Mass General Brigham

Protocol Title: Evaluation of the Impact of a Forward Viewing Scope at Time of ERCP Protocol
Version: 1.2 09/15/2022
MGB IRB Protocol: 2022P001825 (Initial Approval 9/26/2022; Most Recent Approval: 6/6/2024)
NCT #: NCT05627882
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Funder: Boston Scientific

ATTACHMENTS:

Detailed Protocol: Ver 1.2 – 09/15/2022

Institutional Review Board
Intervention/Interaction Detailed Protocol

Principal Investigator:	Marvin Ryou, MD
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1. Background and Significance

Endoscopic retrograde cholangiopancreatography (ERCP) is the current procedure of choice for the treatment for a variety of biliary and pancreatic disorders with over 500,000 procedures performed annually in the United States[1]. While the duodenoscope has a unique side-viewing design in order to provide optimal visualization of the major papilla during the ERCP procedure, the non-forward field of view severely limits a complete endoscopic examination of the esophagus and stomach. As a result, key upper gastrointestinal findings, such as peptic ulcer disease or hemorrhage, may be missed given the non-forward viewing design. In a previous retrospective study by Thomas and colleagues, significant gastrointestinal findings were not visualized during ERCP with a side-viewing duodenoscope among 19.2% of patients[2]. Given the high miss rate associated with ERCP, performing an esophagogastroduodenoscopy (EGD) with a forward-viewing endoscope may increase the yield of upper gastrointestinal lesions and improve overall patient care. Some centers already routinely employ simultaneous EGD/ERCP.

References:
1. Peery AF, Crockett SD, Murphy CC, Lund JL, Dellon ES, Williams JL, Jensen ET, Shaheen NJ, Barritt AS, Lieber SR, Kochar B, Barnes EL, Fan YC, Pate V, Galanko J, Baron TH, Sandler RS. Burden and Cost of Gastrointestinal, Liver, and Pancreatic Diseases in the United States: Update 2018. Gastroenterology. 2019;156:254–272.e11.
2. Thomas A, Vamadevan AS, Slattery E, et al. Performing forward-viewing endoscopy at time of pancreaticobiliary EUS and ERCP may detect additional upper gastrointestinal lesions. Endosc Int Open. 2016;4:E193-7.

2. Specific Aims and Objectives

The primary aim of this study is to determine the miss rate associated with traditional ERCP. This will be done by supplementing a forward-viewing EGD exam to the traditional side-viewing ERCP procedure and comparing outcomes of the procedures.

Additionally, we aim to identify patient characteristics (e.g. demographics, medical history, imaging history, medications, comorbidities, laboratory values, prior endoscopic findings) associated with clinically significant findings with simultaneous EGD/ERCP. We hypothesize that simultaneous EGD during ERCP will discover clinically significant findings missed by ERCP alone.

3. General Description of Study Design

This study will be a prospective, tandem-designed study to determine the proportion of clinically significant missed lesions when using a side- or oblique-viewing endoscope as compared to the standard forward-viewing endoscope. Utilizing standard endoscopy protocols in current practice at Brigham and Women's Hospital, consecutive adult patients undergoing ERCP for traditional reasons will undergo back-to-back tandem EGD and ERCP examinations.

Combination EGD/ERCP is already performed at BWH by some attending physicians but not all, and routinely at other tertiary centers. Possible clinical reasons for combination EGD/ERCP include, but are not restricted to: detailed evaluation and biopsies of the upper gastrointestinal (GI) tract; clearance of food/debris from the GI tract to permit a clear field for ERCP; detailed visualization of the esophagus, gastroesophageal junction, stomach, and duodenum in addition to standard ERCP.

The proposed study design entails an EGD performed by a staff gastroenterologist first. Next, a second blinded staff gastroenterologist will perform ERCP immediately after index EGD. Both endoscopists will note any clinically significant findings, independent of the other providers' procedural findings. Clinically significant findings, defined as endoscopic findings that alter patient management (i.e., esophageal varices, peptic ulcer disease, hemorrhage, mass, etc.) during EGD and ERCP, will be recorded. Additional data to be collected will include procedure time (scope in and out), anesthesia time, staffing (number of RN's, techs, physicians), scopes utilized, consumables utilized, cost of reusable scope reprocessing for both scopes.

4. Subject Selection

Subjects will be selected from the current list of patients undergoing conventional ERCP at Brigham and Women's Hospital. All patients must have a standard indication for the ERCP procedure (i.e., benign or malignant biliary obstruction, choledocholithiasis, etc.) and undergo ERCP with general anesthesia using a conventional duodenoscope to complete the ERCP procedure. Patients undergoing more than one procedure will be eligible to be included in this study for each ERCP procedure. Patients are currently recruited from multiple sources including outpatient and inpatient settings or referred from gastrointestinal, oncologic, or primary care providers. Upon arrival, patients will be approached about the study by the advanced endoscopy fellow, study coordinator, attending physician, or member of the gastrointestinal team. Once identified and

consented, patients will undergo initial EGD (with a conventional EGD scope) followed by tandem ERCP as described above.

To ensure adequate enrollment, a power calculation was performed. Assuming a 19% miss rate[1] and 80% power, 144 patients will be required to detect a significant risk difference. To then assess for clinically significant predictors of positive findings, enrollment is estimated to include up to 500 patients in order to conduct a multivariate regression analysis with multiple potential predictors

Informed consent will be obtained by the principal investigator or co-investigators from any patients who are scheduled for an ERCP procedure for any indication regardless of age, sex, demographics, race and ethnicity to allow for equitable selection of subjects.

Inclusion criteria:

1) Age 18-85+ years of either sex.
2) Scheduled or to be scheduled for an ERCP procedure at BWH

Exclusion criteria:

1) Individuals outside of the allowable age range
2) Contraindication to upper GI endoscopy
3) Pregnant women (ERCP is not typically performed on pregnant women due to the risks to the mother and fetus unless clinically necessary. For this study, we will also exclude pregnant women due to the risk factors)
4) Elevated risk due to comorbid disease, such as, severe cardiopulmonary, renal, liver or contraindications to anesthesiology which would prevent ERCP to be performed
5) Inability to understand the conditions of the study or to provide informed consent

References:

1. Thomas A, Vamadevan AS, Slattery E, et al. Performing forward-viewing endoscopy at time of pancreaticobiliary EUS and ERCP may detect additional upper gastrointestinal lesions. Endosc Int Open. 2016;4:E193-7.

5. Subject Enrollment

Enrollment will occur in the pre-procedure area with no initial pre-screening required. Potential subjects will be contacted prior to their examination date to review the consent form to see if they are interested in participating. Currently, Brigham and Women's Hospital performs >1000 ERCP procedures a year with adequate volume to

enroll patients in this study. Conventional procedural consents including benefits/risks of ERCP will be performed.

Those patients that are recruited from the PI's or Co-I's endoscopy schedule the day of the procedure, to minimize the risk of patients feeling obligated to participate, a physician colleague not part of the study team will initially explain the study to the potential subjects. A physician colleague or research nurse will explain the study or re-contact the patient after initial presentation of the study by the PI. We will also offer the patients the opportunity to review the consent form at home if identified prior to their scheduled exam date. We will also encourage the patients to speak with their primary care providers/specialists about participation in this study.

To those patients identified prior to their procedure date, a health care provider/specialist (licensed physician), who is known to the potential subject and has first-hand knowledge of the patient's medical history will (1) give approval for his/her patient to be contacted for research purposes, (2) initially introduce the study to the patient, and (3) obtain the patient's permission to be contacted by the study team.

Currently, the ERCP consent also includes a consent for EGD. Risks including bleeding, infection, perforation, pancreatitis, aspiration, and abdominal pain are listed on the consent form and are not different between EGD and ERCP. Addition of the EGD to the procedure due to tandem design will not expand further risks to the procedure. For non-English speakers, an in-person or phone interpreter will be utilized in all instances. All findings with EGD and ERCP will be discussed with the patient immediately following the procedure and will become part of their medical record as part of their standard of care.

After full discussion of risks and possible benefits, informed consent will be discussed and obtained by one of the investigators or a designee. This will be done in a private treatment room and the investigators or research staff will be available to assist and answer questions. Our intended population will include all races, genders and ethnicities.

Patients who meet the inclusion criterion and none of the exclusion criteria will be invited to participate in this study. Patients eligible for enrollment shall have the clinical study explained to them, as well as potential risks and benefits of their participation in the study. Each patient who agrees to participate shall sign and date an informed consent document prior to the procedure or any study-specific testing or assessments. Adults will only be considered as children are not seen in the endoscopy center at BWH. Pregnant women will be excluded as they typically do not undergo ERCP unless it is a medical necessity. The risks to the fetus and the mother are unknown, therefore we will exclude this population due to the increased risk.

Consent will be obtained by the Principal Investigator or one of the licensed physician investigators listed on the protocol per HRC policy prior to enrollment. All patients included will be over 18 years of age and, as such, will be able to give consent. Participants will be given a copy of the consent form and will be informed that their participation is voluntary and that they can withdraw at any time.

Consent of subjects who do not speak English will be obtained and documented following the procedures outlined in the PHRC Policy. Individuals who do not speak English and meet all study criteria will be provided an interpreter to translate the consent discussion. A translated version of a 'short form' consent document will be used to document informed consent when a non-English speaking individual is unexpectedly encountered and a written translation of the PHRC-approved consent form is not available.

6. STUDY PROCEDURES

The first gastroenterology attending will perform the initial forward-viewing EGD with a second blinded attending performing the ERCP with the side-viewing duodenoscope. The second gastroenterologist will not have prior knowledge of the findings on initial EGD.

Patients will undergo endoscopy based conventional indications with general anesthesia using a conventional side-viewing duodenoscope to complete the ERCP procedure and EGD with a standard gastroscope. The advanced endoscopy fellow (who has attending privileges) will perform the EGD prior to the ERCP to allow for the gastroenterology attending to be blinded. The study coordinator will record results prior to the subsequent ERCP. The advanced attending will join after completion of the EGD for the ERCP portion of the exam. Blinding will be broken if a finding is found by the advanced endoscopy fellow that would preclude ERCP to involve the advanced attending for patient care and safety. This will be recorded as an aborted procedure given EGD findings.

In scenarios where ERCP is performed, the attending will relay blinded results only after ERCP completion and ERCP reported findings have been recorded for study purposes (to ensure no bias of results). After both the EGD and ERCP procedures are completed all results and findings will be reviewed by both gastroenterologists immediately post-procedure and discussed with the patient. No remuneration is required for this study.

7. Risks and Discomforts

Risks including bleeding, infection, perforation, pancreatitis, aspiration, and abdominal pain are listed on the current consent form. The risks of the EGD are the same as the risks of the ERCP. Endoscopic procedures with multiple scopes are routinely performed to

provide comprehensive clinical care and adding a diagnostic EGD scope to an ERCP is not considered appreciable added risk. This will increase the procedure time by approximately 10 min.

Expected risks or discomforts anticipated as a result of an endoscopic procedure (including ERCP and EGD) include:

- Sore throat, hoarseness, lump in throat feeling (globus pharyngitis)
- Temporary difficulty (dysphagia) or painful swallowing (odynophagia) due to swelling or tissue manipulation
- Nausea, gagging, or vomiting
- Left shoulder pain from C02 insufflation
- Temporary abdominal or other pain which can be treated with standard pain medication

Potential Adverse Events

Details of foreseeable adverse events (AE) and adverse effects (e.g., serious / non-serious related / non-related) are as follows:

- Typical known risks or discomforts anticipated as a result of an endoscopic procedure:
  Temporary dysphagia (difficulty swallowing) or odynophagia (painful swallowing), due to swelling or tissue manipulation, hoarseness, gagging, globus, pharyngitis, or other temporary pain which responds to standard pain medication.

- Unusual risks or discomforts as a result of an endoscopic procedure:
  Injury of mouth and/or teeth, bite block related injury, persistent odynophagia or dysphagia requiring intervention, bleeding, perforation, abrasion, hematoma/edema, laceration, esophageal tear, gas bloat, dyspepsia, diarrhea, infection, fistulae between inner organs, vomiting, nose bleeding from nasal intubation, vocal cord nodules due to intubation, hiccups, and limited neck mobility.

8. Benefits

Given a reported miss rate of approximately 19%, potential benefits include identification of clinically significant findings including but not limited to esophageal varices, peptic ulcer disease, hemorrhage, or mass lesions. Based upon these findings, and identification of a significant miss rate, may result in changes to every day clinical practice and workflow of the Brigham endoscopy unit. Of note, EGDs are performed with endoscopic ultrasound (EUS) and at many other institutions perform EGD with every ERCP. However, this practice is not currently the standard of care at Brigham and Women's Hospital.

9. Statistical Analysis

For the two comparison groups (EGD findings versus ERCP findings), continuous data will be compared using the two-sample t-test or Wilcoxon rank-sum test and categorical data to be compared using the Chi-square or Fisher's exact test, as appropriate. Multivariable analyses will also be performed using logistic regression to determine significant predictors of missed findings (i.e., patient characteristics) and will be reported as standardized β coefficients as well as odds ratio (OR) with corresponding 95% confidence intervals (CIs). Statistical significance will be defined as a two-tailed *P* value <0.05. Statistical analyses will be performed using the Stata 15.0 software package (Stata Corp LP, College Station, TX).

10. Monitoring and Quality Assurance

The PI and study team will utilize the Data and Safety Monitoring Plan (DSMP) below to ensure the safety of participants, and assure the validity of data. The safety reporting system will be continually reviewed by the PI and study team, this also includes the assessment of data integrity by the PI and study team quarterly, ongoing statistical analysis as samples are collected and processed, as well as an annual report submitted to the MGB IRB. The DSMP will include the following elements:

- Documentation of all meetings, discussions, or reports related to regulatory compliance.
- Identification of Partners IRB as monitor to subject accrual and retention, subgroup participation, and protocol adherence.
- Data integrity maintained through protocol adherence, data forms, and internal assessment.
- Participant confidentiality maintained per methods described in the current protocol.
- Safety reporting system continually reviewed to detect any early trends that might affect the safety of the intervention and any effects on the underlying disease in the indicated patients.
- All reporting to the Partners IRB/outside agencies carried out by the principal investigator.
- Ongoing statistical analysis performed to assess for trends that may impact on safety.
- An annual report generated that indicates: 1) list and summary of adverse events, 2) whether adverse event rates are consistent with pre-study assumptions; 3) summary of recruitment and retention and reason for dropouts; 4) whether the study is on track to be completed and accomplish the stated aims.
- All data, clinical outcomes, and safety outcomes reviewed quarterly by the principal investigator for completeness, accuracy, and protocol compliance, as well

as the degree to which measures to protect data integrity and protection are in place, and that all standards of confidentiality are adhered to.

- Tracking documentation will include: a) Recruitment Status, including enrollment by month, comparison of targeted to actual enrollment, and retention, b) Overall subject status, c) adherence to protocol, including visit completion, data outcomes collection, d) participant adherence to intervention components, e) outcomes tabulation and analysis.

Adverse event reporting guidelines:

We will comply with Department of Health and Human Services (DHHS) regulations 45 CFR 46.103(b)(5) and 45 CFR 46.108(a) and the U.S. Food and Drug Administration regulations 21 CFR 56.108(b)(1) that define the procedures for reporting to the Partners IRB, appropriate institutional officials, and the department or agency head/FDA any unanticipated problems involving risks to subjects or others, whether these problems cause actual harm to subjects or place subjects are potential of increased risk of harm. All such unanticipated problems will be reported promptly so that the IRB can consider whether the risks to subjects are still minimized and reasonable in relation to anticipated benefits, if any, and the importance of the knowledge that may reasonably be expected to result, and if any changes to the research or other corrective actions are warranted in order to protect the safety, welfare, or rights of subjects or others. We will report any of the following that occur during the conduct of the study, after study completion, or after subject withdrawal or completion within 5 working days/7 calendar days of the date that we first became aware of the problem.

- Any adverse events that occur during the EGD (while the gastroscope is being used) will be recorded as study AE's, as this is the additional research study procedure. Any adverse events occurring during the ERCP (while the ERCP scope is being used) will not be recorded as part of the study AE's but recorded as part of standard practice. Post-procedural AE's will be noted in the patient's medical record, however we will be unable to differentiate which procedure they are resulting from.
- Internal adverse events that are unexpected, and related or possibly related to the research and that indicate there are new or increased risks to subjects
- Deviation from the approved research protocol or plan without IRB approval in order to eliminate apparent immediate hazard to subjects or harm to others
- Deviation from the approved research protocol or plan that placed subjects or others at an increased risk of harm regardless of whether there was actual harm to subjects or others
- Any event that requires prompt reporting according to the research protocol or investigational plan
- Breach of confidentiality or violation of HIPAA regulations

- Medication, procedural or laboratory error regardless of whether subjects experienced any harm
- Interim analysis, safety monitoring report, publication in a peer-reviewed journal, or other finding that indicates that there are new or increased risks to subjects or others or that subjects are less likely to receive any direct benefits from the research
- Change in FDA labeling, withdrawal from market, manufacturer alert from the sponsor, or recall of an FDA-approved drug, device, or biologic used in the research
- Complaint by/on behalf of a research subject that indicates that the rights, welfare, or safety of the subject have been adversely affected or that cannot be resolved by the investigator
- Incarceration of a research subject during participation in research not approved for involvement of prisoners as subjects.
- Noncompliance with applicable regulations or requirements or determinations of the IRB identified by the research team or others that indicates that the rights, welfare, or safety of subjects have been adversely affected
- Suspension or termination of the research, in whole or in part, based on information that indicates that the research places subjects at an increased risk of harm than previously known or recognized
- Suspension or disqualification of an investigator by FDA, sponsor, or others
- Scientific misconduct

a) Outcomes monitoring:

Outcomes will be monitored by the Research team and reported to Principal Investigator.

b) Adverse event reporting guidelines:

Relevant Definitions:

An Adverse Event (AE) is any untoward medical occurrence in the participant associated with the EGD and ERCP procedure, whether or not considered related to EGD and ERCP.

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that is life threatening or requires inpatient hospitalization or persistent disability/incapacity or can result in death.

AE's will be reported by the participant or when appropriate by a caregiver or a surrogate of the participant or the participants' legally authorized representative. The investigator or any qualified designees are responsible for detecting, documenting and recording events that meet the definition of an AE or SAE and remain responsible for following up

AEs that are serious, considered related to the EGD and ERCP procedure or study procedures that cause the participant to discontinue the study.

In the event any serious adverse events are reported or observed during or after the EGD and ERCP, whether or not attributable to the EGD and ERCP procedure, the event will be reported to the Principal Investigator within 24 hours and to the IRB within 3-5 business days.

The intensity and severity of the event will be classified as follows:

- Mild: that is an awareness of sign of symptom, but easily tolerated.
- Moderate: that is discomfort or sign or symptom, but easily tolerated.
- Severe: at least partially incapacitating (or restricting usual activities)

The following information will be provided in writing: study protocol number, patient's identification code, date of birth and nature of the serious adverse event and the causality assessment. The report of an SAE will be completed and signed by the next working day.

Adverse events will be considered associated with the study procedure if the attribution is possible, probable or very likely. The relationship can be classified as follows:

- Not related: an AE that is not related to the study procedure.
- Doubtful: an AE for which an alternative explanation is more likely.
- Possible: an AE which might be due to study procedure.
- Very Likely: an AE which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation.
- Unknown: it is not possible to assign the reaction to any of the above categories because of insufficient, pending or contradictory information.

11. Privacy and Confidentiality

☒ Study procedures will be conducted in a private setting
☒ Only data and/or specimens necessary for the conduct of the study will be collected
☒ Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)
☐ Specimens collected will be maintained in a secure location with appropriate protections (e.g. locked storage spaces, laboratory areas)
☒ Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol
☒ Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g. encrypted files, password protection, using chain-of-custody procedures, etc.)

- ☒ All electronic communication with participants will comply with Mass General Brigham secure communication policies
- ☒ Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research
- ☒ All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens
- ☒ The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research
- ☐ Additional privacy and/or confidentiality protections

12. References

See above