OFFICE OF RESEARCH OPERATIONS
Dartmouth-Hitchcock

PROTOCOL TITLE: **SOCCER: Study Of forCeps Cannulation during ERcp**

D-HH IRB OVERSIGHT:

One of the following must be true in order to submit to the D-HH IRB. Please check all that apply:

☒ The Principal Investigator is employed by D-H
☒ The study will utilize any D-H data or specimens
☒ The study will enroll D-H patients or recruit from D-H sites
☒ The study will utilize any D-H resources, e.g. study procedures will occur at D-H locations and/or use of D-H equipment or shared resources

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SOCCER: Study Of forCeps Cannulation during ERcp

PRINCIPAL INVESTIGATOR:

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VERSION NUMBER/DATE:

Version 2, June 8, 2022

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
0	February 4, 2022	Original	
1	June 8, 2022	Added ampullary mass to exclusion criteria	no

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1.0 Study Summary

Study Title	SOCCER: Study Of forCeps Cannulation during ERcp
Study Design	Randomized controlled trial
Primary Objective	To determine whether a forceps assisted cannulation leads to less difficult cannulation during ERCPs based on a standard definition of difficult cannulation
Secondary Objective(s)	To determine whether the risk of PEP is reduced by forceps assisted cannulation
Research Intervention(s)/ Investigational Agent(s)	Eligible patients who have consented will either be randomized to cannulation with forceps or cannulation with no forceps
IND/IDE #	N/A
Study Population	Patients undergoing ERCP who have a native papilla
Sample Size	152
Study Duration for individual participants	Time of procedure and telephone call one week post-procedure
Study Specific Abbreviations/ Definitions	AE: adverse event AP: acute pancreatitis CBD: common bile duct DH: Dartmouth-Hitchcock DHMC: Dartmouth-Hitchcock Medical Center Difficult cannulation: any cannulation that results in any of the following: 5 or more minutes, 5 or more cannulation attempts, or 2 or more unintentional pancreatic wire passages ERCP: endoscopic retrograde cholangiopancreatography FDA: Food and Drug Administration GCP: good clinical practice IRB: institutional review board

	MoP: manual of procedures OSH: outside hospital PD: pancreatic duct PEP: post-ERCP pancreatitis PI: principal Investigator RCT: randomized controlled trial SAE: severe adverse SOCCER: study of forceps cannulation during ERCP SOD: Sphincter of Oddi dysfunction

2.0 Objectives

- The objective of our study is to determine whether a forceps assisted cannulation leads to less difficult cannulation during ERCP. Because difficult cannulation is associated with increased risk of PEP, our study investigates whether the forceps assisted cannulation also reduces the incidence of PEP as a secondary outcome.
- We hypothesize that a forceps assisted cannulation will significantly reduce the difficulty of cannulation.

3.0 Background

Endoscopic retrograde cholangiopancreatography (ERCP), an invasive procedure that combines endoscopy and x-ray to treat issues with the bile and pancreatic ducts, carries a two to ten percent risk of causing post-ERCP pancreatitis (PEP) [1]. Because acute pancreatitis is a devastating inflammatory condition that leads to extensive morbidity and mortality, efforts to reduce the risk of PEP in patients undergoing ERCP would enhance patient outcomes and would decrease the economic burden in treating PEP nationwide [2-4].

A difficult cannulation has been identified as one of the high risk factors for developing PEP [5]. A study performed by Scandinavian Association for Digestive Endoscopy (SADE) determined that cannulations with five or more attempts, a duration of five minutes or longer, or two or more unintended pancreatic duct (PD) wire passages significantly increased one's risk for PEP [6]. Thus, SADE defined a difficult cannulation as any cannulation with at least one of the following conditions: five or more attempts, five or more minutes, or two or more unintended PD wire passages [6]. This classification of a difficult cannulation has been adopted and standardized by the European Society of Gastrointestinal Endoscopy [7]. Because no current guidelines defining a difficult cannulation exist from the American College of Gastroenterology or American Gastroenterological Association, the ESGE guidelines as gathered from the SADE study are the worldwide standardized definition of difficult cannulation.

Difficult cannulations have been reported to occur at a frequency of 42 percent for all ERCP exams [8]. The morphology and accessibility of the papilla influence the level of difficulty. Some studies have indicated that different macroscopic appearances of the papilla result in varying cannulation difficulty levels. Based on a study gauging intraobersever and interobserver agreement to the macroscopic appearance of different papillae, papillae are categorized as: Type 1, normal appearing; Type 2, small; Type 3, protruding or pendulous; and Type 4, ridged or creased [9]. Haraldsson et al. found that Type 2 and Type 3 papillae were more difficult to cannulate [8]. Regardless of papilla type, the involvement of a trainee (a GI fellow) resulted in more difficult cannulations [8]. In addition, the presence of redundant tissue, such as periampullary diverticula—which occurs in up to 20 percent of patients undergoing ERCP—results in more challenging cannulations [10]. The use of a forceps to assist in the cannulation is a demonstrated effective technique for cannulating papillae that are difficult to access [10-12].

The forceps clears the redundant tissue to enable access to the papilla, as well as stabilizes the ampullary position to permit an easier cannulation [10]. Currently, no randomized controlled trials that detail to what extent a forceps facilitates cannulation exist. Thus, our study aims to determine whether a forceps assisted cannulation reduces the incidence of difficult cannulations and consequently PEP.

4.0 Study Endpoints

- The primary outcome is difficult cannulation after randomization. A difficult cannulation will be defined as any cannulation that results in any of the following: 5 or more minutes, 5 or more cannulation attempts, or 2 or more unintentional pancreatic wire passages.
- The secondary outcome is PEP. Acute pancreatitis according to the Atlanta guidelines, is at least two of the following: abdominal pain consistent with pancreatitis, lipase or amylase greater than 3 times the upper limit of normal, radiographic evidence of pancreatitis on cross sectional imaging [13].

5.0 Study Intervention/Investigational Agent

- Description: The study intervention is the use of a forceps during the cannulation. This trial will use one type of forceps called SpyBite forceps. Eligible patients who have consented will either be randomized to forceps assisted cannulation or no forceps used during cannulation.
- SpyBite forceps is an FDA approved instrument for usage during endoscopy and during ERCP. The physician performing the procedure will not be blinded. Thus, that doctor will ensure the patient gets the treatment to which the patient was randomized and will ensure proper usage of the forceps. The forceps is an FDA approved instrument and does not put the patient at any higher risk for any AE. Please note that for the explicit purpose of the study the forceps will be used to grab tissue and not take biopsies. The forceps may still be used to take biopsies if the physician believes it is indicated. The trial will run in accordance with federal regulations and IRB determinacy.

6.0 Procedures Involved

- Study Design
    - This investigation is a randomized controlled trial. Eligible patients who have consented will be randomized to either ERCP with forceps assisted cannulation or ERCP with no forceps.
- Study sites

- Dartmouth-Hitchcock Medical Center in Lebanon, New Hampshire will be the only site where the study takes place. There are no satellite sites.

- Recruitment
  - SOCCER plans to enroll 152 patients over 2 years.
  - All patients undergoing ERCP at DHMC endoscopy will be approached and consented for this study. Medical records will be reviewed to see if they meet inclusion/exclusion criteria. Patients will be consented day of the procedure. We will enter a request for HIPAA Authorization Waiver because access to a patient's chart will be required to determine inclusion/exclusion criteria. Please find the waiver request in the recruitment section.
- Procedures
  - All patients at DHMC endoscopy who meet inclusion/exclusion criteria will be approached and consented for this study. Consent will be performed in the endoscopy pre-op area. During the standard of care ERCP, the patients will be randomized intraoperatively to either cannulation with forceps and cannulation with no forceps. Written informed consent will be reviewed and signed before any study related procedures are performed.
  - Please note that the primary outcome refers to a difficult cannulation AFTER randomization when the secondary inclusion criteria has been met. For example, if the secondary inclusion criteria met is difficult cannulation, then the primary outcome would be if from that point forward there were a difficult cannulation. As such, a total cannulation time of 10 minutes would enable the patient to be eligible (the first 5 minutes means the cannulation is difficult) and would mean the subject met the primary outcome (the second 5 minutes means cannulation after randomization is difficult). However, a total cannulation time of 8 minutes means the patient is eligible for the study (first 5 minutes means the cannulation is difficult) but did not meet the primary outcome (after randomization, the cannulation was not difficult because it was only 3 minutes). In a sense, the "difficult cannulation clock" is reset after randomization. If the secondary inclusion criteria met instead is papilla location or type, then the patient is randomized immediately before the cannulation and the difficult cannulation clock starts then. Measurement of difficult cannulation starts immediately after randomization upon the doctor's first cannulation attempt following randomization.

- Chart review will be performed to determine patient's past medical history as it relates to the study—for example, to determine a history of AP or PEP. ERCP will be performed by those who are board certified gastroenterologists. Trainees can be involved so long as they are under supervision of a board certified gastroenterologist who is on faculty at DHMC. The level of involvement in the procedure and level of proficiency of the trainee will be documented and stored in the database.
- Randomization procedure – Randomization will occur in block format. Randomization assignments will be placed in sealed manila envelopes that will be opened at the time of randomization. Manila envelopes will be kept with the study coordinator.
- Randomization will occur when the subject has met necessary inclusion criteria and no exclusion criteria, which will not be known until the doctors are in the procedure. Randomization will thus take place intraprocedurally.
- After consent, data will be collected before, during, and after the procedure. The primary outcome will be measured during the procedure, whereas the secondary outcome will be determined during the 5 day follow up call. The study coordinator, GI fellow, or attending physician will call the patient 5 days (+/- 2 days) post-procedure to determine whether the patient developed PEP. Though it is preferred to contact the patient, other methods (chart review, emergency contact, OSH records) are acceptable for determining the secondary outcome. Patients will be unblinded to their treatment on the follow-up call.
- Data will be stored in a database on Excel. This database will be password protected behind a Dartmouth-Hitchcock firewall and only authorized personnel on the research team will have access to the study materials including the database.

- The site PI will sign off on the end of study of each subject to ensure quality and authenticity of the data.

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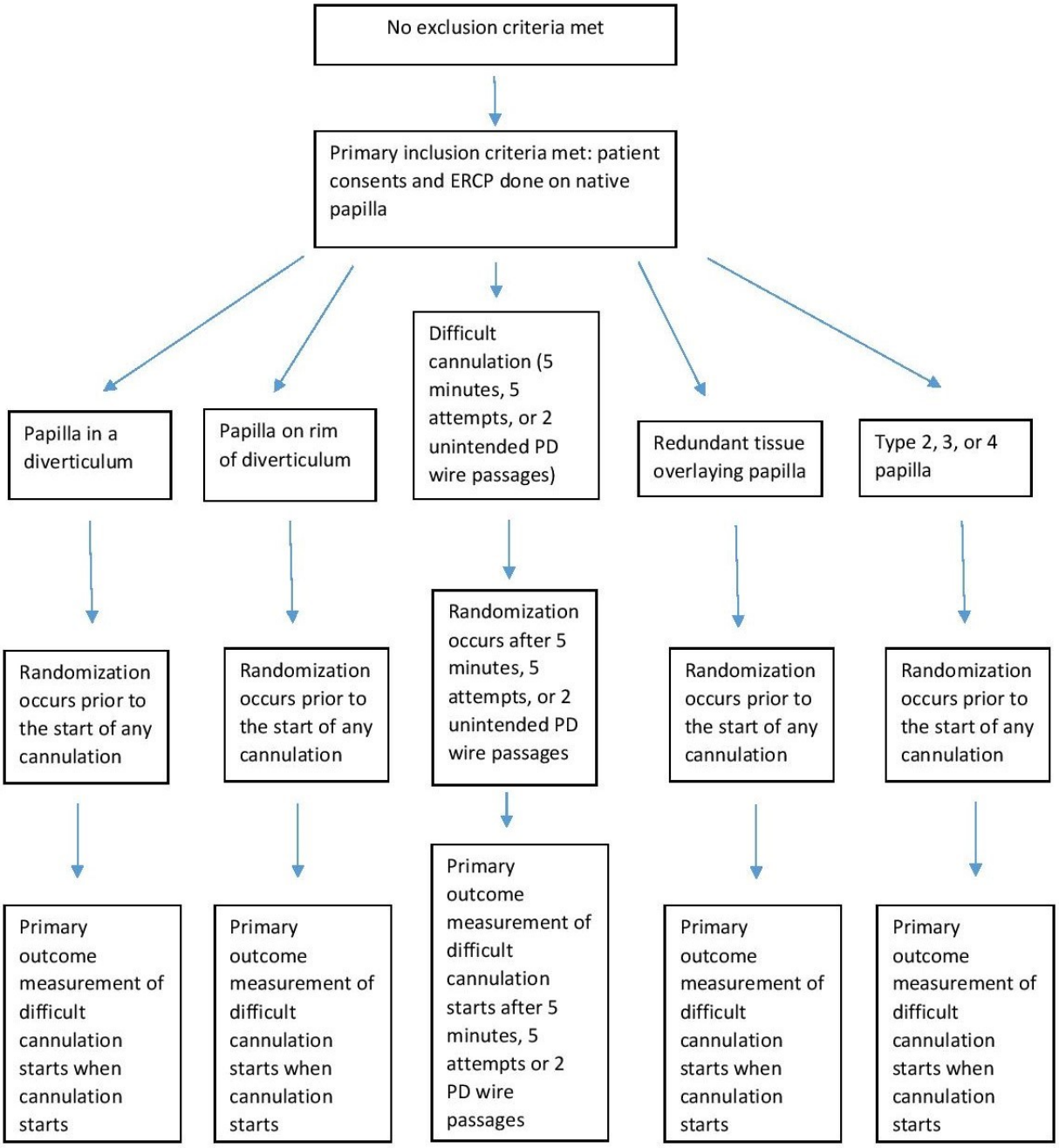
Randomization Flow Chart



7.0 Data and Specimen Banking

- Data is kept in a database on a DH server behind the firewall and password protected. Access to the database will be limited to the research team. Data will be kept for 5 years post publication.

8.0 Sharing of Results with Subjects

- Subjects will be unblinded to their treatment on the follow up call.

9.0 Study Timelines

- A subject will be in the study for a week.
- We plan to enroll 152 patients over the course of 2 years. Our estimated date to complete the study is 2025.

10.0 Inclusion and Exclusion Criteria

Patient must be able to provide informed consent. If patient provides informed consent and meets the following criteria, the patient can participate in the study.

PRIMARY INCLUSION CRITERIA: If the response to any of the questions below is "NO," the patient is NOT ELIGIBLE to participate in the study.		
Patient consented?	☐ YES	☐ NO
ERCP done on native papilla	☐ YES	☐ NO
SECONDARY INCLUSION CRITERIA: If the response to any of the questions below is "YES," the patient IS eligible		
Papilla in a diverticulum	☐ YES	☐ NO
Papilla on rim of a diverticulum	☐ YES	☐ NO
Difficult cannulation (5 attempts, 5 minutes, or 2 unintended PD wire passages)	☐ YES	☐ NO
Redundant tissue overlaying papilla	☐ YES	☐ NO
Type 2, 3, or 4 papilla (see figure below for reference)	☐ YES	☐ NO

EXCLUSION CRITERIA: If the response to any of the questions below is "YES," the patient is NOT ELIGIBLE to participate in the study.		
Prior ampullectomy	☐ YES	☐ NO

Ampullary mass	☐ YES	☐ NO
Known pregnancy, positive test, breastfeeding	☐ YES	☐ NO
Clinical contraindication to ERCP	☐ YES	☐ NO
Metal allergy	☐ YES	☐ NO
Prior sphincterotomy	☐ YES	☐ NO
Inability to follow protocol	☐ YES	☐ NO
<18 years old	☐ YES	☐ NO
Enrolled in another ERCP	☐ YES	☐ NO
Biliary/PD stent in place	☐ YES	☐ NO

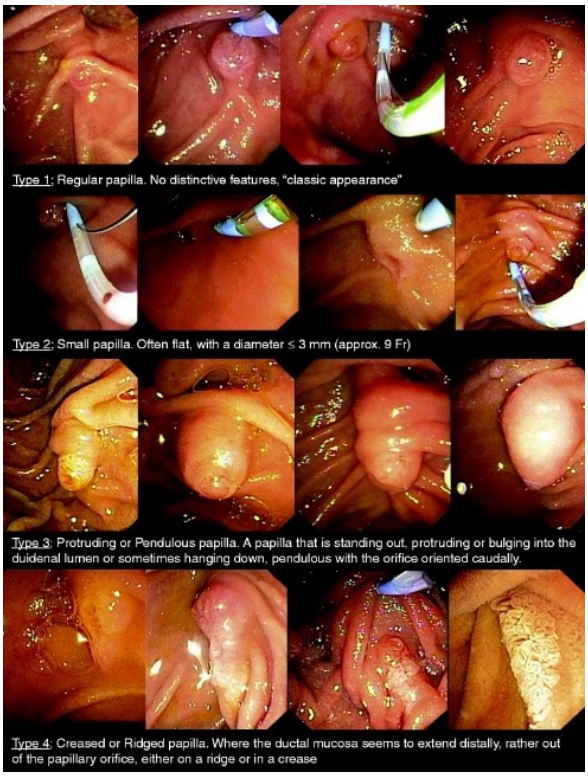


Figure from Haraldsson E, Lundell L, Swahn F, et al. Endoscopic classification of the papilla of Vater. Results of an inter- and intraobserver agreement study. *United European Gastroenterol J.* 2017;5(4):504-510. doi:10.1177/2050640616674837

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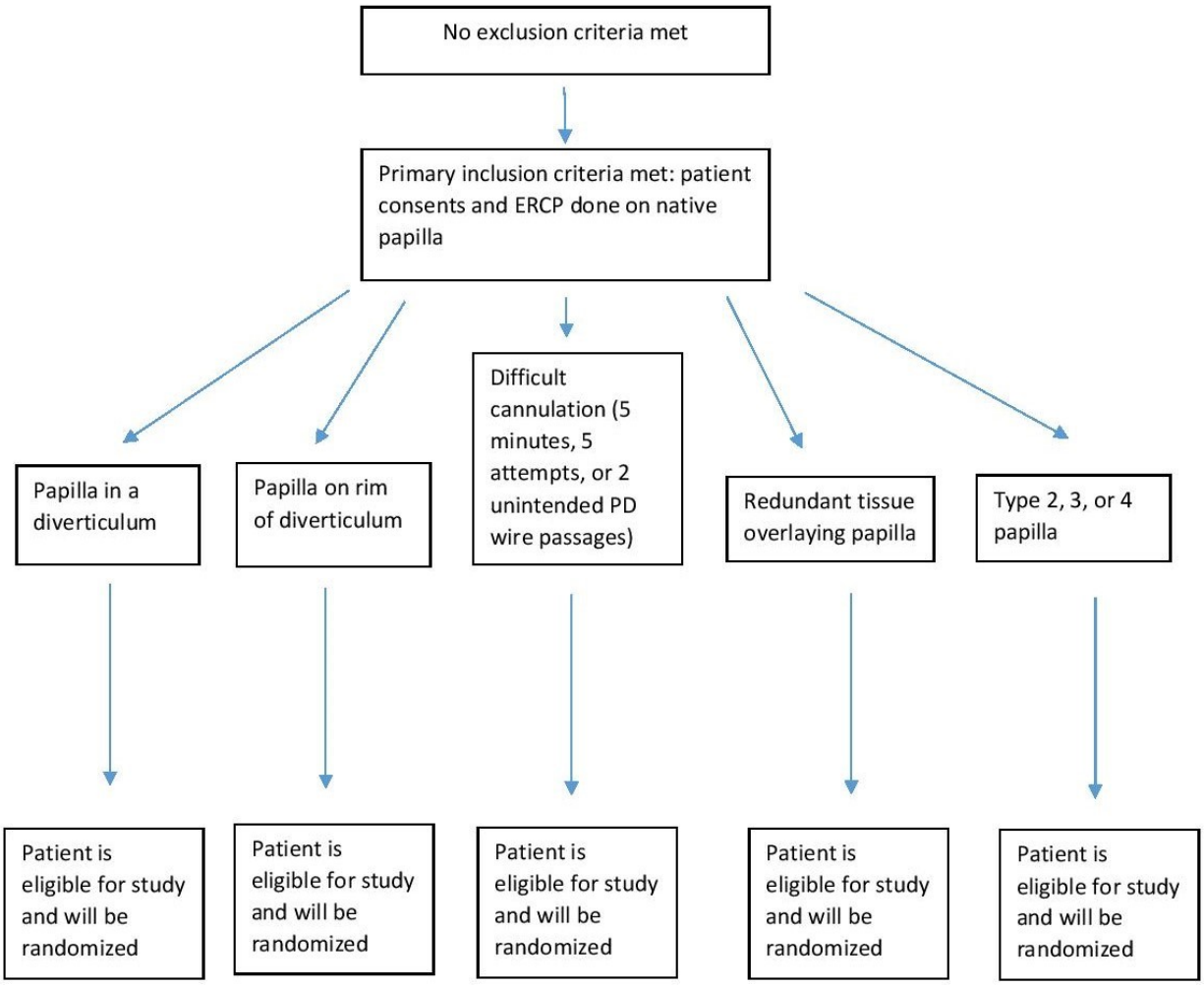
Eligibility Flow Chart



11.0 Vulnerable Populations

- The study will not involve any patients in vulnerable populations.

12.0 Local Number of Subjects

- 152 patients will be enrolled.
- Our power calculation was performed using Sample Size Calculator from ClinCalc LLC [14]. Based on our experience, we believe that a forceps

assisted cannulation results in a 50 percent decrease in the incidence of a difficult cannulation. Data has demonstrated that a difficult cannulation has an incidence of 42 percent [8]. Thus, by setting the incidence of difficult cannulation in our two groups at 42 percent and 21 percent, we determined our sample size is 152 patients with 76 in each treatment group. Alpha value is $p<0.05$ and power is set to 80 percent. Data analysis will involve chi square tests for categorical variables and student's t-tests for continuous variables. Analysis will be conducted using Microsoft Excel (Microsoft Corporation, Redmond, WA).

13.0 Recruitment Methods

- All patients undergoing ERCP at DHMC will be approached for the study. A HIPAA Authorization waiver will be required so that patients can be screened in the electronic health records prior to procedure for inclusion/exclusion criteria.
- GI Research has the resources needed to conduct this study and the support of the GI providers to help identify and recruit subjects.
- The GI Research team is made up of four coordinators, a research nurse, the research operations manager, and any physicians involved in the study who are fully dedicated to running clinical research.
- The GI Research study team has locked offices and access to all technology needed to successfully run a study.
- No payment or advertising will be done.

The GI Research Team also request a Waiver of the HIPAA Authorization for recruitment. GI Research Team members, who are workforce members of D-H, will use eDH (medical records) to identify potential research participants for this study.

The GI Research Team agrees that:

- The use or disclosure is sought solely to review PHI as necessary to prepare the research
- No PHI will be removed from the covered entity during the review
- The PHI that the researcher seeks to use or access is necessary for the research purpose

The GI Research Team further agrees that:

1. The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:

    a. an adequate plan to protect the identifiers from improper use and disclosure –

Identifiers used in recruitment will not be shared with anyone outside of the GI Research Team.

b. an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law;
Identifiers that do not lead to recruitment will be destroyed at the end of the study. Identifiers that lead to recruitment will be linked to the Case Report Forms via a key that will be kept by the GI Research Team and only shared in accordance with the terms set forth in the Informed Consent document.

c. adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by this subpart;
Protected Health Information (PHI) will only be used or disclosed as outlined in the protocol for this research project.

2. The research could not practicably be conducted without the waiver or alteration;
The GI Research Team cannot practicably identify and recruit subjects without this waiver.

3. The research could not practicably be conducted without access to and use of the protected health information.

   The GI Research Team cannot practicably identify and recruit subjects without access to their PHI for screening purposes.

14.0 Withdrawal of Subjects

- If cannulation reaches 30 minutes without success, and the attending physician believes it to be in the patient's best interest to switch treatment groups, then the attending may switch treatments. These patients will be followed in the study with intention to treat analysis.
- If during the procedure, the attending notices that a patient who had consented to the study meets exclusion criteria or no inclusion criteria, then the subject will be withdrawn from the study and be informed following the procedure.
- If patients decide not to continue in the study after initially giving consent, they must submit their request in writing to the site PI. These patients will not be followed in order to respect their autonomy. However, data will be collected and analyzed up until the point at which they revoke their consent for participation in the study.

- If a patient exits the study due to an SAE, the patient will be followed still with an intention to treat analysis. Data will be collected from chart review, OSH records, or emergency contact.

15.0 Risks to Subjects

- The risk to the subjects is no greater than the standard risks of an ERCP, which is the procedure they would already be receiving. Participants will sign a separate consent form to give permission for the procedure, as is standard of care. The study intervention of the forceps does not put the subjects at any greater risk for harm.
- Because the ERCP is standard of care, the cost of the procedure is covered by the patient's insurance and will not result in any additional cost for the patient. The cost of forceps will be covered by established DHMC GI department research funds (Dartmouth Pancreas Research Fund) in order to make sure there is no increased or additional cost for the patient. A grant to the American Society of Gastrointestinal Endoscopy will also be submitted in December 2022 to cover the cost of the forceps – although a negative review from this grant application will not inhibit study completion.

16.0 Potential Benefits to Subjects

- Though we can make no guarantees, it is our hope that the forceps assisted cannulation reduces the difficulty of cannulation in an effort to reduce the risk of PEP and to decrease procedure time. We hope to gather information that will improve the procedure in the future.

17.0 Data Management and Confidentiality

- All data is secured in a database on a DH server behind the DH firewall and password protected. Access to the database will be limited to the research team
- Our power calculation was performed using Sample Size Calculator from ClinCalc LLC [14]. Based on our experience, we believe that a forceps assisted cannulation results in a 50 percent decrease in the incidence of a difficult cannulation. Data has demonstrated that a difficult cannulation has an incidence of 42 percent [8]. Thus, by setting the incidence of difficult cannulation in our two groups at 42 percent and 21 percent, we determined our sample size is 152 patients with 76 in each treatment group. Alpha value is $p<0.05$ and power is set to 80 percent. Data analysis will involve chi square tests for categorical variables and student's t-tests for continuous variables. Analysis will be conducted using Microsoft Excel (Microsoft Corporation, Redmond, WA).

- The PI will sign off on every patient's end of study to verify the authenticity of the data as a quality control measure.

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

- We will have no formal data monitoring committee, but the PI will review and sign off on every patient's end of study to verify the authenticity of the data as a quality control measure

19.0 Provisions to Protect the Privacy Interests of Subjects

- Subject Case Report Forms (CRFs) will only include the subject's study number. The research team will have a key linking the subject to his/her study number. The key will be housed on a DH server, password protected and behind the DH firewall. No PHI will be published or shared.

20.0 Compensation for Research-Related Injury

- No compensation will be provided. The research does not involve more than minimal risk to subjects.

21.0 Economic Burden to Subjects

- There is no additional cost for the subjects. The ERCP, as a standard of care procedure, is covered by their insurance plans and will be billed to the subject or his/her insurance. The cost of the forceps will be covered by the study to ensure that subjects will not have any additional cost.

22.0 Consent Process

- Consent will take place in the endoscopy suite at DHMC in Lebanon, New Hampshire the day of the patient's ERCP. Eligible patients will be approached to determine interest in participation.
- The study will be following SOP: Informed Consent Process for Research (HRP-090).

Non-English Speaking Subjects

- Non-English speakers will not be included in the study.

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

- Not applicable because the research does not involve any of the elements in bold above.

Subjects who are not yet adults (infants, children, teenagers)

- The study does not include subjects who are not yet adults.

Cognitively Impaired Adults

- The study does not include subjects who are cognitively impaired.

. ***Adults Unable to Consent NA***

- The study does not include subjects who are not able to consent.

23.0 Process to Document Consent in Writing

- We will follow HRP 091(SOP: Written Documentation of Consent).

24.0 Setting

- Our research will be conducted at DHMC in Lebanon, New Hampshire. Study procedures will be conducted in the DHMC Lebanon endoscopy suite.

25.0 Resources Available

- GI Research has the resources needed to conduct this study and the support of the GI providers to help identify and recruit subjects.
- The GI Research team is made up of four coordinators, a research nurse, the research operations manager, and any physicians involved in the study who are fully dedicated to running clinical research.
- The GI Research study team has locked offices and access to all technology needed to successfully run a study.

26.0 Multi-Site Research

- DHMC in Lebanon, New Hampshire is the only site for the research.

27.0 References

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