ensure that the site records match those captured in the EDC system:

1. Demographics (100%). To ensure subject identities based on the site's medical records.
2. Medical history. To ensure that sites have entered all relevant inclusion/exclusion criteria into the EDC system (100%).
3. Confirmation of subject's visit to the clinical site (100% of first three subjects).
4. Review of office medical records (100% of first three subjects).

When findings indicate that retraining is required, the monitor will retrain site staff as soon as possible.

5.2 Central Monitoring

Data managers (DM) will perform central monitoring through data review and cleaning:

1. A 100% review of all entered forms and issue queries, if needed.
2. Review and take appropriate action for all online and batch edit checks.

DM will review periodically the EDC for accuracy and completeness. Risk-based monitoring meetings will take place when 20, 40, 80, and 120 cases have accumulated, and will involve DM, the monitor, biostatistician (as needed), to review the progress of the clinical trial. Items to be reviewed at the risk-based monitoring meetings may include:

1. Enrollment and dropout status
2. An assessment of edit checks and queries that are being filed, by form as well as by variable
3. Reasons for changes to the database by the clinical site
4. Adverse events
5. Medications
6. Protocol deviations and violations
7. Monitoring procedures
8. Other items that may arise

9. Action items

The project manager will record meeting minutes and follow-up actions. The schedule of meetings and the clinical monitoring plan may be modified depending on findings. The decisions and the rationale for changing any of the procedures will be documented.

6. Startup meeting

The purpose of a startup meeting is to train investigators and site personnel on the specific requirements and procedures needed to perform the clinical trial. The startup meeting will be held during the risk-based monitoring meeting, or if it is determined that a specific site requires additional training, as appropriate. Sites will not enroll subjects into the trial until the startup meeting has been satisfactorily completed.

At a minimum, the agenda for the startup meeting must include the following elements:

1. Review of the protocol
2. Training appropriate staff on:
   A) GCP regulations
   B) SAE reporting requirements
   C) Subject management
   D) Handling of colonoscopy examination
   E) Handling of safety colonoscopy examination
   F) EDC system
   G) Certification of original records
   H) Direct data entry process

7. Interim Monitoring Visits

The purpose of an interim monitoring visit will be to ensure that the rights and well-being of each subject are protected; trial data are accurate, complete, and verifiable; the trial is being conducted according to ICH GCP guidelines and Ethical Guidelines for Medical and Health Research Involving Human Subjects; and the trial site and staff remain trained and qualified. Monitoring of the clinical trial can occur both by onsite visits and through central monitoring procedures.

8. Closeout Visit

The purpose of a closeout visit will be to bring official completion to all trial-related activities at the site.