Statistical Analysis Plan (SAP)

Accuracy of Magnetically Maneuvered Capsule Endoscopy for Detection of Esophagogastric Varices in Patients with Cirrhosis (CENTERS study)

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Contents

1. Administrative information

1.1 Study identifiers

• Protocol Version: 4.0, Date: 15 June 2021

• ClinicalTrials.gov register Identifier: NCT03748563

1.2 Revision history

Version	Date	Details
0.1	27 April 2023	First draft by Yan Hou
0.2	12 May 2023	New version following review by Zhuan Liao
1.0	19 May 2023	Final version

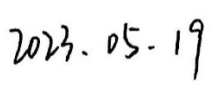
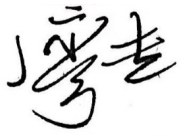
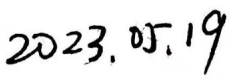
1.3 Contributors to the statistical analysis plan

1.3.1 Roles and responsibilities

Name	Affiliation	Role on study	SAP contribution
Prof. Yan Hou	Department of Biostatistics, Peking University, China	Study statistician	Prepared initial draft and revisions
Prof. Zhuan Liao	Department of Gastroenterology, Changhai Hospital, Naval Medical University, China	Principal Investigator	Reviewed all versions

1.3.2 Approvals

The undersigned have reviewed this plan, approve it as final and as consistent with the requirements of the protocol as it applies to their respective areas. They agree that the planned statistical analyses are appropriate for this study and in accordance with the study objectives and are consistent with the statistical methodology described in the protocol and all applicable regulatory guidance and guidelines. They confirm that this analysis plan was developed in a completely blinded manner, that is without knowledge of the effect of the intervention(s) being assessed.

Name	Signature	Date
Yan Hou		
Zhuan Liao		

2. Abbreviations

AE	adverse events
BBS	black brown spots
CE	capsule endoscopy
CECR	capsule endoscopy completion rate
CI	confidential interval
CRF	case report form
CRS	cherry red spots
DSMB	data safety monitoring board
ds-MCE	detachable string magnetically maneuvered capsule endoscopy
EC	ethics committee
EGD	esophagogastroduodenoscopy
EGV	esophagogastric varices
ETT	esophageal transit time
EV	esophageal varices
FPI	first patient in
GET	gastric examination time
GOV	gastroesophageal varices
GTT	gastric transit time
GV	gastric varices
HRV	high-risk varices
LC	liver cirrhosis
LLT	lower level term
MCE	magnetically maneuvered capsule endoscopy
mITT	modified intent-to-treat
MLP	mosaic like pattern
NPV	negative predictive value
OC	observed cases
PHE	portal hypertensive enteropathy
PHG	portal hypertensive gastropathy
PPS	per protocol set
PPV	positive predictive value
PT	preferred term
RPL	red point lesions
SAE	serious adverse events
SAP	Statistical Analysis Plan
SAS	safety analysis set
SBTT	small bowel transit time
SOC	primary system organ class
TRT	total recording time
WOCF	worst outcome carried forward

3.Introduction

Esophagogastric varices (EGV) are the major cause of morbidity and mortality in cirrhotic patients due to the risk of variceal hemorrhage. It has been estimated that at least two thirds of cirrhotic patients develop esophageal varices (EV) during their lifetime. Gastric varices (GV) are seen in 15–20% of cirrhotic patients with a high mortality rate and a greater propensity to rebleed. Since the risk of variceal bleeding mostly depends upon the size of EV and the presence of “red sign” on varices can be reduced with appropriate medical or endoscopic treatment in patients with high-risk varices (HRV), international practice guidelines recommended endoscopic screening and periodic surveillance for EGV and provide prophylactic treatment for HRV to prevent variceal bleeding. Esophagogastroduodenoscopy (EGD) is recognized as the gold standard for detection of EGV in cirrhotic patients, allowing for direct mucosal visualization. However, EGD is an invasive procedure which is potentially associated with serious, even if rare, complications. In addition, it is often carried out with the patients under sedation, which involves additional costs and complications, which may be more frequent in patients with liver cirrhosis (LC). These factors lead to a decrease of patient compliance as well as the effectiveness of the endoscopic screening program.

The capsule endoscopy (CE) provides a noninvasive and relatively comfortable approach to visualize the GI tract without the need for sedation. Several studies have confirmed its safety and tolerability in diagnosis of EV. However, the accuracy of CE is not currently sufficient to replace EGD for the detection and grading of EV, which mainly restricted by the inability to distend the distal esophagus, wash bubbles, active control of CE or repeated real-time visualization of key areas during esophageal examination. Furthermore, CE has poor visualization of the stomach so that gastric varices, portal hypertensive gastropathy (PHG) and other clinically significant gastric lesions couldn’t be accurately detected. Up to now, guideline of European Society of Gastrointestinal Endoscopy does not recommend CE for screening of EGV.

To overcome these limitations, a new technique, so-called detachable string magnetically maneuvered capsule endoscopy (ds-MCE) (Ankon Technologies, Wuhan, China) was developed. The ds-MCE system consists of two parts: the magnetically maneuvered capsule endoscopy (MCE) system and a transparent latex sleeve with a hollow string. The capsule, which is partially enclosed within the sleeve, can be actively

moved in the esophagus by the control of string. After completion of the esophageal examination, the string could be separated from the CE by injecting 5mL of air and removed from the mouth; the CE continued into the stomach. During the gastric examination, CE can be actively controlled by external magnetic field. Previous studies have demonstrated that the diagnostic accuracy of MCE for detecting gastric focal lesions is comparable with that of conventional EGD. Two pilot studies of ds-MCE confirmed it was a feasible, safe and well-tolerated method for detecting EGV in patients with cirrhosis. Besides, the 8-10h battery life of the ds-MCE enables further evaluation of the portal hypertensive enteropathy (PHE) in small-bowel, providing a more comprehensive evaluation of gastrointestinal changes in cirrhotic patients.

The study of magnetically maneuvered Capsule ENdoscopy for deTection of Esophagogastric vaRices in patients with cirrhosiS (CENTERS) is a multicenter, prospective diagnostic accuracy study, assessing the diagnostic performance of ds-MCE in detecting and grading EGV in patients with cirrhosis, using EGD as the reference.

4. Study Objective

4.1 Primary objective

- To estimate the diagnostic accuracy of ds-MCE in identifying EGV in patients with cirrhosis, using the detection by EGD as the reference.

4.2 Secondary objectives

4.2.1 Key secondary objective

- To estimate the diagnostic accuracy of ds-MCE in identifying high-risk EV, using the detection by EGD as the reference.

4.2.2 Other secondary objectives

- To estimate the diagnostic accuracy of ds-MCE in identifying high-risk EGV, using the detection by EGD as the reference.
- To estimate the diagnostic accuracy of ds-MCE in identifying EV, using the detection by EGD as the reference.
- To estimate the diagnostic accuracy of ds-MCE in identifying large EV, using the

detection by EGD as the reference.

- To estimate the diagnostic accuracy of ds-MCE in identifying red signs of EV, using the detection by EGD as the reference.
- To estimate the diagnostic accuracy of ds-MCE in identifying GV, using the detection by EGD as the reference.
- To estimate the diagnostic accuracy of ds-MCE in identifying cardiofundal GV, using the detection by EGD as the reference.
- To estimate the diagnostic accuracy of ds-MCE in identifying PHG, using the detection by EGD as the reference.
- To assess the incidence of PHE in small bowel under ds-MCE.
- To evaluate the examination time of ds-MCE and EGD procedures.
- To assess the patient satisfaction score of the ds-MCE and EGD procedures.
- Safety evaluation: to record the adverse events occurring during the study.

5. Design

5.1 Overview

This is a multicenter, prospective, single-arm confirmatory diagnostic accuracy study. EGD is the reference standard against which ds-MCE is compared, and it is performed within 48 hours after ds-MCE examination.

5.2 Eligibility criteria

5.2.1 Inclusion Criteria

Subjects meeting all of the following criteria are eligible for enrollment as study participants:

(1) Gender is not limited.

(2) Patients aged 18 years or older.

(3) Both inpatients and outpatients.

(4) Clinically evident or biopsy-proven liver cirrhosis.

(5) Able to provide informed consent.

5.2.2 Exclusion Criteria

Subjects meeting any of the following criteria are not eligible for enrollment as study

participants:

(1) Patients aged less than 18 years.
(2) Patients with dysphagia.
(3) Patients with Zenker's diverticulum.
(4) Suspected or known intestinal stenosis or other known risk factors for capsule retention.
(5) Pregnancy or suspected pregnancy.
(6) Patients with active gastrointestinal bleeding.
(7) Patients with cardiac pacemaker or other implanted electromedical devices which could interfere with magnetic resonance.
(8) Patients with life-threatening conditions.
(9) Patients plan to undergo magnetic resonance imaging examination before excretion of the MCE.
(10) Patients who are participating in or have participated in other clinical trials.
(11) Patients who refuse to give informed consent.
(12) Patients with any condition that precludes compliance with the study.

5.3 Sample size

As a single-arm confirmatory diagnostic accuracy study, we primarily aimed to test whether both the sensitivity and the specificity of ds-MCE for detecting EGV would be >85%. With estimated sensitivity of 90%, specificity of 94%, a two-sided alpha of 5%, power of 80%, EGV prevalence of 62%, and a dropout rate of 3%, 591 patients would be needed[1].

When considering the accuracy of ds-MCE for detecting high-risk EV (key secondary outcome), the validation cohort of approximately 200 patients would provide an estimation precision (CI width/2) of <7%, with estimated sensitivity of 90% and specificity of 94%, using CENTERS luminal circumference percentage threshold derived from the training cohort, and high-risk EV prevalence of 40%.

5.4 Randomization

Randomization is not an option in this investigation. All subjects will utilize both the ds-MCE and the EGD during the study.

5.5 Blinding

(1) The ds-MCE operator will be aware of the subject's medical history and blinded to the EGV-related imaging and endoscopic findings of the enrolled subjects;
(2) The EGD operator will be aware of the subject's medical history, but will be blinded to the ds-MCE examination results;
(3) The independent ds-MCE imaging readers will be blinded to the EGD assessment results of the enrolled subjects;
(4) The independent EGD readers will be blinded to the ds-MCE assessment results of the enrolled subjects.

6. Efficacy and Safety outcomes

6.1 Efficacy outcomes

6.1.1 Primary Outcome

The primary outcome is the sensitivity and specificity of ds-MCE to identify EGV in patients with cirrhosis, using detection by EGD as the reference.

6.1.2 Secondary Outcomes

6.1.2.1 Key Secondary Outcome

1) The sensitivity, specificity of ds-MCE in detection of high-risk EV, using the detection by EGD as the reference.
   The high-risk EV was identified by either large EV or small EV with presence of red signs according to the Baveno VI consensus[2].

6.1.2.2 Other Secondary Outcomes

2) The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall diagnostic accuracy of ds-MCE in detection of high-risk EGV, using the detection by EGD as the reference.
   High-risk EGV are defined as high-risk EV or any GV[3,4].
3) The sensitivity, specificity, PPV, NPV and overall diagnostic accuracy of ds-MCE in detection of EV, using the detection by EGD as the reference.
4) To investigate the optimal threshold of the proportion of ds-MCE esophageal luminal circumference occupied by the largest EV present in differentiating large

EV from small or no EV, using the detection by EGD as the reference.

a) EV identified during EGD are classified based on the standard Baveno III consensus to differentiate between large EV (varix diameter ⩾5mm) and small EV (varix diameter <5mm)[5].

b) As grading EV by endoscopy requires fully distention of the esophagus with air insufflation, which is lacking in CE, there has been no consensus on the standard classification of large EV under ds-MCE. In this study, we grade the EV under ds-MCE according to the proportion of the esophageal luminal circumference occupied by the largest EV present[6].

c) The Youden Index, defined as [(sensitivity＋specificity)-1], will be calculated to determine the optimal ds-MCE luminal circumference percentage threshold derived from the training cohort that resulted in the best combination of specificity and sensitivity for distinguishing large EV, using the results of EGD as the reference standard.

5) The sensitivity, specificity, PPV, NPV and overall diagnostic accuracy of ds-MCE in detection of large EV, using the detection by EGD as the reference.

a) EV under EGD are classified into three grades: no, small or large, with the latter signifying a diameter ≥5 mm.

b) EV under ds-MCE are classified into three grades: no, small or large, with the latter signifying that the esophageal varix occupied more than the prespecified "optimal threshold" proportion of the esophageal luminal circumference.

6) The sensitivity, specificity, PPV, NPV and overall diagnostic accuracy of ds-MCE in detection of the red sign of EV, using the detection by EGD as the reference.

7) The sensitivity, specificity, PPV, NPV and overall diagnostic accuracy of ds-MCE in detection of gastric varices (GV), using the detection by EGD as the reference. GV are classified according to Sarin's classification[7]. GV could be classified on the basis of its location in the stomach and its relationship with EV during ds-MCE procedure and EGD procedure. These are divided into two groups: gastroesophageal varices (GOV) and isolated gastric varices (IGV). GOV1 are the extension of esophageal varices which across the cardia onto the lesser curve, and GOV2 extend onto the fundus. Isolated gastric varices (IGV) are vascular protrusions without direct connection to the esophageal varices. IGV1 are located in the fundus, while IGV2 are located elsewhere in the stomach, typically in the

distal body and antrum.

8) The sensitivity, specificity, PPV, NPV and overall diagnostic accuracy of ds-MCE in detection of cardiofundal GV, using the detection by EGD as the reference.
Cardiofundal gastric varices including GOV2 and IGV1 are at high risk of bleeding due to the unique vascular anatomy as opposed to lesser-curvature gastric varices (GOV1)[8].

9) The sensitivity, specificity, PPV, NPV and overall diagnostic accuracy of ds-MCE in detection of portal hypertensive gastropathy (PHG), using the detection by EGD as the reference.
The PHG is classified as four elementary gastric endoscopic signs proposed by the NIEC group: mosaic like pattern (MLP); red point lesions (RPL); cherry red spots (CRS); black brown spots (BBS)[9,10].

10) The incidence of PHE in small bowel under ds-MCE.
Endoscopic findings of PHE include mucosal inflammatory-like abnormalities, vascular lesions and spontaneous bleeding induced by mucosal inflammatory-like abnormalities or vascular lesions[11-13].

11) Examination time of ds-MCE and EGD procedures.
Examination time of ds-MCE include esophageal transit time (ETT), gastric examination time (GET), gastric transit time (GTT), small bowel transit time (SBTT), and total running time (TRT). ETT is defined as the time between the first esophageal image and the first gastric image. GET is defined as the time for examination of whole stomach twice. GTT is defined as the time between the first gastric image and the first duodenal image. SBTT is defined as the time between the first duodenal image and the first cecal image. TRT is defined as the time of the last picture taken by the capsule. Capsule endoscopy completion rate (CECR) is also recorded which defined as the proportion of the capsule that has a complete visualization of the entire small bowel[14]. Examination time of EGD is defined as the duration from the endoscope entering to exiting from the esophagus.

12) Patient satisfaction score of ds-MCE and EGD procedures.
After completing the ds-MCE procedure or EGD procedure, patients will undergo a face-to-face interview at which they are asked to respond to the questions on the three-item questionnaire that addressed procedure satisfaction.
a) Did you experience discomfort during the ds-MCE/EGD procedure?
4 = none; 3 = minor; 2 = mild; 1 = severe; 0 = intolerable

b) Did you experience discomfort after the ds-MCE/EGD procedure?

4 = none; 3 = minor; 2 = mild; 1 = severe; 0 = intolerable

c) How would you rate the entire ds-MCE/EGD examination procedure?

4 = very comfortable; 3 = comfortable; 2 = tolerable; 1 = uncomfortable; 0 = very uncomfortable

6.2 Safety outcomes

Safety outcomes in this study will be assessed based on adverse event reporting. All adverse events that occur during the course of the study will be diligently recorded and documented.

7. Statistical Considerations

7.1 Objective and Hypothesis

Objective

The primary aim of this study is to assess the accuracy of ds-MCE for detection of EGV in patients with liver cirrhosis.

Hypothesis

The primary objective of this study is to evaluate the diagnostic performance of ds-MCE in detecting EGV by assessing its sensitivity and specificity, using EGD as the reference standard. The hypothesis is that both the sensitivity and specificity of ds-MCE for detecting EGV will exceed 85% when compared to EGD. The target value of 85% was set based on literature review[15] and expert consensus from the steering committee.

$$H_{01}: \text{Sensitivity} \leq 85\%$$
$$H_{11}: \text{Sensitivity} > 85\%$$
$$H_{02}: \text{Specificity} \leq 85\%$$
$$H_{12}: \text{Specificity} > 85\%$$

7.2 Statistical Analysis Set

The analyses will be performed on modified intent-to-treat (mITT), per protocol set

(PPS) and safety analysis set (SAS). Each analysis set will summarize the number of subjects and its percentage from subjects.

Efficacy set: The analysis of mITT is primary, and PPS is a sensitivity analysis of mITT.

The effectiveness analyses will be based on mITT population who go through procedures of ds-MCE and EGD modalities and can be evaluated for the results of EV and GV.

The effectiveness analyses will also be conducted on the PPS, which includes all subjects in the mITT population who have no major protocol deviations (defined to be protocol violations that may have a significant impact on subject outcomes) and who do not meet any of the following criteria:

- Subject withdraws
- Capsule ingestion failure
- Esophageal or gastric examination failure under ds-MCE
- Esophageal or gastric examination failure under EGD
- System technical failure of ds-MCE or EGD

Safety Set: The evaluation of safety parameters will be conducted on the SAS

SAS (Safety Analysis Set): actual data that has been inspected at least once and has safety indicators recorded. Security missing values do not need to be carried forward.

7.3 Statistical Analyses

7.3.1 General Analysis Considerations and Convention

Descriptive statistics for continuous variables will include arithmetic mean (standard deviation) or median (interquartile ranges) as appropriate. Frequency and percentage will be calculated for categorical variables. Unless otherwise specified, for continuous variables, comparisons between groups will be assessed using the paired *t* test or Wilcoxon signed-rank test as appropriate. Categorical variables will be compared using the McNemar test as appropriate.

All statistical analyses will be performed using SAS version 9.4 (SAS Institute Inc, Cary, NC) and R version 4.2.2 (R Foundation for Statistical Computing). Unless otherwise specified, all significance testing will be 2-tailed using $\alpha = 0.05$. Tests will be declared statistically significant if the calculated p-value was <0.05.

7.3.2 Interim Analyses

No interim analysis is planned for this study.

7.3.3 Missing data

The primary analysis will be conducted on both mITT and PPS. For mITT analysis, the observed cases (OC) for each visit will be used and the worst outcome carried forward (WOCF) method will be applied for the primary endpoint to impute missing data, unless otherwise specified.

No imputation for missing data will be performed for the secondary and safety outcomes analysis.

7.3.4 Multiple Comparisons

Since the primary outcome hypothesis testing based on the two primary endpoints should be met simultaneously, no multiplicity adjustment will be performed.

For the analysis of the secondary and safety outcomes, no adjustment for multiple comparisons will be made.

7.3.5 Subject Enrollment Status

(1) Subject Disposition

The disposition of all subjects will be summarized. Subject disposition tables will include the number (percent) of subjects who are:

Screened subjects and ineligible subjects;

Included in each analysis populations;

Discontinued from the study early, summarized by reasons for discontinuation.

(2) Subject Disposition by Study Site

Subject disposition by study site will be summarized by number of enrolled subjects, number (percent) of subjects who completed the study and who discontinued from the study early.

(3) Protocol Violations

Major protocol violations that led to the exclusion from PPS will be listed.

7.3.6 Demographics and Baseline Characteristics

All data recorded at baseline will be summarized and presented for each analysis set. Summary tables (descriptive statistics and/or frequency tables) will be provided for all

variables at different endpoints. For continuous variables, means and standard deviations will be presented, unless the variable has a skewed distribution, in which case medians, 25th and 75th percentiles will be presented. For categorical variables, the number and percentage of participants within each category will be presented. For each variable (continuous or categorical), the number of missing values will be reported.

Subjects' baseline characteristics include: Age (continuous), sex (male/ female), body-mass index (continuous), time since diagnosis of cirrhosis (continuous), etiology (hepatitis B virus infection/hepatitis C virus infection/alcoholic liver disease/ autoimmune hepatitis/primary biliary cirrhosis/non-alcoholic steatohepatitis /cryptogenic/other), Child-Pugh score (continuous), Child-Pugh Class (class A/class B/class C),decompensated cirrhosis (yes), indication for endoscopy (screening/ surveillance), clinical events (ascites/history of splenectomy/TIPS insertion/ history of endoscopic variceal therapy/ history of bleeding esophagogastric varices).

7.3.7 Efficacy Analysis

7.3.7.1 Analyses for Primary Outcome

The primary outcome is the diagnostic accuracy of ds-MCE for discrimination of patients with EGV using sensitivity and specificity, along with the corresponding 95% CIs estimated using the Wilson's method[16]. Sensitivity and specificity will be compared with 85% using one-sample exact test. The accuracy, and positive and negative predictive values (PPV and NPV) will be calculated as other measures simultaneously, along with the corresponding 95% CIs estimated using the Wilson's method.

- True Positive (a): Both ds-MCE diagnosis and EGD results determine the presence of esophageal or gastric varices, and the location (esophagus or stomach) is consistent.
- False Negative (c): ds-MCE diagnosis determines no cases of esophageal or gastric varices, while EGD results determine the presence of esophageal or gastric varices.
- True Negative (d): Both ds-MCE diagnosis and EGD results determine the absence of esophageal or gastric varices.
- False Positive (b_1): ds-MCE diagnosis and EGD results both determine the presence of esophageal or gastric varices, but the locations (esophagus or stomach) are inconsistent.
- False Positive (b_2): ds-MCE diagnosis determines the presence of esophageal or

gastric varices, while EGD results determine the absence of esophageal or gastric varices.

Table1. Four-grid table for ds-MCE and EGD assessment results

ds-MCE	**EGD**		
	Varices		Non-varices
	Consistent location in the stomach or esophagus	Inconsistent location in the stomach or esophagus	
Varices	a	b_1	b_2
Non-varices	c		d

Sensitivity (SE)=$a/(a+b_1+c)\times100\%$

Specificity (SP)=$d/(b_2+d)\times100\%$

Accuracy=$(a+d)/(a+b_1+b_2+c+d)\times100\%$

PPV=$a/(a+b_1+b_2)\times100\%$;

NPV=$d/(c+d)\times100\%$;

Sensitivity Analyses for the Primary Outcome

No sensitivity analysis will be conducted for this study.

7.3.7.2 Analyses for Secondary Outcomes

The training cohort and validation cohort will be divided based on centers, in the order of the first patient in (FPI). Centers with earlier FPI date will be allocated to the training cohort (whose sample size should meet approximately 2/3 of the total sample size), and the remaining centers with later FPI date will be allocated to the validation cohort.

(1) Optimal threshold based on the Training Cohort

The optimal esophageal luminal circumference percentage threshold will be chosen with the Youden Index[17]. The Youden Index, defined as [(sensitivity＋specificity)-1], will be calculated to determine the ds-MCE optimal luminal circumference percentage threshold derived from the training cohort that resulted in the best combination of specificity and sensitivity for distinguishing large EV, using the results of EGD as the reference standard. When the optimal threshold has decimals, its integer portion will be set as the modified optimal threshold for internal and external validation (for the ease of clinical application and ensuring sensitivity). Based on the training cohort, the modified optimal threshold is internally validated with bootstrap method, with 1000 replicates.

(2) The diagnostic accuracy of high-risk EV will be assessed on the basis of the modified optimal threshold above in the validation cohort using accuracy, sensitivity, specificity, PPV and NPV, corresponding 95% CIs calculated using the Wilson's method.

(3) The diagnostic accuracy of high-risk EGV will be assessed on the basis of the modified optimal threshold above in the validation cohort using accuracy, sensitivity, specificity, PPV and NPV, corresponding 95% CIs calculated using the Wilson's method.

(4) The diagnostic accuracy of large EV will be assessed on the basis of the modified optimal threshold above in the validation cohort using accuracy, sensitivity, specificity, PPV and NPV, corresponding 95% CIs calculated using the Wilson's method.

(5) The diagnostic accuracy of ds-MCE in detection of EV compared with the EGD will be assessed using accuracy, sensitivity, specificity, PPV and NPV, corresponding 95% CIs calculated using the Wilson's method.

(6) The diagnostic accuracy of ds-MCE in detection of red signs of EV compared with the EGD will be assessed using accuracy, sensitivity, specificity, PPV and NPV, corresponding 95% CIs calculated using the Wilson's method.

(7) The diagnostic accuracy of ds-MCE in detection of gastric varices (GV) compared with the EGD will be assessed using accuracy, sensitivity, specificity, PPV and NPV, corresponding 95% CIs calculated using the Wilson's method.

(8) The diagnostic accuracy of ds-MCE in detection of cardiofundal GV compared with the EGD will be assessed using accuracy, sensitivity, specificity, PPV and NPV, corresponding 95% CIs calculated using the Wilson's method.

(9) The diagnostic accuracy of ds-MCE in detection of portal hypertensive gastropathy (PHG) compared with the EGD will be assessed using accuracy, sensitivity, specificity, PPV and NPV, corresponding 95% CIs calculated using the Wilson's method.

(10) The incidence of PHE in small bowel under ds-MCE will be described using the methodology described in Section 7.3.1.

(11) The examination times of ds-MCE and EGD procedures will be described using the methodology described in Section 7.3.1.

(12) The patient satisfaction score of ds-MCE and EGD procedures will be described using the methodology described in Section 7.3.1.

7.3.8 Subgroup analysis

To determine whether the accuracy is consistent across subgroups, the estimate of the between-group accuracy for EGV, high-risk EV based on the modified optimal threshold value, high-risk EGV based on the modified optimal threshold value will be estimated within each category of the following classification variables:
Cirrhosis stage (compensated phase, decompensated phase);
Indication for endoscopy (screening, surveillance).

7.3.9 Safety Analyses

All adverse events (AE) and serious adverse events (SAE) during the study will be listed. The AE verbatim descriptions collected from the Case Report Form (CRF) will undergo classification into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the most appropriate MedDRA lower level term (LLT) that closely matches the verbatim term. The associated MedDRA preferred term (PT) and primary system organ class (SOC) will also be recorded in the database.
Summary tables will only include those adverse events that considered related to trial procedure. However, subject data listings will include all adverse events, regardless of whether or not considered related to trial procedure. This approach ensures that adverse events considered related to trial procedure are appropriately captured and analyzed, while all adverse events are documented for comprehensive reporting and analysis.

7.3.9.1 Serious Adverse Events (SAE)

A Serious Adverse Event is any unfavorable event within the study timeframe fulfilling at least one of the following criteria:

- results in death;
- life-threatening (at the time of the event);
- inpatient hospitalization required or prolonged;
- event that results in persistent or significant disability/incapacity;
- medically important event or event that requires a medical or surgical intervention to prevent one of the above health implications.

Any other important medical event that did not result in any of the outcomes listed above due to interventions but could have been based upon appropriate medical judgment. An elective hospital admission will not be considered as a serious adverse

event.

As far as possible, each SAE should be evaluated to determine the severity grade (mild, moderate, severe); its relationship to the study procedure; its duration (start and end dates or if continuing at final exam); action taken (no action taken; hospitalization).

Serious adverse events will be immediately, after coming to notice of the investigator, reported to the trial coordinator, who is 24/7 available. The investigator will report the following SAEs occurring in the study period to the sponsor without undue delay of obtaining knowledge of the events: death from any cause; esophagogastric variceal hemorrhage during ds-MCE examination; acute esophagogastric variceal hemorrhage during EGD examination; acute esophagogastric variceal hemorrhage during ds-MCE examination. The investigator should report to the sponsor and ethics committee (EC) within 24 hours of SAEs. SAEs need to be documented additionally on a separate SAE form.

7.3.9.2 Follow-up of Adverse Events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. Assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study, the interventions required to treat it and the outcome. For a follow-up report, the investigator may be required to collect further information for a detailed description and a final evaluation of the case, including copies of hospital reports, autopsy reports, or other relevant documents.

SAEs need to be reported till the end of the study in China, as defined in the protocol.

7.3.9.3 Monitoring of safety risks

For the monitoring of safety risks and potential harms for the study participants caused by study procedure or study design, the sponsor and a Data Safety Monitoring Board (DSMB) will carefully review all (S)AEs. In case of any safety issue that might change the risk benefit balance unfavorable the sponsor will take appropriate measures to guarantee the safety of the patients.

8. References

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